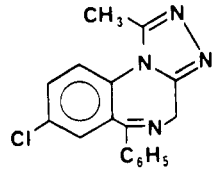
ALPRAZOLAM

Therapeutic Function: Tranquilizer

Chemical Name: 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a] [1,4] benzodiazepine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 28981-97-7

Trade Name	Manufacturer	Country	Year Introduced
Xanax	Upjohn	U.S.	1981
Xanax	Upjohn	Switz.	1982
Xanax	Upjohn	U.K.	1983
Xanax	Upjohn	Australia	1983

Raw Materials

2,6-Dichloro-4-phenylquinoline
Hydrazine Hydrate
Triethyl Orthoacetate
Sodium Periodate
Paraformaldehyde
Phosphorus Tribromide
Ammonia

Manufacturing Process

6-Chloro-2-hydrazino-4-phenylquinoline: A stirred mixture of 2,6-dichloro-4-phenylquinoline (2.7 g, 0.01 mol) and hydrazine hydrate (6.8 g) was refluxed under nitrogen for 1 hour and concentrated in vacuo. The residue was suspended in warm water, and the solid was collected by filtration, dried and recrystallized from ethyl acetate-Skelly B hexanes to give 1.81 g (67% yield) of 6-chloro-2-hydrazino-4-phenylquinoline of melting point 156.5°–157°C.

7-Chloro-1-methyl-5-phenyl-s-trizolo[4,3-a] quinoline: A stirred mixture of 6-chloro-2-hydrazino-4-phenylquinoline (1.4 g, 0.0052 mol), triethyl-orthoacetate (0.925 g, 0.0057 mol) and xylene (100 ml) was refluxed, under nitrogen, for 2 hours 40 minutes. During this period the ethanol formed in the reaction was removed by distillation through a short, glass helix-packed column. The mixture was concentrated to dryness in vacuo and the residue was crystallized from methanol-ethyl acetate to give: 1.28 g of 7-chloro-1-methyl-5-phenyl-s-triazolo[4,3-a]-quinoline (83.9% yield). The analytical sample was crystallized from methylene chloride:methanol and had a melting point 252.5°–253.5°C.

5-Chloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)benzophenone (Oxidation of 7-chloro-1-methyl-5-phenyl-s-trizolo[4,3-a] quinoline): A stirred suspension of 7-chloro-1-methyl-5-phenyl-s-triazolo[4,3-a] quinoline (2.94 g, 0.01 mol) in acetone (110 ml) was cooled in an ice-bath and treated slowly with a solution prepared by adding sodium periodate (2 g) to a stirred suspension of ruthenium dioxide (200 mg) in water (35 ml). The mixture became dark. Additional sodium periodate (8 g) was added during the next 15 minutes. The ice-bath was removed and the mixture was stirred for 45 minutes. Additional sodium periodate (4 g) was added and the mixture was stirred at ambient temperature for 18 hours and filtered. The solid was washed with acetone and the combined filtrate was concentrated in vacuo. The residue was suspended in water and extracted with methylene chloride. The extract was dried over anhydrous potassium carbonate and concentrated. The residue was chromatographed on silica

gel (100 g) with 10% methanol and 90% ethyl acetate; 50 ml fractions were collected. The product was eluted in fractions 10–20 and was crystallized from ethyl acetate to give: 0.405 g of melting point 168°–169.5°C and 0.291 g of melting point 167.5°–169°C (23.4% yield) of 5-chloro-2-(3-methyl-4H-1,2,4-triazol-4-yl)benzophenone. The analytical sample had a melting point of 168°C.

5-Chloro-2-[3-(hydroxymethyl)-5-methyl-4H-1,2,4-triazol-4-yl]benzophenone: A stirred mixture of 5-chloro-2-(3-methyl-4H-1,2,4-triazolo-4-yl)benzophenone, (2.98 g, 0.01 mol) paraformaldehyde (3 g) and xylene (100 ml) was warmed under nitrogen, in a bath maintained at 125°C for 7 hours. The mixture was then concentrated in vacuo. The residue was chromatographed on silica gel (150 g) with 3% methanol-97% chloroform. Fifty ml fractions were collected. The product was eluted in fractions 20–44. The fractions were concentrated and the residue was crystallized from ethanol-ethyl acetate to give: 1.64 g of melting point 138°–142°C; 0.316 g of melting point 138.5°–141°C; 0.431 g of melting point 139°–141°C (72.8% yield) of 5-chloro-2-[3-(hydroxymethyl)-5-methyl-4H-1,2,4-triazol-4-yl] benzophenone. The analytical sample had a melting point of 138°–139°C.

5-Chloro-2-[3-(bromomethyl)-5-methyl-4H-1,2,4-triazol-4-yl] -benzophenone: A solution of 5-chloro-2-[3-(hydroxymethyl)-5-methyl-4H-1,2,4-triazol-4-yl] -benzophenone (328 mg, 0.001 mol) in dry, hydrocarbon-stabilized chloroform (5 ml) was cooled in an ice-bath and treated with phosphorus tribromide (0.1 ml). The colorless solution was kept in the ice-bath for 55 minutes, at ambient temperature (22°–24°C), for 5 hours. The resulting yellow solution was poured into a mixture of ice and dilute sodium bicarbonate. This mixture was extracted with chloroform. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was crystallized from methylene chloride-ethyl acetate to give: 0.285 g of melting point 200°–240°C (decomposition) and 0.030 g of melting point 200°–220°C (decomposition) of 5-chloro-2-[3-(bromomethyl)-5-methyl-4H-1,2,4-triazol-4-yl] -benzophenone. The analytical sample had a melting point of 200°–240°C.

8-Chloro-1-methyl-6-phenyl-4H-s-triazolo-[4,3-a] [1,4] -benzodiazepine: A stirred suspension of 5-chloro-2-[3-(bromomethyl)-5-methyl-4H-1,2,4-triazol-4-yl] -benzophenone (391 mg, 0.001 mol) in tetrahydrofuran (15 ml) was cooled in an ice-bath and treated with a saturated solution of ammonia in methanol (12.5 ml). The resulting solution was allowed to warm to ambient temperature and stand for 24 hours. It was then concentrated in vacuo. The residue was suspended in water, treated with a little sodium bicarbonate and extracted with methylene chloride. The extract was washed with brine, dried with anhydrous potassium carbonate and concentrated. The residue was crystallized from methylene chloride-ethyl acetate to give 0.220 g of crude product of melting point 227°–228.5°C. Recrystallization of this material from ethyl acetate gave 0.142 g of melting point 228°–229.5°C of 8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a] [1,4] -benzodiazepine.

References

Merck Index 303
DFU 1 (12) 551 (1976)
Kleeman & Engel p. 30
PDR p. 1865
OCDS Vol. 3 p. 197 (1984)
DOT 11 (5) 179 (1975)
I.N. p. 60
Hester, J.B., Jr.; U.S. Patent 3,681,343; August 1, 1972; assigned to The Upjohn Company.
Hester, J.B., Jr.; U.S. Patent 3,781,289; December 25, 1973; assigned to The Upjohn Company.
Hester, J.B., Jr.; U.S. Patent 3,709,898; January 9, 1973; assigned to The Upjohn Company.

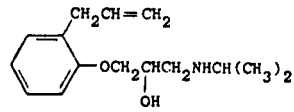
ALPRENOLOL HYDROCHLORIDE

Therapeutic Function: Beta blocker

Chemical Name: 1-[(1-Methylethyl)amino]-3-[2-(2-propenyl)phenoxy]-2-propanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 13655-52-2 (Base); 13707-88-5 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Aptol	Globopharm	Switz.	–
Aptin	Astra France	W. Germany	1967
Aptine	Lematte/Boinot	France	1971
Aprobal	Fujisawa	Japan	1971
Aptin	Byk Gulden	Italy	1972
Apllobal	Hassle	Sweden	–
Aptina	Made	Spain	–
Aptol-Duriles	Astra	–	–
Betacard	Beecham	U.K.	–
Betaptin	–	–	–
Elperl	Sawai	Japan	–
Gubernal	Geigy	France	–
Regletin	Teikoku	Japan	–
Sinalol	Kaken	Japan	–
Yobir	Maruko	Japan	–

Raw Materials

o-Allyl Epoxy Propoxy Benzene
Ammonia
Hydrogen Chloride
Sodium Borohydride
Acetone

Manufacturing Process

A solution of 24.6 g of o-allyl-epoxypropoxybenzene dissolved in 250 ml of absolute ethanol saturated with ammonia was placed in an autoclave and heated on a steam-bath for 2 hours. The alcohol was then removed by distillation and the residue was redissolved in a mixture of methanol and ethylacetate. Hydrogen chloride gas was introduced into the solution. The hydrochloride salt was then precipitated by the addition of ether to yield 11.4 g of product. Five grams of the amine-hydrochloride thus formed were dissolved in 50 ml of methanol and 9 ml of acetone. The resulting solution was cooled to about 0°C. At this temperature 5 g of sodium borohydride were added over a period of 1 hour. Another 2.2 ml of acetone and 0.8 g of sodium borohydride were added and the solution was kept at room temperature for 1 hour, after which 150 ml of water were added to the solution. The solution was then extracted with three 100-ml portions of ether which were combined, dried over potassium carbonate, and evaporated. The free base was then recrystallized from petrol ether (boiling range 40°–60°C) to yield 2.7 g of material having a melting point of 57°C.

The corresponding hydrochloride was prepared by dissolving 2 g of the product, prepared above, in 20 ml of acetone, and adding to the resulting solution acetone saturated with hydrogen chloride until the pH was reduced to about 3. The precipitated hydrochloride salt was then recrystallized from acetone.

References

Merck Index 304

Kleeman & Engel p. 31
OCDS Vol. 1 p. 177 (1977)
DOT 9 (6) 245 (1973)
I.N. p. 60
Brandstrom, A.E., Corrodi, H.R. and Alblad, H.R.G.; U.S. Patent 3,466,376; September 9, 1969; assigned to Aktiebolaget Hassle.

