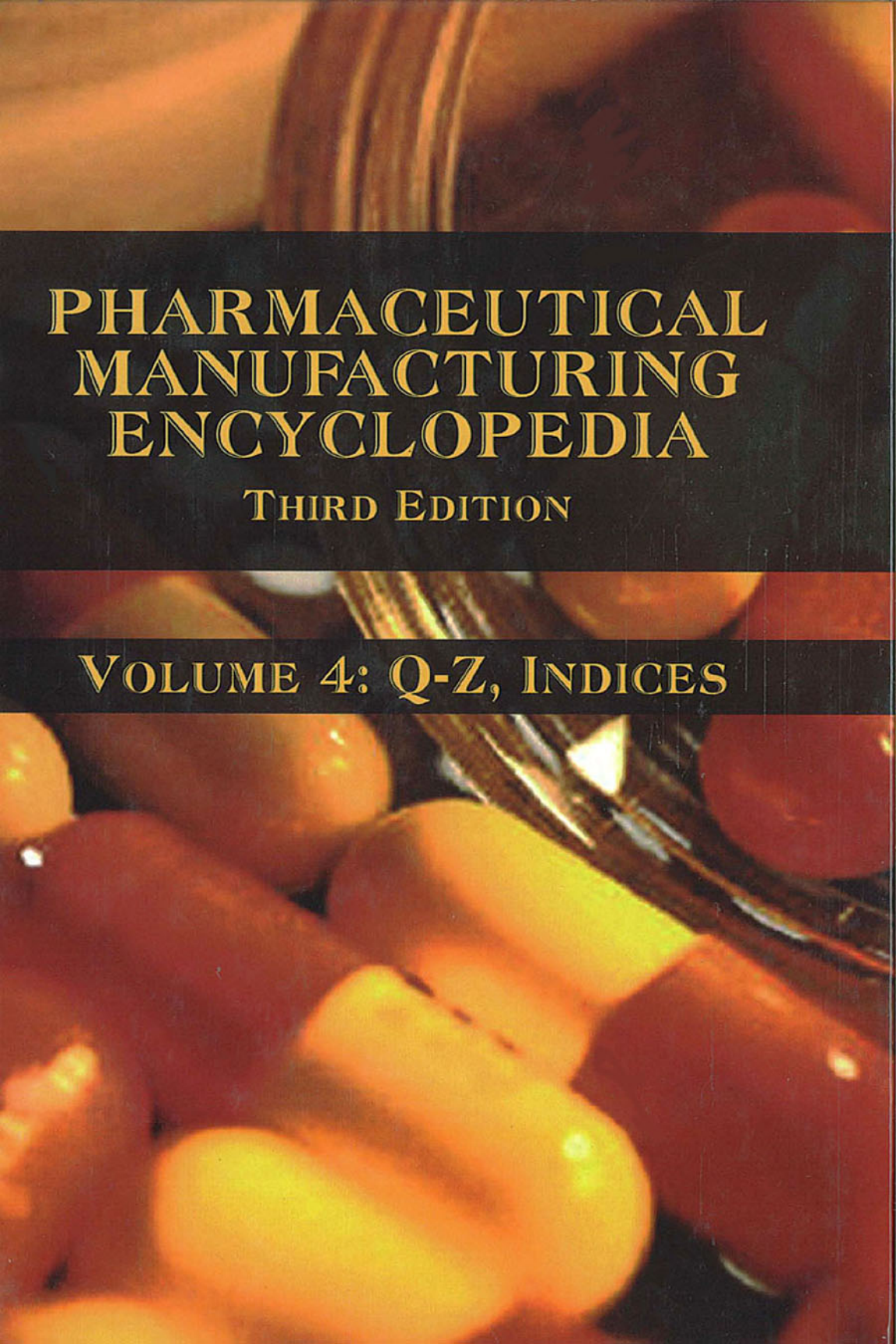
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A

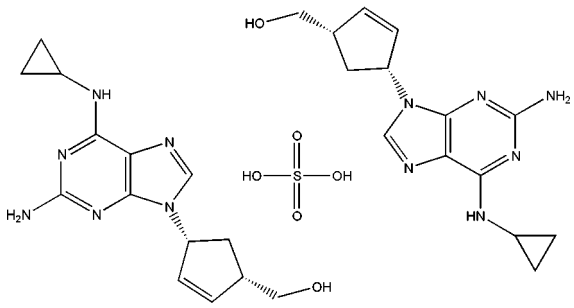
ABACAVIR SULFATE

Therapeutic Function: Antiviral

Chemical Name: 2-Cyclopentene-1-methanol, 4-(2-amino-6-(cyclopropylamino-9H-purin-9-yl), sulfate (salt) (2:1), (1S,4R), sulfate