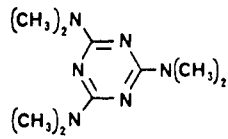
ALTRETAMINE

Therapeutic Function: Antitumor agent

Chemical Name: 2,4,6-Tris(dimethylamino)-1,3,5-triazine

Common Name: Hexamethylmelamine

Structural Formula:



Chemical Abstracts Registry No.: 645-05-6

Trade Name	Manufacturer	Country	Year Introduced
Hexastat	Roger Bellon	France	1979
Hexastat	Rhone Poulenc	Switz.	1981
Altretamine	Rhone Poulenc	W. Germany	1982

Raw Materials

Hexamethylolmelamine-Hexamethyl Ether
Hydrogen

Manufacturing Process

50 g of hexamethylolmelamine-hexamethyl ether in 950 cc methanol are hydrogenated, at 90° to 100°C, in the presence of 2 g Raney nickel with 100 atmospheres excess pressure of hydrogen in a steel autoclave holding 2 ℓ until the absorption of hydrogen is terminated. After the catalyst has been filtered off with suction, the methanol is distilled off. As a result, 23.1 g (86% of the theoretical) of crude hexamethylmelamine are formed having a melting point of 158° to 162°C. After recrystallization from methanol, the pure product is obtained having a melting point of 168°C.

References

Merck Index 310
DFU 5 (10) 492, 635 (1980)
DOT 18 (4) 165 (1982)
I.N. p. 61
von Brachel, H. and Kindler, H.; U.S. Patent 3,424,752; January 28, 1969; assigned to Casella Farbwerke Mainkur AG

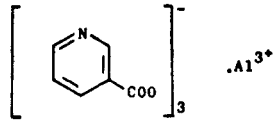
ALUMINUM NICOTINATE

Therapeutic Function: Peripheral vasodilator

Chemical Name: 3-pyridinecarboxylic acid aluminum salt

Common Name: Tris(nicotinato)aluminum

Structural Formula:



Chemical Abstracts Registry No.: 1976-28-9

Trade Name	Manufacturer	Country	Year Introduced
Nicalex	Merrell-Dow	U.S.	1960
Alunitine	Continental Pharma	Belgium	—

Raw Materials

Nicotinic Acid
Aluminum Hydroxide

Manufacturing Process

Aluminum nicotinate is prepared by dissolving nicotinic acid in hot water and adding a slurry of aluminum hydroxide to it. A slight excess of aluminum hydroxide is used in order that the final product would be free of nicotinic acid. The precipitate is collected on a filter and dried. The final product contains a mixture of aluminum nicotinate and a small but acceptable amount of aluminum hydroxide.

References

Merck Index 346
Kleeman & Engel p. 33
I.N. p. 62
Miale, J.P.; U.S. Patent 2,970,082; January 31, 1961; assigned to Walker Laboratories, Inc.

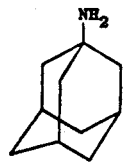
AMANTIDINE HYDROCHLORIDE

Therapeutic Function: Antiviral, anti-Parkinsonism

Chemical Name: 1-adamantanamine hydrochloride

Common Name: 1-aminoadamantane hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 665-66-7

Trade Name	Manufacturer	Country	Year Introduced
Symmetrel	DuPont (Endo)	U.S.	1966
Symmetrel	Geigy	W. Germany	1966
Symmetrel	Geigy	U.K.	1971
Mantadan	De Angeli	Italy	1971
Mantadix	Theraplix	France	1973
Symmetrel	Fujisawa	Japan	1975
Amantadin	Ratipharm	W. Germany	–
Amantan	Byk-Gulden	–	–
Amazolon	Sawai	Japan	–
Antadine	DuPont	Australia	–
Atarin	Medica	Finland	–
Contenton	SK Dauelsberg	W. Germany	–
Influenol	Santos	Spain	–
Midantan	–	–	–
Paramantin	Orion	Finland	–
Paritrel	Trima	Israel	–
PK-Mertz	Mertz	W. Germany	–
Protexin	Landerlan	Spain	–
Solu-Contenton	SK&F	W. Germany	–
Trivaline	Farmex	France	–
Viregyt	Egyt	Hungary	–
Virofral	Duphar	Belgium	–
Virofral	Ferrosan	Denmark	–
Virosol	Phoenix	Argentina	–

Raw Materials

Adamantane
Hydrocyanic Acid
Sodium Hydroxide
Hydrogen Chloride

Manufacturing Process

360 ml of 96% sulfuric acid and a solution of 13.6 grams (0.1 mol) of adamantane in 100 ml of n-hexane were emulsified in the apparatus described and provided with an inclined centrifugal stirrer. Then a mixture of 46 grams (1.7 mols) of liquid hydrocyanic acid and 29.6 grams (0.4 mol) of tertiary butanol was added dropwise within 1.5 hours at about 25°C.

After 30 minutes of postreaction, the product was poured on ice. The granular mass which precipitated [N-(adamantyl-1)formamide] was sucked off and washed with water. The raw product (37 grams) was then refluxed for 10 hours with a solution of 60 grams of NaOH in 600 ml of diethylene glycol.

After cooling, the solution was diluted with 1.5 liters of water and subjected to three extractions with ether. The amine was extracted from the ethereal solution with 2 N HCl and liberated therefrom by the addition of solid NaOH (while cooling). The alkaline solution was extracted with ether and the ethereal solution was dried with solid NaOH. Distillation resulted in 10.6 grams (70% of the theory) of 1-aminoadamantane which, after sublimation, melted at 180° to 192°C (seal capillary). It is converted to the hydrochloride.

References

Merck Index 373
Kleeman & Engel p. 33
PDR p. 862
OCDS Vol. 2 p. 18 (1980)

DOT 3 (1) 6 (1967) and 7 (2) 44 (1971)
I.N. p. 63
REM p. 927
Haaf, W.; U.S. Patent 3,152,180; October 6, 1964; assigned to Studiengesellschaft Kohle mbH, Germany

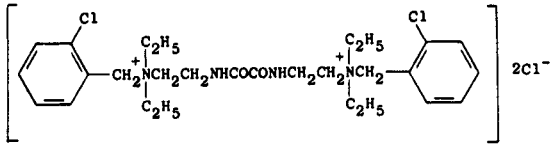
AMBENONIUM CHLORIDE

Therapeutic Function: Cholinesterase inhibitor

Chemical Name: N,N'-[(1,2-dioxo-1,2-ethanediyl)bis(imino-2,1-ethanediyl)] bis[2-chloro-N,N-diethylbenzenemethanaminium] dichloride

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 115-79-7

Trade Name	Manufacturer	Country	Year Introduced
Mytelase CL	Winthrop	U.S.	1956
Mytelase	Winthrop	W. Germany	—
Mytelase	Winthrop	France	1950
Mytelase	Winthrop	U.K.	1970
Mytelase	Nippon Shoji	Japan	—
Mysuran	Winthrop	—	—

Raw Materials

2-Diethyl Amino Ethyl Amine
Ethyl Oxalate
2-Chlorobenzyl Chloride

Manufacturing Process

N,N'-Bis(2-Diethylaminoethyl)Oxamide: A solution of 150 grams (1.32 mol) of 2-diethylaminoethylamine in 250 ml of xylene was gradually added to a solution of 73.0 grams (0.5 mol) of ethyl oxalate in 250 ml of xylene, with external cooling. The mixture was then refluxed for eight hours, cooled and diluted with ether. The ether-xylene solution was extracted with 10% hydrochloric acid, and the hydrochloric acid extracts were in turn extracted with ether and then made alkaline with 35% sodium hydroxide solution. The organic material which separated was extracted with ether, and the ether solution was dried over anhydrous sodium sulfate and concentrated, giving 106.5 grams of N,N'-bis(2-diethylaminoethyl)oxamide, MP 40°-42°C.

N,N'-Bis(2-Diethylaminoethyl)Oxamide Bis(2-Chlorobenzochloride): A solution of 7 grams (0.025 mol) of N,N'-bis(2-diethylaminoethyl)oxamide and 16.1 grams (0.1 mol) of 2-chlorobenzyl chloride in 100 ml of acetonitrile was refluxed for eleven hours. The solid which separated upon cooling was collected by filtration and recrystallized by dissolving it in

ethanol and adding ether to cause the product to separate. After drying at about 60°C (1-3 mm) there was obtained 4.1 grams of N,N'-bis(2-diethylaminoethyl)oxamide bis(2-chlorobenzochloride), MP 196°-199°C.

References

Merck Index 378
Kleeman & Engel p. 34
I.N. p. 64
REM p. 898
Kirchner, F.K.; U.S. Patent 3,096,373; July 2, 1963; assigned to Sterling Drug Inc.
Behr, L.C. and Schreiber, R.S.; U.S. Patent 2,438,200; March 23, 1948; assigned to E.I. du Pont de Nemours and Co.