Common Name: Abacavir sulfate

Structural Formula:



Chemical Abstracts Registry No.: 188062-50-2; 136470-78-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ziagen	GlaxoSmithKline	-	-
Ziagen	Glaxo Wellcome	-	-
Ziagenavir	Glaxo Wellcome	-	-

Raw Materials

2,5-Diamino-4,6-dihydroxypyrimidine
(Chloromethylene)dimethylammonium chloride
(1S,4R)-4-Amino-2-cyclopentene-1-methanol
Triethylamine
Tartaric acid, dibenzoate, (-)-
Orthoformate or diethoxymethyl acetate
Cyclopropylamine

Manufacturing Process

Treatment of 2,5-diamino-4,6-dihydroxypyrimidine (I) with (chloromethylene)dimethylammonium chloride yielded the dichloropyrimidine with both amino groups derivatized as amidines. Partial hydrolysis with aqueous HCl in hot ethanol gave N-(2-amino-4,6-dichloro-pyrimidin-5-yl)-N,N-dimethylformamidene (II). Subseqent buffered hydrolysis at pH 3.2 yielded the (2-amino-4,6-dichloro-pyrimididin-5-ylamino)acetaldehyde (III). Condensation chloropyrimidine (III) with (1S,4R)-4-amino-2-cyclopentene-1-methanol (IV) in the presence of triethylamine and NaOH gave [2-amino-4-chloro-6-(4-hydroxymethyl-cyclopent-2-enylamino)pyrimidin-5-ylamino]-acetaldehyde (V). The correct enantiomer (IV) of racemic aminocyclopentene was obtained by resolution of diastereomeric salts with D-dibenzoyltartaric acid. Cyclization of (V) to the corresponding purine was accomplished with refluxing triethyl orthoformate or diethoxymethyl acetate to give nucleoside analogue [4-(2-amino-6-chloro-purin-9-yl)-cyclopent-2-enyl]methanol (VI). Displacement of chloride in the purine nucleus with cyclopropyl amine in refluxing butanol afforded abacavir. The structure of obtained compound was confirmed by 1H NMR method and elemental analysis.

In practice it is usually used as sulfate salt.

References

Huff J.R.; Bioorg. Med. Chem., 7, (1999), 2667-2669
Daluga S.M.; European Patent No. 0,434,450; Dec. 12, 1990

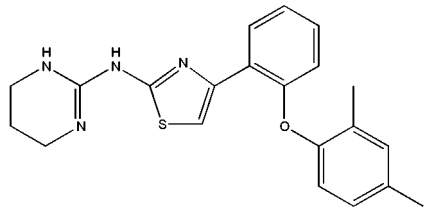
ABAFUNGIN

Therapeutic Function: Antibacterial, Antifungal

Chemical Name: N-{4-[2-(2,4-Dimethylphenoxy)phenyl]thiazol-2-yl}-1,4,5,6-tetrahydro-pyrimidinamine

Common Name: Abafungin; BAY w 6341

Structural Formula:



Chemical Abstracts Registry No.: 129639-79-8

Trade Name	Manufacturer	Country	Year Introduced
Abafungin	York Pharma	-	-

Raw Materials

N-(1,4,5,6-Tetrahydropyrimidinyl)thiourea
2-(2,4-Dimethylphenoxy)phenacyl chloride

Manufacturing Process

15.8 g (0.12 mole) N-(1,4,5,6-tetrahydropyrimidinyl)thiourea were added to 27.45 g (0.1 mole) 2-(2,4-dimethylphenoxy)phenacyl chloride in 100 ml acetone and heated to reflux for 2 hours. On cooling the falling out product was filtered off, washed with acetone and dried. N-[4-[2-(2,4-Dimethylphenoxy)phenyl]-2-thiazolyl]-1,4,5,6-tetrahydro-2-pyrimidinamine hydrochloride was prepared. Yield 91.4%; MP: 160°C.