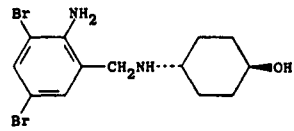
AMBROXOL

Therapeutic Function: Expectorant

Chemical Name: 4-[[(2-Amino-3,5-dibromophenyl)methyl] amino] -cyclohexanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 18683-91-5

Trade Name	Manufacturer	Country	Year Introduced
Mucosolvan	Thomae	W. Germany	1980
Mucosolvan	De Angeli	Italy	1981
Mucosolvon	Boehringer-Ingel	Switz.	1982
Fluixol	Ripari-Gero	Italy	–
Fluibron	Chiesi	Italy	–
Muciclar	Piam	Italy	–

Raw Materials

N-(trans-p-hydroxy-cyclohexyl)-(2-aminobenzyl)-amine
Bromine

Manufacturing Process

6.5 g of N-(trans-p-hydroxy-cyclohexyl)-(2-aminobenzyl)-amine were dissolved in a mixture of 80 cc of glacial acetic acid and 20 cc of water, and then 9.6 g of bromine were added dropwise at room temperature while stirring the solution. After all of the bromine had been added, the reaction mixture was stirred for two hours more and was then concentrated in a water aspirator vacuum. The residue was taken up in 2 N ammonia, the solution was extracted several times with chloroform, and the organic extract solutions were combined and evaporated. The residue, raw N-(trans-p-hydroxy-cyclohexyl)-(2-amino-3,5-dibromobenzyl)-amine, was purified with chloroform and ethyl acetate over silica gel in a chromatographic column, the purified product was dissolved in a mixture of ethanol and ether, and the solution was

acidified with concentrated hydrochloric acid. The precipitate formed thereby was collected and recrystallized from ethanol and ether, yielding N-(trans-p-hydroxy-cyclohexyl)-(2-amino-3,5-dibromobenzyl)-amine hydrochloride, MP 233°-234.5°C (decomposition).

References

Merck Index 383
DFU 1 (3) 95 (1976)
Kleeman & Engel p. 35
I.N. p. 64
Keck, J., Koss, F.W., Schraven, E. and Beisenherz, G.; U.S. Patent 3,536,713; October 27, 1970; assigned to Boehringer Ingelheim G.m.b.H.

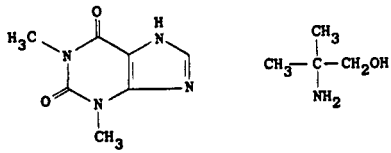
AMBUPHYLLINE

Therapeutic Function: Diuretic, smooth muscle relaxant

Chemical Name: 3,7-Dihydro-1,3-dimethyl-1H-purine-2,6-dione compound with 2-amino-2-methyl-1-propanol (1:1)

Common Name: Theophylline aminoisobutanol; Bufylline

Structural Formula:



Chemical Abstracts Registry No.: 5634-34-4

Trade Name	Manufacturer	Country	Year Introduced
Butaphyllamine	Merrell-Dow	U.S.	1944
Buthoid	Merrell-Dow	U.S.	–

Raw Materials

Theophylline
2-Amino-2-methyl-1-propanol

Manufacturing Process

Equimolecular proportions of theophylline and 2-amino-2-methyl-1-propanol are dissolved in water and the water is evaporated until crystallization is almost complete. The crystals are filtered off and dried. The product has a melting point of 254°-256°C, softening at 245°C. It has a water solubility of about 55%. It may be compounded in the form of tablets, for oral administration, or may be prepared in solution for distribution in ampoules. For the manufacture of solutions for packaging in ampoules, it is more convenient to simply dissolve the theophylline and the butanol amine in water, without going through the intermediate step of separating the crystalline salt.

References

Merck Index 385
I.N. p. 64
Shelton, R.S.; U.S. Patent 2,404,319; July 16, 1946; assigned to The Wm. S. Merrell Co.

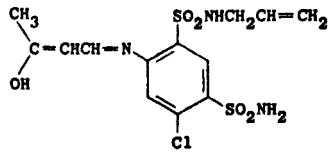
AMBUSIDE

Therapeutic Function: Diuretic, antihypertensive

Chemical Name: N'-allyl-4-chloro-6-[(3-hydroxy-2-butenylidene)amino]-m-benzenedisulfonamide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 3754-19-6

Trade Name	Manufacturer	Country	Year Introduced
Hydrion	Robert Carriere	France	1970

Raw Materials

2-Allylsulfamyl-5-chloro-4-sulfamylaniline
Acetaldehyde Dimethylacetal

Manufacturing Process

Preparation of 2-Allylsulfamyl-4-Sulfamyl-5-Chloro-N-(3-Hydroxy-2-Butenylidene)Aniline or Ambuside: 2-allylsulfamyl-5-chloro-4-sulfamylaniline monohydrate (6.9 grams, 0.020 mol) was dissolved in 14 ml acetylacetaldehyde dimethylacetal at room temperature and the viscous solution was filtered. Addition of 6 drops of 10:1 H_2O/concentrated HCl, and stirring for 20 hours gave a heavy suspension. Dilution with 150 ml of ethanol, collection of the solid, washing twice with 40 ml portions of ethanol, and drying gave 6.2 grams (78%) of product, MP 204°-206°C.

References

Merck Index 386
Kleeman & Engel p. 35
OCDS Vol. 2 p. 116 (1980)
I.N. p. 64
Robertson, J.E.; U.S. Patent 3,188,329; June 8, 1955; assigned to Colgate-Palmolive Co.

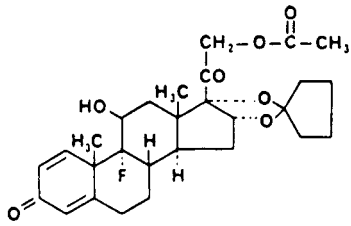
AMCINONIDE

Therapeutic Function: Topical steroid; antiinflammatory agent

Chemical Name: 16α,17α-Cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione-21-acetate

Common Name: Amcinopol

Structural Formula:



Chemical Abstracts Registry No.: 51022-69-6

Trade Name	Manufacturer	Country	Year Introduced
Cyclocort	Lederle	U.S.	1979
Amcinonid	Cyanamid	W. Germany	1981
Visderm	Lederle	Japan	1982
Penticort	Lederle	France	—
Mycoderm	Lederle	—	—

Raw Materials

16α,17α-Cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione
Acetic Anhydride

Manufacturing Process

An 11.1 g (24.1 mmol) portion of the compound 16α,17α-cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione is placed in a 250 ml round-bottom flask. A 100 ml portion of pyridine is added and the mixture is stirred to a complete solution. A 5.5 ml (54.6 mmol) portion of acetic anhydride is added dropwise and the mixture is stirred for 2½ hours. An 11 ml portion of methanol is added and the mixture is stirred an additional hour. This mixture is concentrated under reduced pressure to about 10 to 15 ml and then poured slowly into a mixture of ice, water and dilute hydrochloric acid. This mixture is stirred and the solid which forms is collected by filtration, washed with water to a neutral pH and air dried yielding 11.5 g. This solid is taken up in hot acetone, treated with activated charcoal and filtered while hot through diatomaceous earth. The filtrate is concentrated on a steam bath while adding n-hexane to the point of incipient crystallization. This mixture is allowed to cool to room temperature. The solid which forms is collected by filtration, washed with acetone-n-hexane (1:14) and air dried yielding 7.0 g of the desired product.

References

Merck Index 389
DFU 3 (5) 337 (1978)
Kleeman & Engel p. 36
PDR p. 1007
DOT 16 (10) 322 (1980)
I.N. p. 65
REM p. 972
Schultz, W., Sieger, G.M. and Krieger, C.; British Patent 1,442,925; July 14, 1976; assigned to American Cyanamid Company.

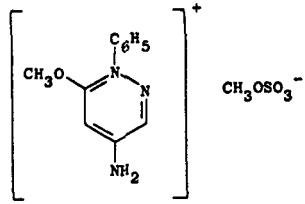
AMEZINIUM METHYL SULFATE

Therapeutic Function: Antihypotensive

Chemical Name: 4-Amino-6-methoxy-1-phenylpyridazinium methyl sulfate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 30578-37-1

Trade Name	Manufacturer	Country	Year Introduced
Regulton	Nordmark	W. Germany	1981
Regulton	Knoll	Switz.	1983

Raw Materials

1-Phenyl-4-aminopyridazone
Dimethyl Sulfate

Manufacturing Process

18.7 parts of 1-phenyl-4-aminopyridazone-(6) and 19 parts of dimethyl sulfate in 400 parts of xylene are kept at 120°C for one hour while mixing well. The reaction mixture is suction filtered, 28 parts (89.5% of the theory) of 1-phenyl-4-amino-6-methoxypyridazinium methosulfate is obtained having a melting point of 173° to 174°C after recrystallization from acetonitrile. The perchlorate has a melting point of 179° to 182°C.

References

Merck Index 395
DFU 5 (4) 207 (1980)
DOT 18 (7) 317 (1982)
I.N. p. 66
Reicheneder, F. and Kropp, R.; U.S. Patent 3,631,038; December 28, 1971; assigned to Badische Anilin und Soda-Fabrik A.G.

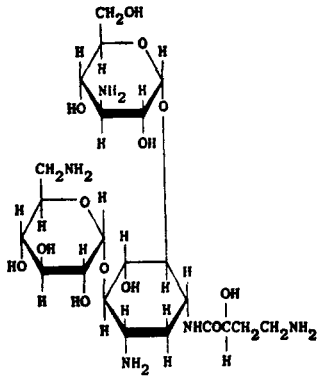
AMIKACIN

Therapeutic Function: Antibacterial

Chemical Name: (S)-O-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-O-[6-amino-6-deoxy-α-D-glucopyranosyl-(1→4)]-N^1-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-D-streptamine

Common Name: 1-N-[L(-)-4-amino-2-hydroxybutyryl] kanamycin A

Structural Formula:



Chemical Abstracts Registry No.: 37517-28-5; 39831-55-5 (Sulfate)

Trade Name	Manufacturer	Country	Year Introduced
Amikin	Bristol	U.S.	1976
Amiklin	Bristol	France	1976
Biklin	Gruenenthal	W. Germany	1976
Amikin	Bristol	U.K.	1976
Biklin	Bristol Banyu	Japan	1977
BB-K8	Bristol	Italy	1978
Amiglyde-V	Bristol	—	—
Amisin	Faro	Turkey	—
Biklin	Frika	Austria	—
Briclin	Mead-Johnson	—	—
Kaminax	Ausonia	Italy	—
Likacin	Lisapharma	Italy	—
Novamin	Bristol	—	—
Amikacin	Banyu-Seiyaku	Japan	—

Raw Materials

L-(−)-γ-Amino-α-hydroxybutyric Acid
N-hydroxysuccinimide
6'-Monobenzyloxy-carbonyl-kanamycin A
Sulfuric Acid
Sodium Hydroxide
Carbobenzoxy Chloride
Hydrogen

Manufacturing Process

Preparation of L-(-)-γ-Benzyloxycarbonylamino-α-Hydroxybutyric Acid: L-(-)-γ-amino-α-hydroxybutyric acid (7.4 g, 0.062 mol) was added to a solution of 5.2 grams (0.13 mol) of sodium hydroxide in 50 ml of water. To the stirred solution was added dropwise at 0°-5°C over a period of 0.5 hour, 11.7 grams (0.068 mol) of carbobenzoxy chloride and the mixture was stirred for another hour at the same temperature. The reaction mixture was washed with 50 ml of ether, adjusted to pH 2 with dilute hydrochloric acid and extracted with four 80 ml portions of ether. The ethereal extracts were combined, washed with a small amount of saturated sodium chloride solution, dried with anhydrous sodium sulfate and filtered. The filtrate was evaporated in vacuo and the resulting residue was crystallized from benzene to give 11.6 grams (74%) of colorless plates; MP 78.5° to 79.5°C.