20.72 g (0.05 mole) above product was stirred with 300 ml 1 N sodium hydroxide for 30 minutes at room temperature. The insoluble product was filtered off, washed and dried. Yield of N-[4-[2-(2,4-dimethylphenoxy)phenyl]-2-thiazolyl]-1,4,5,6-tetrahydro-2-pyrimidinamine was 16.2 g (86%). MP: 191°-192°C.

References

Ippen. Joachim et al.; D.B. Patent No. 3,836,161 A1; Nov. 24, 1988; Bayer AG, 5090 Leverkusen, DE

ABAMECTIN

Therapeutic Function: Antiparasitic

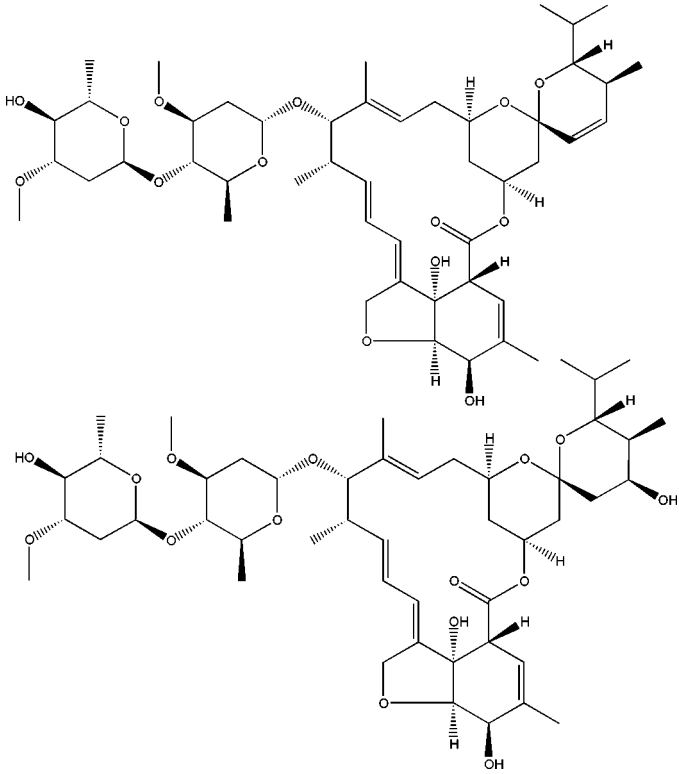
Chemical Name: Avermectin B_1

Common Name: Abamectin; MK-936, Zectin

Chemical Abstracts Registry No.: 71751-41-2; 65195-55-3

Trade Name	Manufacturer	Country	Year Introduced
Abamectin	Yellow River Enterprise Co. (a.k.a Yelori)	-	-
Kraft TM	Cheminova	-	-
Abamectin 1.8%	LIFES Labo	-	-
Abamectin	Ningbo Sega Chemical Company	-	-
Avomec	Institutul Pasteur Romania	-	-
Duotin	Merial	-	-
Enzec	Merck Sharp and Dohme Ltd	-	-

Structural Formula:



Raw Materials

Streptomyces avermitilis MA-4680
Nutrient medium

Manufacturing Process

1. The contents of a lyophilized tube of Streptomyces avermitilis MA-4680 is transferred aseptically to a 250 ml Erlenmeyer flask containing 305 ml of Medium 1: Dextrose 20 g, Peptone 5 g, Meat Extract 5 g, Primary Yeast 3 g, NaCl 5 g, $CaCO_3$ (after pH adjustment) 3 g, Distilled water 1000 ml, pH 7.0. The inoculated flask is incubated for 3 days at 28°C on a rotary shaking machine at a speed of 220 RPM in a 2 inch radius circular orbit. At the end of this time, a 250 ml Erlenmeyer flask containing 50 ml of Medium 2 [Tomato Paste 20 g, Modified Starch (CPC) 20 g, Primary Yeast 10 g, $CoCl_2 \cdot 6H_2O$ 0.005 g, Distilled water 1000 ml, pH 7.2-7.4] is inoculated with a 2 ml sample from the first flask. This flask is incubated for 3 days at 28°C on a rotary shaking machine at a speed of 220 RPM in a 2 inch diameter circular orbit. 50 Ml of the resulting fermentation broth containing C-076 is effective against an N.dubius infection in mice.