Preparation of N-Hydroxysuccinimide Ester of L-(-)-γ-Benzyloxycarbonylamino-α-Hydroxybutyric Acid: A solution of 10.6 grams (0.042 mol) of L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyric acid and 4.8 grams (0.042 mol) of N-hydroxysuccinimide in 200 ml of

ethyl acetate was cooled to 0°C and then 8.6 grams (0.042 mol) of dicyclohexylcarbodiimide was added. The mixture was kept overnight in a refrigerator. The dicyclohexylurea which separated was filtered off and the filtrate was concentrated to about 50 ml under reduced pressure to give colorless crystals of L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyric acid which were collected by filtration; 6.4 grams, MP 121°-122.5°C. The filtrate was evaporated to dryness in vacuo and the crystalline residue was washed with 20 ml of a benzene-n-hexane mixture to give an additional amount of L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyric acid. The total yield was 13.4 grams (92%).

Preparation of 1-[L-(-)-γ-Benzyloxycarbonylamino-α-Hydroxybutyryl]-6'-Carbobenzoxykanamycin A: A solution of 1.6 grams (4.6 mmol) of L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyric acid in 40 ml of ethylene glycol dimethyl ether (DME) was added dropwise to a stirred solution of 2.6 grams (4.2 mmol) of 6'-monobenzyloxycarbonylkanamycin A in 40 ml of 50% aqueous ethylene glycol dimethyl ether and the mixture was stirred overnight. The reaction mixture was evaporated under reduced pressure to give a brown residue 1-[L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyryl]-6'-carbobenzoxykanamycin A which was used for the next reaction without further purification.

Preparation of 1-[L-(-)-γ-Amino-α-Hydroxybutyryl] Kanamycin A: The crude product 1-[L-(-)-γ-benzyloxycarbonylamino-α-hydroxybutyryl]-6'-carbobenzoxykanamycin A was dissolved in 40 ml of 50% aqueous dioxane and a small amount of insoluble material was removed by filtration. To the filtrate was added 0.8 ml of glacial acetic acid and 1 gram of 10% palladium-on-charcoal and the mixture was hydrogenated at room temperature for 24 hours in a Parr hydrogenation apparatus. The reaction mixture was filtered to remove the palladium catalyst and the filtrate was evaporated to dryness in vacuo.

The residue was dissolved in 30 ml of water and chromatographed on a column of CG-50 ion exchange resin (NH_4^+ type, 50 cm x 1.8 cm). The column was washed with 200 ml of water and then eluted with 800 ml of 0.1 N NH_4OH, 500 ml of 0.2 N NH_4OH and finally 500 ml of 0.5 N NH_4OH. Ten milliliter fractions were collected and fractions 146 to 154 contained 552 mg (22%, based on carbobenzoxykanamycin A, 6'-monobenzyloxycarbonylkanamycin A) of the product which was designated BB-K8 lot 2. MP 187°C (dec). Relative potency against *B. subtilis* (agar plate) = 560 mcg/mg (standard: kanamycin A free base).

A solution of 250 mg of BB-K8 lot 2 in 10 ml of water was subjected to chromatography on a column of CG-50 (NH_4^+ type, 30 cm x 0.9 cm). The column was washed with 50 ml of water and then eluted with 0.2 N NH_4OH. Ten milliliter fractions were collected. Fractions 50 to 63 were combined and evaporated to dryness under reduced pressure to give 98 mg of the pure product base.

Preparation of the Monosulfate Salt of 1-[L-(-)-γ-Amino-α-Hydroxybutyryl] Kanamycin A: One mol of 1-[L-(-)-γ-amino-α-hydroxybutyryl] kanamycin A is dissolved in 1 to 3 liters of water. The solution is filtered to remove any undissolved solids. To the chilled and stirred solution is added one mol of sulfuric acid dissolved in 500 ml of water. The mixture is allowed to stir for 30 minutes, following which cold ethanol is added to the mixture till precipitation occurs. The solids are collected by filtration and are determined to be the desired monosulfate salt.

References

Merck Index 405
Kleeman & Engel p. 38
PDR p. 692
DOT 12 (5) 202 (1976)
I.N. p. 68
REM p. 1180
Kawaguchi, H., Naito, T. and Nakagawa, S.; U.S. Patent 3,781,268; December 25, 1973; assigned to Bristol-Myers Company.

Schreiber, R.H. and Kell, J.G.,; U.S. Patent 3,974,137; August 10, 1976; assigned to Bristol-Myers Company.

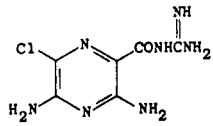
AMILORIDE HYDROCHLORIDE

Therapeutic Function: Potassium-sparing diuretic

Chemical Name: 3,5-Diamino-N-(aminoiminomethyl)-6-chloropyrazine carboxamide

Common Name: Guanamprazine; amipramidin; amipramizide

Structural Formula:



Chemical Abstracts Registry No.: 2016-88-8, 2609-46-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Midamor	Merck	U.K.	1971
Modamide	Merck	France	1973
Arumil	Sharp & Dohme	W. Germany	1975
Midamor	Merck	U.S.	1981
Colectril	Merck	U.S.	—
Moducren	Dohme-Chibret	France	—
Moduretic	Merck	—	—
Nilurid	Merck	—	—
Pandiuren	Sintyal	Argentina	—
Puritrid	Leiras	Finland	—

Raw Materials

Methyl-3-aminopyrazinoate
Sulfuryl Chloride
Ammonia
Sodium
Guanidine
Hydrogen Chloride

Manufacturing Process

Step A: Preparation of methyl 3-amino-5,6-dichloropyrazinoate—Methyl 3-aminopyrazinoate (765 g, 5 mols) is suspended in 5 liters of dry benzene. While stirring under anhydrous conditions sulfuryl chloride (1.99 liters, 3,318 g, 24.58 mols) is added over a period of 30 minutes and stirring is continued for 1 hour. During this period, the temperature rises to about 50°C and then begins to drop. The mixture is heated cautiously to reflux (60°C), refluxed for 5 hours and then stirred overnight at room temperature. The excess sulfuryl chloride is distilled off at atmospheric pressure (distillation is stopped when vapor temperature reaches 78°C). The dark red mixture is chilled to 6°C. The crystals are filtered off, washed by displacement with two 100 ml portions of cold (8°C) benzene, then washed with 300 ml petroleum ether and dried in vacuo at room temperature, yielding 888 g (80%) of methyl 3-amino-5,6-dichloropyrazinoate in the form of red crystals, MP 228°-230°C. The crude product is dissolved in 56 liters of boiling acetonitrile and passed through a heated (70°-80°C) column of decolorizing charcoal (444 g). The column is washed with 25 liters of hot acetonitrile, the combined eluate concentrated in vacuo to about 6 liters and chilled to 5°C. The crystals that form are filtered, washed three times with cold acetonitrile, and air dried to constant weight, yielding

724 g (82% recovery, 66% overall) of methyl 3-amino-5,6-dichloropyrazinoate in the form of yellow crystals, MP 230°-234°C. After additional recrystallizations from acetonitrile the product melts at 233°-234°C.

Step B: Preparation of methyl 3,5-diamino-6-chloropyrazinoate—In a 2-liter, 3-necked flask fitted with a a mechanical stirrer, thermometer and gas inlet tube is placed dry dimethyl sulfoxide (1 liter). Methyl 3-amino-5,6-dichloropyrazinoate (100 g, 0.45 mol) is added and the mixture stirred and heated at 65°C on a steam bath until solution is effected. A stream of dry ammonia gas is admitted to the solution with continuous stirring, over a period of 45 minutes while the temperature is maintained at 65°-70°C. The solution is cooled to about 10°C with continuous stirring and ammonia gas is admitted for an additional 1¼ hours. The yellow reaction mixture is poured, with stirring, into cold water (2 liters) and the light yellow solid that separates is removed by filtration, thoroughly washed with water, and dried in a vacuum desiccator to give 82.5 g (91%) of methyl 3,5-diamino-6-chloropyrazinoate, MP 210°-212°C. Recrystallization from acetonitrile gives material melting at 212°-213°C.

Step C: Preparation of the base—A 300 ml one-necked, round-bottomed flask, equipped with a water-cooled condenser, calcium chloride tube and magnetic stirrer is charged with anhydrous methanol (150 ml) and sodium metal (5.75 g, 0.25 g atom). When the reaction is complete, the solution is treated with dry guanidine hydrochloride (26.3 g, 0.275 mol) and stirred for 10 minutes. The sodium chloride that forms is removed by filtration. The solution is concentrated in vacuo to a volume of 30 ml and the residue treated with the product of Step B, heated one minute on a steam bath and kept at 25°C for 1 hour. The product is filtered, washed well with water, dissolved in dilute hydrochloric acid and the free base precipitated by addition of sodium hydroxide to give the amiloride product base, a solid which melts at 240.5°-241.5°C.

To produce the hydrochloride, the base is suspended in water (70 ml) and treated with sufficient 6 N hydrochloric acid to dissolve the free base. The solution is filtered and treated with concentrated hydrochloric acid (5 ml). The hydrochloride salt (2.2 g, 97%) separates and is recrystallized from water (50 ml) containing concentrated hydrochloric acid (3 ml).

References

Merck Index 406
Kleeman & Engel p. 40
PDR p. 1199
OCDS Vol. 1 p. 278 (1977)
DOT 19 (3) 172 (1983)
I.N. p. 69
REM p. 941
Cragoe, E.J., Jr.; U.S. Patent 3,313,813; April 11, 1967; assigned to Merck & Co., Inc.

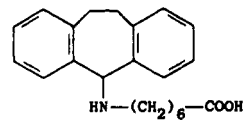
AMINEPTINE HYDROCHLORIDE

Therapeutic Function: CNS Stimulant

Chemical Name: 7-[(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl-amino] heptanoic acid hydrochloride

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 57574-09-1 (Base); 30272-08-3 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Survector	Eutherapie	France	1978
Survector	Servier	Italy	1982
Maneon	Poli	Italy	1982

Raw Materials

5-Chloro-10,11-dihydro-5H-dibenzo(a,d)cycloheptene
Ethyl 7-aminoheptanoate

Manufacturing Process

6.5 g of 5-chloro-10,11-dihydro-5H-dibenzo(a,d)cycloheptene in 60 ml of nitromethane and 10.8 g of ethyl 7-aminoheptanoate in 12 ml of nitromethane were mixed at ambient temperature. The reaction was slightly exothermic. The reaction mixture was left to stand overnight and the solvent was evaporated in vacuo. The residue was taken up in normal hydrochloric acid and the resulting precipitate was filtered off.

10.5 g of crude ethyl 7-[dibenzo(a,d)cycloheptadiene-5-yl] aminoheptanoate hydrochloride were obtained, of which a sample recrystallized from benzene gave a pure product melting instantaneously at 166° to 168°C.

The hydrochloride of the crude ester obtained above was added to 25 ml of 2 N hydrochloric acid. The whole was kept under reflux for 2 hours. The material dissolved and a new hydrochloride then reprecipitated. After cooling, the hydrochloride of the crude acid was filtered off, washed with iced water and then recrystallized from distilled water. 5.7 g of 7-[dibenzo(a,d)cycloheptadien-5-yl] aminoheptanoic acid hydrochloride were obtained, melting instantaneously at 226° to 230°C.

References

Merck Index 409
Kleeman & Engel p. 40
DOT 19 (10) 547 (1983)
I.N. p. 69
Melen, C., Danree, B. and Poignant, J.C.; U.S. Patent 3,758,528; September 11, 1973; assigned to Societe en nom Collectif Science Union et Cie; Societe Francaise de Recherche Medicale
Melen, C., Danree, B. and Poignant, J.C.; U.S. Patent 3,821,249; June 28, 1974; assigned to Societe en nom Collectif Science Union et Cie; Societe Francaise de Recherche Medicale

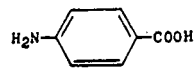
AMINOBENZOIC ACID

Therapeutic Function: Sunscreen agent, antirickettsial

Chemical Name: p-aminobenzoic acid

Common Name: Vitamin H, Vitamin B_x, PABA

Structural Formula:



Chemical Abstracts Registry No.: 150-13-0

Trade Name	Manufacturer	Country	Year Introduced
Pabalate	Robins	U.S.	1949
Ambin	—	—	—
Hachemina	Medea	Spain	—
Pabacyd	—	—	—
Pabafilm	Owen	U.S.	—
Pabagel	Owen	U.S.	—
Pabanol	Elder	U.S.	—
Pabasin	—	—	—
Paraminol	—	—	—
Potaba	Westwood	U.S.	—
Pre-Sun	Westwood	U.S.	—
Sunbrella	Dorsey	U.S.	—

Raw Materials

Xylene
Ammonium Sulfate
Sodium Hypochlorite

Manufacturing Process

The following example illustrates in detail the preparation of amino benzoic acids from the hot reaction product obtained by the oxidation of a xylene and containing a mixture of salt, amide salt and diamide of a phthalic acid.

800 cc of hot aqueous oxidation product, obtained from the oxidation of para-xylene with ammonium sulfate, hydrogen sulfide and water are boiled and agitated for 4 hours to remove carbon dioxide, hydrogen sulfide and ammonia, sufficient water being added to maintain a constant volume. The mixture is filtered to remove a precipitate containing elemental sulfur. 12 grams of activated charcoal are added to the filtrate and the mixture held at a temperature of 180°F for 20 minutes. Filtration through diatomaceous earth removes color bodies formed during the oxidation process and yields a pale yellow filtrate. The filtrate is acidified with sulfuric acid to a pH of 3 or less to precipitate approximately 49 grams of white solid, comprising a mixture of terephthalic acid and amides of terephthalic acid, which are removed by filtration. This solid is then washed with water at 200°F and redissolved in 200 cc of water containing 28.6 grams of sodium hydroxide.

A mixture of sodium hypochlorite and sodium hydroxide is prepared by adding 27.5 grams of chlorine to a vessel equipped with cooling means and containing a solution of 50 grams of sodium hydroxide in 375 cc of water, thereafter adding sufficient water to produce 500 cc of solution. 190 cc of this cold solution are slowly added to the acid-amide solution previously prepared so as to keep the temperature of the mixture below 55°F. The mixture is stirred for 15 minutes and then heated rapidly to 200°F and maintained at that temperature for one hour. 2 grams of sodium thiosulfate are added to consume excess sodium hypochlorite. The solution is acidified to a pH of 3 or less and filtered hot. The filter cake, comprising about 26.9 grams of terephthalic acid, is then suspended in 300 cc of dilute sulfuric acid of pH about 2, heated to 200°F and filtered hot.

The filtrates are combined, cooled, and extracted with three successive 200 cc portions of ether. The pH of the filtrate is then raised to 3.5 with sodium hydroxide and the filtrate extracted with six successive 200 cc portions of ether to yield the balance of the product. The crude para-aminobenzoic acid product is recovered by evaporation of ether and is suspended in hot benzene, cooled and filtered to remove benzoic and toluic acids together with small amounts of impurities soluble in the filtrate. Recrystallization of the product from 200 cc of water yields 14.5 grams of light tan needles of para-aminobenzoic acid having an acid number of 411 (theoretical value 409).

Aminobenzoic acid can be then purified and decolorized by a process described in U.S. Patent 2,735,865.

References

Merck Index 423
PDR pp. 926, 1894
I.N. p. 1012
REM p. 787
Toland, W.G. and Heaton, C.D.; U.S. Patent 2,878,281; March 17, 1959; assigned to California Research Corporation
Spiegler, L.; U.S. Patent 2,947,781; August 2, 1960; assigned to E.I. Du Pont de Nemours and Company
Lyding, A.R.; U.S. Patent 2,735,865; February 21, 1956; assigned to Heyden Chemical Corporation

AMINOCAPROIC ACID

Therapeutic Function: Antifibrinolytic

Chemical Name: 6-aminohexanoic acid

Common Name: Epsilcapramin

Structural Formula: $H_2N(CH_2)_5COOH$

Chemical Abstracts Registry No.: 60-32-2

Trade Name	Manufacturer	Country	Year Introduced
Epsilon	Roche	W. Germany	1962
Epsilon-Aminoca	Roche	W. Germany	1962
Capramol	Choay	France	1963
Amicar	Lederle	U.S.	1964
Epsikapron	Kabi Vitrum	U.K.	1967
Acikaprin	Polfa	Poland	—
Amicar	Lederle	U.S.	—
Capracid	Kabi Vitrum	Sweden	—
Capracid	Bonomelli-Hommel	Italy	—
Capralense	Choay	France	—
Capramol	Italfarmaco	Italy	—
Caprolisin	Malesci	Italy	—
EACA	Kasi Vitrum	Sweden	—
Ekaprol	Difrex	Australia	—
Epsilon	Star	Finland	—
Hemocaprol	Delagrange	France	—
Capusumine	Nichiiko	Japan	—
Hemotin	Hokuriku	Japan	—
Ipsilon	Daiichi	Japan	—
Resplamin	Kyorin	Japan	—

Raw Materials

Caprolactam
Water

Manufacturing Process

5 kg of caprolactam were heated with 40 liters of water in a pressure vessel at 250°C for

a period of four hours. These quantities of reactants correspond to a water:lactam molecular ratio of 50:1. After cooling, the small quantity of the nonsoluble substance that is formed is filtered off, and the filtrate is evaporated as far as possible. The resulting concentrate is mixed with three times its volume of strong alcohol, thereby causing the desired product, epsilon-aminocaproic acid (6-aminohexanoic acid), to crystallize out. After seperating the crystalline product thus obtained, a further quantity of epsilon-aminocaproic acid can be obtained from the mother liquid if desired.