2. A lyophilized tube of Streptomyces avermitilis MA-4680 is opened aseptically and the contents suspended in 50 ml of Medium 1 in a 250 ml Erlenmeyer flask. This flask is shaken for 3 days at 28°C on a rotary shaking machine 220 RPM with a 2 inch diameter circular orbit. A 0.2 ml portion of this seed medium is used to inoculate a Slant of Medium 3: Dextrose 10.0 g , Bacto Asparagine 0.5 g, K_2HPO_4 40.5 g, Bacto Agar 15.0 g , Distilled water 1000 ml, pH 7.0. The inoculated slant medium is incubated at 28°C for 10 days and stored at 4°C until used to inoculate 4 more slants of Medium 3. These slants are incubated in the dark for 8 days. One of these slants is used to inoculate 3 baffled 250 ml Erlenmeyer flasks containing 50 ml of No. 4 Seed Medium: Soluble Starch 10.0 g, Ardamine 5.0 g, NZ Amine E 5.0 g, Beef Extract 3.0 g, $MgSO_4 \cdot 7H_2O$ 0.5 g, Cerelose 1.0 g, Na_2HPO_4 0.190 g, KH_2PO_4 182 g, $CaCO_3$ 0.5 g, Distilled water 1000 ml, pH 7.0-7.2. The seed flasks are shaken for 2 days at 27-28°C on a rotary shaking machine at 220 RPM with a 2 inch diameter circular orbit. The contents of these flasks are pooled and used to inoculate (5% inoculum) baffled 250 ml Erlenmeyer flasks containing 40 ml of various production media. Flasks containing media 2, 5 and 6 are incubated for 4 days at 28°C on a rotary shaking machine at 220 RPM with a 2 inch diameter circular orbit. The resulting broth containing C-076 is then harvested and tested for anthelmintic activity. In all cases 6.2 ml of whole broth and the solids obtained from centrifuging 25 ml of whole broth are fully active against N.dubius helminth infections in mice.

3. The one of the four slants of Medium 3 prepared as in Example 2 is used to inoculate a baffled 250 ml Erlenmeyer flask containing 50 ml of Seed Medium No. 4. The seed flask is shaken for 1 day at 27- 28°C on a rotary shaking machine at 220 RPM with a 2 inch diameter circular orbit. The seed flask is then stored stationary at 4°C until it is ready to be used. The contents of this flask are then used to inoculate (5% inoculum) 20 unbaffled 250 ml Erlenmeyer flasks containing 40 ml of Medium No. 2. After 4 days incubation at 28°C on a rotary shaking machine at 220 RPM with a 2 inch diameter circular orbit, 19 of the flasks are harvested and pooled. The combined fermentation broths

containing C-076 are filtered affording 500 ml of filtrate and 84 g of mycelia. 78 G of mycelia are extracted with 150 ml of acetone for ½ hour with stirring and the mixture filtered. The filter cake is washed with 50 ml of acetone and the filtrate and washings are combined and concentrated to 46.5 ml 30 Ml of the concentrate is adjusted to pH 4 with dilute hydrochloric acid and extracted 3 times with 30 ml portions of chloroform. The extracts are dried by filtering through dry Infusorial Earth (Super-Cel) combined and concentrated to dryness in vacuum. The oily residue of C-076 weighing 91.4 mg is dissolved in chloroform sufficient to make 3 ml of solution which represents 1% of broth volume. The C-076 (Abamectin) obtained in this recovery procedure is fully active against N.dubius infections in mice. In addition, the chloroform extraction achieved a 70 fold purification of C-076 from the whole broth.

References

Albers-Schonberg G., Wallick H., Ormond R.E., Miller Thomas W., Burg Richard W.; US Patent No. 4,310,519; Jan. 12, 1982; Assigned to Merck and Co., Inc. (Rahway, NJ)

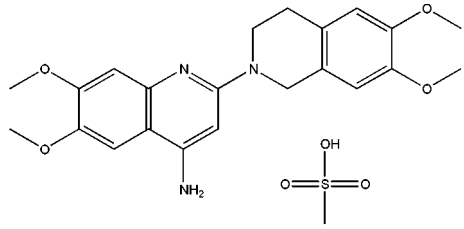
ABANOQUIL MESYLATE

Therapeutic Function: Antiarrhythmic, Coronary vasodilator

Chemical Name: 4-Amino, 2-(3,4-dihydro-6,7-dimethoxy-2(1H)-isoquinolyl)-6,7- dimethoxyquinoline monomethanesulfonate