References

Merck Index 433
Kleeman & Engel p. 41
PDR pp. 872, 997
I.N. p. 13
REM p. 831
Koch, T.; U.S. Patent 2,453,234; November 9, 1948; assigned to American Enka Corporation

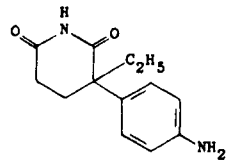
AMINOGLUTETHIMIDE

Therapeutic Function: Cytostatic

Chemical Name: 3-(4-Aminophenyl)-3-ethyl-2,6-piperidinedione

Common Name: α-(p-aminophenyl)-α-ethyl-glutarimide

Structural Formula:



Chemical Abstracts Registry No.: 124-84-8

Trade Name	Manufacturer	Country	Year Introduced
Ellipten	Ciba	U.S.	1960
Cytadren	Ciba-Geigy	U.S.	1980
Orimeten	Ciba-Geigy	Switz.	1981
Orimeten	Ciba-Geigy	U.K.	1982

Raw Materials

α-Phenyl-α-ethyl Glutarimide
Nitric Acid
Hydrogen

Manufacturing Process

The α-(p-nitrophenyl)-α-ethyl-glutarimide starting material can be prepared as follows: 217 g of α-phenyl-α-ethyl-glutarimide are dissolved in 800 g of concentrated sulfuric acid with subsequent cooling to about -10°C and nitration is carried out at -10° to +10°C by slow addition of a mixed acid consisting of 110 g of concentrated sulfuric acid and 110 g of 63% nitric acid. The nitration solution is stirred into ice, the separated nitro compound taken up in methylene or ethylene chloride, the solution washed with water and sodium carbonate solution until

neutral and the solvent evaporated under vacuum. The residue is crystallized from methanol or ethyl acetate, whereby a yellowish crystal powder of MP 128°–136°C is obtained in a yield of about 85% which consists for the most part of α-(p-nitrophenyl)-α-ethyl-glutarimide. By recrystallization from methanol the pure p-nitrophenyl compound is obtained of MP 137°–139°C. From the residues of the mother liquors a small quantity of the isomeric α-(o-nitrophenyl)-α-ethyl-glutarimide of MP 170°–172°C can be obtained.

26.2 g of α-(p-nitrophenyl) -α-ethyl-glutarimide of MP 137°–139°C dissolved in ethyl acetate, are reduced in the presence of nickel with hydrogen in a shaking flask at 50°–70°C until the absorption of hydrogen falls off. The catalyst is then filtered off with suction and the solution concentrated and cooled, as a result of which colorless crystals of MP 146°–149°C are obtained. Recrystallization from methanol gives pure α-(p-aminophenyl)-α-ethyl-glutarimide of MP 149°–150°C (yield 97%).

Instead of ethyl acetate another solvent can be used in the above reduction, such as methanol or ethanol.

The hydrochloride of MP 223°–225°C is obtained by dissolving the base with alcohol and the corresponding quantity of hydrochloric acid gas in the hot with subsequent cooling of the solution. Colorless crystals are formed of MP 223°–225°C, which are easily soluble in water.

References

Merck Index 443
PDR p. 794
OCDS Vol. 1 p. 257 (1977)
I.N. p. 71
REM p. 1143
Hoffmann, K. and Urech, E.; U.S. Patent 2,848,455; August 19, 1958; assigned to Ciba Pharmaceutical Products, Inc.

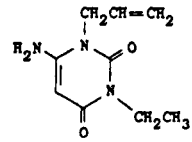
AMINOMETRADINE

Therapeutic Function: Diuretic

Chemical Name: 6-Amino-3-ethyl-1-(2-propenyl)-2,4(1H,3H)-pyrimidinedione

Common Name: Aminometramide

Structural Formula:



Chemical Abstracts Registry No.: 642-44-4

Trade Name	Manufacturer	Country	Year Introduced
Mincard	Searle	U.S.	1954
Mictine	Searle	—	—

Raw Materials

Monoallyl Urea
Cyanoacetic Acid
Sodium Hydroxide
Diethyl Sulfate

Manufacturing Process

85 parts of monoallylurea are dissolved in 105 parts of acetic anhydride, and 85 parts of cyanoacetic acid are added gradually and the mixture is maintained at 65°C for 2.5 hours. The mixture is distilled at 20 mm until a syrup remains. 50 parts of water are added to this syrup and distillation is resumed. The resulting syrup is dissolved in 96% ethanol at 60°C, stirred with charcoal and filtered. One to one and one-half volumes of ether are added to the filtrate at 40°C. Upon cooling the N-cyanoacetyl-N'-allylurea precipitates. It is collected on a filter and washed with ether. The white crystals melt at about 142°-143°C. The N-cyanoacetyl-N'-allylurea is dissolved by warming with 10% sodium hydroxide. Sufficient 70% sodium hydroxide is added to raise the pH to 10. The solution is maintained at 60°C for five minutes. After cooling the crystals are collected on a filter and recrystallized from water. 1-allyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione is obtained in the form of white crystals melting at 270°-272°C.

334 parts of 1-allyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione are dissolved in a solution of 88 parts of sodium hydroxide in 1,100 parts of water. While this mixture is stirred rapidly at 50°C, 430 parts of diethyl sulfate are added in the course of 30 minutes. Stirring is continued at 50°-55°C for one hour longer, and an alkaline reaction is maintained by occasional additions of small portions of 20% aqueous sodium hydroxide solution, about 300 parts in all being required. On cooling, the 1-allyl-3-ethyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione separates as the monohydrate; it is filtered off, washed with cold water, and recrystallized from water containing a small amount of sodium hydroxide to hold in solution any unreacted 1-allyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione. The air dried product thus obtained contains 1 mol of crystal water and melts over a wide range with dehydration at 75°-115°C. After dehydration by treatment with anhydrous ether, the anhydrous 1-allyl-3-ethyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione melts sharply at about 143°-144°C.

References

Merck Index 455
OCDS Vol. 1 p. 265 (1977)
I.N. p. 72
Papesch, V. and Schroeder, E.F.; U.S. Patent 2,650,922; September 1, 1953; assigned to G.D. Searle & Co.

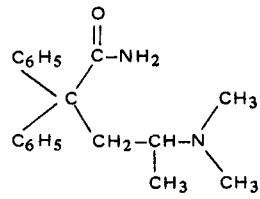
AMINOPENTAMIDE

Therapeutic Function: Anticholinergic

Chemical Name: 4-(Dimethylamino)-2,2-diphenylvaleramide

Common Name: Dimevamide

Structural Formula:



Chemical Abstracts Registry No.: 60-46-8

Trade Name	Manufacturer	Country	Year Introduced
Centrine	Bristol	U.S.	1953

Raw Materials

α,α-Diphenyl-γ-dimethylamino Valeronitrile
Hydroxylamine Hydrochloride

Manufacturing Process

A mixture of 14 g (0.05 mol) of α,α-diphenyl-γ-dimethylaminovaleronitrile, 16 g (0.2 mol) of sodium acetate, 14 g (0.2 mol) of hydroxylamine hydrochloride and 75 ml of ethyl alcohol was refluxed 18 hours. The mixture was cooled, poured into water and neutralized with ammonium hydroxide. The heavy white precipitate solidified on standing. The material was filtered and recrystallized from isopropanol. After three recrystallizations the aminopentamide product melted at 177° to 179°C.

The product is often used as the acid sulfate which is produced as follows: 252.0 g (0.85 mol) of α,α-diphenyl-γ-dimethylaminovaleramide was dissolved in one liter of isopropanol, and 70 ml of concentrated sulfuric acid was added as rapidly as possible. The mixture was heated until clear, then filtered and diluted with 1,500 ml of anhydrous ethyl acetate. The solution was cooled and filtered, and the white crystalline product was dried in vacuo over P_2O_5.

References

Merck Index 463
I.N. p. 342
Specter, M.E.; U.S. Patent 2,647,926; August 4, 1953; assigned to Bristol Laboratories, Inc.

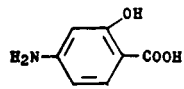
AMINOSALICYLIC ACID

Therapeutic Function: Antitubercular

Chemical Name: 4-amino-2-hydroxybenzoic acid

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 65-49-6

Trade Name	Manufacturer	Country	Year Introduced
Pamisyl	Parke David	U.S.	1948
Parasal	Panray	U.S.	1950
Rexipas	Squibb	U.S.	1954
Aminacyl	Wander	U.K.	—
B-Pas	Salvoxyl-Wander	France	—
Enseals	Lilly	U.S.	—
Nemasol	I.C.N.	Canada	—
Neopasalate	Mallinckrodt	U.S.	—
Panacyl	Pharma Rheinpreussen	W. Germany	—
Paramisan	Smith & Nephew	U.K.	—
Para-Pas	Gold Leaf	U.S.	—
Pas	Sumitomo	Japan	—

Trade Name	Manufacturer	Country	Year Introduced
Pasido	Ferrosan	Sweden	–
Propasa	Merck Sharp & Dohme	–	–
Rezipas	Squibb	U.S.	–
Sanpas	Sanyo	Japan	–
Sta-Pas	Debat	France	–
Tebacin Acid	Consol, Midland	U.S.	–

Raw Materials

Sodium-p-aminosalicylate
m-Aminophenol
Ammonium Carbonate

Manufacturing Process

As described in U.S. Patent 427,564, aminosalicylic acid may be prepared from m-aminophenol by heating with ammonium carbonate in solution under pressure.

Alternatively, aminosalicylic acid may be made from sodium p-aminosalicylate as described in U.S. Patent 2,844,625 as follows: 196 grams of commercial sodium para-aminosalicylate (18.5% H_2O) was dissolved in 196 ml of water and 150 ml of isopropanol. 6 grams of sodium bisulfite was dissolved in the solution and the solution filtered. While stirring and keeping the temperature between 25°-31°C, seven grams of 85% formic acid and 27.5 grams of 95% sulfuric acid in 150 ml of water was added during 1½ hours. The mixture was stripped 1 hour longer, cooled to 23°C and filtered. The filter cake was washed with 100 cubic centimeters of water, further washed with 100 cc of 25% isopropanol and 100 cc of water, and vacuum dried to constant weight at 45°-50°C. Weight of p-amino-salicylic acid was 76.5 grams (92.7% yield) exhibiting a bulk density of 47 cc/oz.

References

Merck Index 485
Kleeman & Engel p. 43
I.N. p. 74
REM p. 1213
Gnehm, R. and Schmid, J.; U.S. Patent 427,564; May 13, 1890
Centolella, A.P.; U.S. Patent 2,844,625; July 22, 1958; assigned to Miles Laboratories, Inc.
Doub, L.; U.S. Patent 2,540,104; February 6, 1951; assigned to Parke Davis & Co.