Common Name: Abanoquil mesylate

Structural Formula:



Chemical Abstracts Registry No.: 118931-00-3; 90402-40-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Abanquil	Onbio Inc.	-	-

Raw Materials

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline
Acetic anhydride
Phosphorus(V) oxychloride
2-Amino-4,5-dimethoxybenzonitrile
Sodium hydroxide
Zinc chloride
Fumaric acid

Manufacturing Process

Synthesis of 1-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethanone:

To a stirred solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3.00 g, 15.4 mmol, 1.00 equiv.) in anhydrous pyridine (100 mL) under argon at room temperature was added acetic anhydride (14.5 mL, 154 mmol, 10.0 equiv.) over 15 min. The resulting mixture was stirred at room temperature for 2 h, and then at reflux for 6 h. The volatiles were removed by rotary evaporation at 80°C under high vacuum. The residue was flash chromatographed on silica gel (MeOH-CH_2Cl_2 8:92) to afford 3.21 g (89%) of 1-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethanone as a viscous brown oil. The H-NMR spectrum reflected the presence of two slowly interconverting conformers in a ratio of 1.2:1 at room temperature.

Synthesis of 2-[1-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethylidineamino]-4,5-dimethoxybenzonitrile:

To a stirred solution of 1-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethanone (1.00 g, 4.25 mmol, 1.00 equiv.) in $CHCl_3$ at room temperature under argon was added $POCl_3$ (143 μL, 1.53 mmol, 0.36 equiv.). After 10 min, 2-amino-4,5-dimethoxybenzonitrile (763 mg, 4.28 mmol, 1.01 equiv.) was added and the mixture was heated at reflux overnight. The mixture was cooled to room temperature and poured into 1 M aq. NaOH solution (50 mL), and the aqueous phase was extracted with CH_2Cl_2. The combined organic solutions were dried over MgSO4 and concentrated. The residue was flash chromatographed on silica gel (MeOH-CH_2Cl_2, 2 5:95) to afford 482 mg (28%) of 2-[1-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethylidineamino]-4,5-dimethoxybenzonitrile as an yellow solid.

Synthesis of 2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-6,7-dimethoxyquinolin-4-ylamine hemifumarate hydrate (abanoquil):

To a stirred solution of 2-[1-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethylidineamino]-4,5-dimethoxybenzonitrile (471 mg, 1.19 mmol, 1.00 equiv.) in refluxing anhydrous N,N-dimethylacetamide (24 mL) under argon was added $ZnCl_2$ (339 mg, 2.49 mmol, 2.10 equiv.) in three portions over 1 h. The solvent was removed by distillation at 70°C under high vacuum. Ether (40 mL) was added to the residue, which was broken up with a stirring rod, and the mixture was stirred at 0°C to precipitate the product. The supernatant was discarded, and the precipitate was washed twice more at 0°C with ether. The solid residue was stirred with 1 M aq. NaOH (25 mL) and CH_2Cl_2 (25 mL) for 10 min, and the aqueous phase was extracted with CH_2Cl_2. The combined organic solutions were dried over $MgSO_4$ and concentrated to give 493 mg of brown oil, which was flash chromatographed on silica gel (MeOH-CH_2Cl_2,12:88 followed by 2-propylamine-CH_2Cl_2, 5:95) to afford 151 mg (38%) of 2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-6,7-dimethoxyquinolin-4-ylamine as a tan solid.

To a solution of 2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-6,7-dimethoxyquinolin-4-ylamine (150 mg) in hot CH_2Cl_2 (4.5 mL) and MeOH (1.5 mL) was added a solution of fumaric acid (22.8 mg, 0.196 mmol, 0.50 equiv.) in hot MeOH (3.0 mL). The resulting mixture was concentrated and the product was recrystallized from MeOH with hot filtration to afford, after filtration, 85 mg of light brown solid: m.p. 239-240°C.

In practice it is usually used as mesylate.