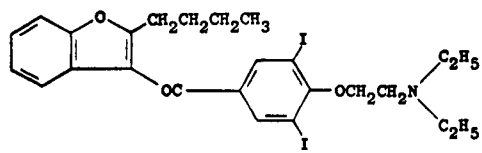
AMIODARONE HYDROCHLORIDE

Therapeutic Function: Coronary vasodilator

Chemical Name: (2-butyl-3-benzofuranyl)[4-[2-diethylamino)ethoxy]-3,5-diiodophenyl]-methanone hydrochloride

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 1951-25-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cordarone	Labaz	France	1968
Cordarone	Sigma Tau	Italy	1971
Cordarone X	Labaz	U.K.	1980
Cordarone	Labaz	Switz.	1981
Cordarexne	Labaz	W. Germany	1982
Amiodacore	C.T.S.	Israel	—
Atlansil	Roemmers	Argentina	—
Miodarone	Biosintetica	Brazil	—
Procor	Unipharm	Israel	—
Ritmocardyl	Bago	Argentina	—
Trangorex	Labaz	—	—
Uro-Septra	Biosintetica	Brazil	—

Raw Materials

2-n-Butyl-3-(3,5-diiodo-4-hydroxybenzoyl)benzofuran
Sodium Methoxide
β-Diethylaminoethyl Chloride

Manufacturing Process

135 grams of 2-n-butyl-3-(3,5-diiodo-4 hydroxybenzoyl)benzofuran dissolved in 600 cc of ethyl carbonate were treated with 5.7 grams of sodium in the form of sodium methoxide in methanol. Then, β-diethylaminoethyl chloride which had been obtained from 51.6 grams of the hydrochloride in ethyl carbonate was introduced into a suspension of the sodium salt. The mixture was heated to a temperature of approximately 90°C which was maintained for approximately 2 hours. The mixture was cooled and allowed to stand overnight during which time the sodium chloride settled down.

The toluene solution containing diethylaminoethylether was extracted with increasingly diluted aqueous hydrochloric acid solutions while stirring. Extraction was continued until the alkalized solution produced no further precipitate. The combined aqueous solutions were washed with ether and then made strongly alkaline with aqueous sodium hydroxide. Extraction with ether was carried out three times. The organic layers were washed with water and then dried over anhydrous potassium carbonate. In order to produce the hydrochloride, the carbonate was filtered off and then the hydrochloride was precipitated from the ether solution with an ethereal hydrochloric acid solution. After the solution had been allowed to stand for a few hours, decantation was carried out and the syrupy hydrochloride residue was taken up in 500 cc of boiling acetone. The salt crystallized out by cooling. The substance was allowed to stand overnight at 0°C, and centrifuged, washed with ethyl acetate and then with ether and dried. 130 grams of 2-n-butyl-3-(3,5-diiodo-4-β-N-diethylaminoethoxybenzoyl)benzofuran hydrochloride in the form of a crystalline powder which melts at 156°C were obtained.

References

Merck Index 491
Kleeman & Engel p. 43
DOT 5 (4) 123 (1969)
I.N. p. 75
Tondeur, R. and Binon, F.; U.S. Patent 3,248,401; April 26, 1966; assigned to Societe Beige de l'Azote et des Produits Chimiques du Marly, SA, Belgium

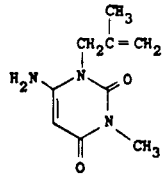
AMISOMETRADINE

Therapeutic Function: Diuretic

Chemical Name: 6-Amino-3-methyl-1-(2-methyl-2-propenyl)-2,4(1H,3H)-pyrimidinedione

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Rolicton	Searle	U.S.	1956

Raw Materials

Methallylamine
Methyl Isocyanate
Cyanoacetic Acid
Sodium Hydroxide

Manufacturing Process

Preparation of the ethyl analog is as follows (methyl isocyanate is used in amisometradine manufacture).

To a cooled and stirred solution of 142 parts of methallylamine in 900 parts of benzene, 156 parts of ethyl isocyanate are added dropwise. Upon concentration in vacuum N-ethyl-N'-methallylurea is obtained.

260 parts of this urea derivative are dissolved in 500 parts of acetic anhydride and treated with 157 parts of cyanoacetic acid at 60°C and heated at that temperature for 2 hours. The solution is then concentrated in vacuum to a syrup. 100 parts of water are added and the vacuum distillation is repeated. The remaining syrup contains a mixture of N-cyanoacetyl-N-ethyl-N'-methallylurea and a small quantity of N-cyanoacetyl-N-methallyl-N'-ethylurea.

This syrup is treated with sufficient 20% sodium hydroxide solution to raise the pH to 10. A violent reaction occurs. The reaction mixture is diluted with 50 parts of water, stirred, cooled and filtered. The material collected on the filter is recrystallized from 10% ethanol to yield a mixture of 1-methallyl-3-ethyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione and 1-ethyl-3-methallyl-6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione melting at about 157°-159°C.

References

Merck Index 493
OCDS Vol. 1 p. 266
I.N. p. 76
Papesch, V. and Schroeder, E.F.; U.S. Patent 2,729,669; January 3, 1956; assigned to G.D. Searle & Co.

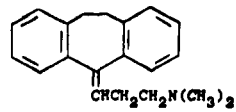
AMITRIPTYLINE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: 3-(10,11-dihydro-5H-dibenzo[a,d] -cyclohepten-5-ylidene)-N,N-dimethyl-1-propaneamine hydrochloride

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 549-18-8; 50-48-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Elavil HCl	Merck Sharp & Dohme	U.S.	1961
Elavil	DDSA	U.K.	1962
Triptizol	Merck Sharp & Dohme	Italy	1962
Laroxyl	Roche	Italy	1962
Endep	Roche	U.S.	1975
Amitril	WL/PD	U.S.	1978
Amitid	Squibb	U.S.	1979
Amavil	Mallard	U.S.	1980
Enovil	Hauck	U.S.	1982
Adepril	Lepetit	Italy	—
Adepress	Essex-Shionogi	Japan	—
Ami-Anelun	Llorente	Spain	—
Amilent	Warner-Lambert	U.S.	—
Amiprin	Kobayashi	Japan	—
Amiptanol	Kanto	Japan	—
Amitrip	Glebe	Australia	—
Amitriptol	Bracco	Italy	—
Annolytin	Kodama	Japan	—
Annolytin	Nippon Shoji	Japan	—
Deprestat	Script Intal	South Africa	—
Domical	Berk	U.K.	—
Elatrol	ICN	Canada	—
Elatrol	Teva	Israel	—
Elatrolet	Teva	Israel	—
Lantron	Yamanouchi	Japan	—
Lentizol	Warner-Lambert	U.S.	—
Levate	ICN	Canada	—
Limbitrol	Roche	France	—
Limbitrol	Roche	U.S.	—
Mareline	Elliott-Marion	Canada	—
Meravil	Medic	Canada	—
Miketorin	Mitsui	Japan	—
Mitaptyline	Toyo Pharm.	Japan	—
Mutanxion	Cetrane	France	—
Mutaspline	Cetrane	France	—
Normaln	Sawai	Japan	—
Novotriptyn	Novopharm	Canada	—
Redomex	Labaz	—	—
Saroten	Lundbeck	W. Germany	—
Saroten	Tropon	W. Germany	—
Saroten	Warner	U.K.	—
Sarotex	Lundbeck	W. Germany	—
Schuvel	Tokyo-Hosei	Japan	—
Sensival	Pfizer Taito	Japan	—

Trade Name	Manufacturer	Country	Year Introduced
Teperin	Egyt	Hungary	–
Trepiline	Lennon	South Africa	–
Triavil	Merck Sharp & Dohme	U.S.	–
Triptilin	Kimya Evi	Turkey	–
Triptyl	Farmos	Finland	–
Tryptal	Unipharm	Israel	–
Tryptanol	Merck-Banyu	Japan	–
Tryptizol	Sharpe & Dohme	W. Germany	–
Tryptizol	Sharpe & Dohme	U.K.	–

Raw Materials

Phthalic Anhydride
3-(Dimethylamino)propyl Chloride
Hydrochloric Acid
Hydrogen
Phenylacetic Acid

Manufacturing Process

Phthalic anhydride is reacted with phenylacetic acid to form 3-benzylidenephthalide which is then hydrogenated to 2-phenethylbenzoic acid. Conversion to the acid chloride followed by intramolecular dehydrochlorination yields the ketone, 5H-dibenzo[a,d]cyclohepten-5-one. The ketone undergoes a Grignard reaction with 3-(dimethylamino)propyl chloride to give 5-(γ-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene.

Then, as described in U.S. Patent 3,205,264, a solution of 5-(γ-dimethylaminopropylidene)-5H-dibenzo-[a,d]-cycloheptene (42 grams; 0.153 mol) in 105 ml of ethanol is hydrogenated over Raney nickel (1.5 grams) at 65°C under an initial hydrogen pressure of 450 lb. After 1 mol of hydrogen is absorbed (3.5 hours), the reaction mixture is filtered to remove the catalyst and is acidified with 80 ml of 2.5 N hydrochloric acid (0.2 mol). The acidic solution is concentrated to dryness under vacuum and is flushed three times with 100 ml of benzene to remove residual water. The solid residue then is dried under vacuum at 40°C to yield 44.9 grams (94% of theory) of the product, MP 187°-189.5°C, equivalent weight 307, ultraviolet absorption A% 2380^{432}. Recrystallization from isopropyl alcohol and ether affords the product in high purity.

References

Merck Index 496
Kleeman & Engel p. 44
PDR pp. 673, 993, 1174, 1217, 1314, 1509, 1513, 1569, 1606, 1617
OCDS Vol. 1 pp. 151, 404
DOT 9 (6) 219 (1973)
I.N. p. 76
REM p. 1093
Tristram, E.W. and Tull, R.J.; U.S. Patent 3,205,264; September 7, 1965; assigned to Merck & Co., Inc.

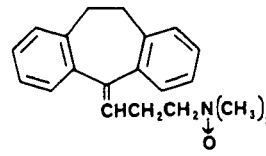
AMITRIPTYLINE OXIDE

Therapeutic Function: Antidepressant

Chemical Name: 3-(3'-Dimethylaminopropylidene)dibenzo[a,d]cyclohepta-1,4-diene N-oxide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 4317-14-0

Trade Name	Manufacturer	Country	Year Introduced
Equilibrin	Nattermann	W. Germany	1980
Ambivalon	Nattermann	W. Germany	—

Raw Materials

Dibenzo[a,d]cyclohepta-1,4-diene-5-one
3-Dimethylaminopropanol Magnesium Chloride
Hydrogen Peroxide

Manufacturing Process

31.3 g (0.1 mol) of 3-(3'-dimethylaminopropylidene)dibenzo[a,d]cyclohepta-1,4-diene hydrochloride are dissolved in water, and the free base is liberated by means of a 28% aqueous solution of sodium hydroxide. The free base is sucked off, washed with water, and dissolved in 100 ml of methanol. To the solution are added 31 ml of 30% hydrogen peroxide. After 7 days, the reaction mixture is diluted with 200 ml of water, and the major part of the methanol is evaporated in vacuum. The precipitated N-oxide crystals are filtered off, washed with water, and dried, yielding 27 g of the dihydrate of 3-(3'-dimethylaminopropylidene)dibenzo-[a,d]cyclohepta-1,4-diene N-oxide with melting point of 102° to 103°C. In dehydrated state the melting point is 228° to 230°C.

By dissolving the N-oxide in acetone, and bubbling dry hydrogen chlorine gas through the solution until slightly acid reaction, the hydrochloride of the N-oxide is precipited as a white crystalline substance with melting point of 172° to 173.6°C.

The starting material can be prepared in known manner from dibenzo[a,d]cyclohepta-1,4-diene-5-one by a Grignard reaction with 3-dimethylaminopropyl magnesium chloride, hydrolysis and dehydration of the resulting carbinol.

References

Merck Index 497
DFU 5 (7) 329 (1980)
Kleeman & Engel p. 45
DOT 18 (3) 110 (1982)
I.N. p. 77
Pedersen, J.B.; British Patent 991,651; May 12, 1965; assigned to A/S Dumex (Dumex, Ltd.)
Merck & Co., Inc.; British Patent 1,095,786; December 20, 1967
Pedersen, J.B.; U.S. Patent 3,299,139; January 17, 1967; assigned to A/S Dumex (Dumex, Ltd.)

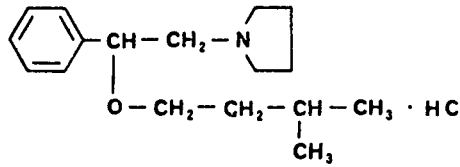
AMIXETRINE HYDROCHLORIDE

Therapeutic Function: Antiinflammatory; anticholinergic; antidepressant

Chemical Name: N-(2-Phenyl-2-isoamyloxy)-ethylpyrrolidine hydrochloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 24622-52-4; 24622-72-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Somagest	Riom	France	1972

Raw Materials

Styrene
Isoamyl Alcohol
Hydrogen Chloride
t-Butyl Hypobromite
Pyrrolidine

Manufacturing Process

There is heated under reflux with stirring for 10 hours: 117 g of (2-phenyl-2-isoamyloxy)-ethyl bromide, 61.5 g of pyrrolidine and 250 ml of toluene.

After filtration of the pyrrolidine hydrobromide, the toluene is removed under reduced pressure. The residue is then taken up with 4N HCl. The aqueous solution is washed with ether. It is made alkaline by a solution of 50% NaOH. It is extracted with ether. The ethereal phase is dried over anhydrous sodium sulfate, and rectified under reduced pressure after removing the solvent. There is thus obtained 90 g of a colorless oil with an amine odor.

The hydrochloride is prepared in the usual manner by dissolving the amine in anhydrous ether and adding to it the requisite amount of dry gaseous hydrochloric acid, dissolved in absolute alcohol. There is obtained a white crystalline powder melting at 150°C, very soluble in water and alcohol, very slightly soluble in ether and ethyl acetate.

The starting material above is prepared by reacting styrene with isoamyl alcohol and then reacting that product with t-butyl hypobromite.

References

Merck Index 499
Kleeman & Engel p. 46
DOT 8 (9) 334 (1972)
I.N. p. 77
Centre Europeen de Recherches Mauvernay, RIOM; British Patent 1,253,818; November 17, 1971

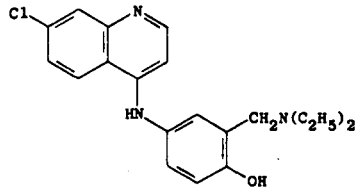
AMODIAQUIN

Therapeutic Function: Antimalarial

Chemical Name: 4-[(7-Chloro-4-quinolinyl)amino]-2-[(diethylamino)-methyl]phenol

Common Name: 4-(3'-diethylaminomethyl-4'-hydroxyanilino)-7-chloroquinoline

Structural Formula:



Chemical Abstracts Registry No.: 86-42-0 (Base); 69-44-3 (Dihydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Camoquin HCl	Parke Davis	U.S.	1950
Flavoquine	Roussel	France	1979
Corbutyl	I.S.H.	France	–
Camoquin	Parke-Davis	U.K.	–

Raw Materials

p-Aminophenol Hydrochloride
4,7-Dichloroquinoline
Diethylamine
Paraformaldehyde

Manufacturing Process

72.8 g (0.5 mol) of p-aminophenol hydrochloride is dissolved in 500 cc of water and added to 99 g (0.5 mol) of 4,7-dichloroquinoline. After a few minutes of warming in a steam bath, 4-(4'-hydroxyanilino)-7-chloroquinoline hydrochloride, of sufficient purity for use in further experiments, precipitates as a yellow crystalline solid. Recrystallized from methanol, the MP is over 300°C.

A mixture consisting of 13.5 g of 4-(4'-hydroxyanilino)-7-chloroquinoline hydrochloride dissolved in absolute ethanol is treated with a solution of 4.38 g of diethylamine and 1.8 g of paraformaldehyde in 20 cc of absolute ethanol. The reaction mixture is heated under reflux for 16 hours, evaporated to one-half volume and the warm solution treated with an excess of hydrogen chloride dissolved in absolute ethanol. Acetone is added to the warm solution until it becomes turbid and then the solution is cooled. The crude dihydrochloride which separates is collected and purified by recrystallization from methanol; MP 240°–242°C.

By using an equivalent amount of 4-(4'-hydroxyanilino)-7-bromoquinoline in the above procedure, 4-(3'-diethylaminomethyl-4'-hydroxyanilino)-7-bromoquinoline dihydrochloride is obtained; MP (base) 206°–208°C dec.

References

Merck Index 593
Kleeman & Engel p. 47
I.N. p. 78
REM p. 1217
Burckhalter, J.H., Jones, E.M., Rawlins, A.L., Tendick, F.H. and Holcomb, W.F.; U.S. Patent 2,474,821; July 5, 1949; assigned to Parke, Davis & Co.

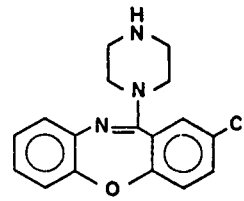
AMOXAPINE

Therapeutic Function: Antidepressant

Chemical Name: 2-Chloro-11-(1-piperazinyl)dibenz[b,f] [1,4] oxazepine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 14028-44-5

Trade Name	Manufacturer	Country	Year Introduced
Asendin	Lederle	U.S.	1980
Moxadil	Lederle	France	1980
Amoxan	Lederle	Japan	1981
Omnipress	Cyanamid	W. Germany	1983
Demolox	Lederle	–	–

Raw Materials

o-(p-Chlorophenoxy)aniline Hydrochloride
N-Carbethoxypiperazine
Ethyl Chlorocarbonate
Phosphorus Pentoxide

Manufacturing Process

A mixture of 125 g of o-(p-chlorophenoxy)aniline hydrochloride and 100 ml of dry pyridine is treated cautiously with a solution of 90 ml of ethyl chlorocarbonate in 150 ml of ether. The mixture is kept at room temperature for 3 days, diluted with about 500 ml of water and extracted with 300 ml of ether. The ethereal extract is washed with 300 ml of water, dried over calcium chloride, filtered and concentrated. The resulting ethyl o-(p-chlorophenoxy)carbanilate is obtained in a viscous oil suitable for use in the next step without further purification.

A solution of 70 g of ethyl o-(p-chlorophenoxy)carbanilate and 120 g of N-carbethoxypiperazine in 100 ml of benzene containing a little sodium methoxide is heated on a steam bath for about 5 days. The solvent is removed by distillation and the residue is triturated with water. The resulting solid is dissolved in ether and dried over sodium sulfate. Filtration and concentration then yields ethyl 4-[[o-(p-chlorophenoxy)phenyl]carbamoyl]-1-piperazinecarboxylate, melting at 89° to 91°C, and suitable for cyclization.

A mixture of 10 g of the above piperazine carboxylate ester, 8 g of phosphorus pentoxide and 20 ml of phosphorus oxychloride is heated under reflux for about 1 day, diluted with 100 ml each of chloroform and benzene and quenched with 200 g of ice. The mixture is made basic with 10% sodium hydroxide. The organic layer is isolated and extracted with 150 ml of dilute hydrochloric acid. The product is precipitated from the aqueous layer by addition of 10% sodium hydroxide, extracted with benzene and dried over potassium carbonate. Recrystallization from benzene-petroleum ether gives 2-chloro-11-(1-piperazinyl)dibenz[b,f][1,4]-oxazepine which melts at 175° to 176°C.

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