References

Craig D.A., Forrey C.C., Gluchovski Ch., Branchek T.A.; US Patent No. 5,610,174; March 11, 1997; Assigned to Synaptic Pharmaceutical Corporation (Paramus, NJ)

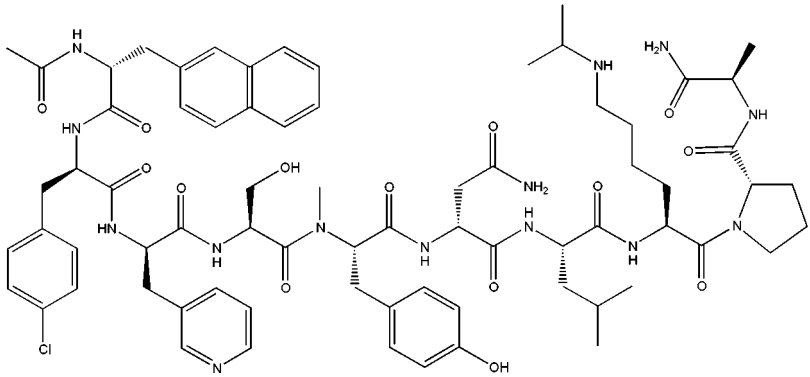
ABARELIX

Therapeutic Function: LHRH antagonist

Chemical Name: D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-N-methyl-L-tyrosyl-D-asparaginyl-L-leucyl-N^6-(1-methylethyl)-L-lysyl-L-prolyl-

Common Name: Abarelix; PPI-149

Structural Formula:



Chemical Abstracts Registry No.: 183552-38-7

Trade Name	Manufacturer	Country	Year Introduced
Plenaxis	Praecis Pharmaceuticals	-	-

Raw Materials

Thioanisole
Trifluoroacetic acid
1-Hydroxybenzotriazole
Dicyclohexylcarbodiimide
2-Iodopropane
Methylbenzyhydramine resin
Diisopropylethylamine
Boc-protected amino acids
Silver(I) oxide
m-Chloroperbenzoic acid
Boc-D-Pal (Boc-D- 3-(3'-pyridyl)alanine)

Manufacturing Process

Abbreviation Residue or moiety:

Nal - 3-(2-naphthyl)alaninyl

4-Cl-Phe - (4'-chlorophenyl)alaninyl

Pal - 3-(3'-pyridyl)alaninyl

Pal(N-O) - 3-(3'-pyridine-N-oxide)alaninyl

Pal(iPr) - 3-N-(2-propyl)-3'-pyridinium)alaninyl

BOC - N-t-butyoxycarbonyl

DCC - dicyclohexylcarbodiimide

Abarelix was synthesized by the solid phase method using an automated synthesizer (e.g. Beckman Model 990). The amino acid residues used can be purchased from commercial sources (e.g. Aldrich Chemical Co., Milwaukee, Wis.), or can be produced from commercially available starting materials according to known methods. Amino acids which are not obtained commercially can be synthesized in a protected form for coupling, or, if appropriate, can be coupled to form a peptide and subsequently modified to the desired form.

For example, Boc-D-Pal(iPr) was prepared next way:

Boc-D-Pal (4.0 g, 17.7 mmol) and Ag_2O (8.0 g, 34.4 mmol) in 22 ml water was stirred at room temperature for 4 hours. The reaction vessel was cooled to 0°C, and 2-iodopropane (20.4 g, 120 mmol) in 40 ml 2-propanol was added. After addition was complete, the mixture was allowed to warm to room temperature and stirred for 4 days. Additional Ag_2O (2 g) and 2-iodopropane (2 g) were added after 24 hours and again after 48 hours. The mixture was filtered, and the precipitate was washed with ethanol (2x15 ml). The filtrate was evaporated to yield 4.3 g of a yellow oil. Crystallization from ethanol/ethyl acetate gave light yellow crystals (3.0 g); Yield: 63%; m.p. 182°-185°C.

Synthesis of Boc-D-Pal(N-O):

Boc-D-Pal (2.0 g, 7.5 mmole) was dissolved in 40 ml acetone and 2.48 g (16.5 mmol) of m-chloroperbenzoic acid (MCPBA) (57-86%; purchased from Aldrich and used as received) in 80 ml acetone was added in one portion. The mixture was stirred at room temperature for 40 hours; a small amount of white precipitate formed as the reaction proceeded. The precipitated was filtered and the mother liquor evaporated to yield a white precipitate. The combined solids were washed with ether (to remove chlorobenzoic acid) and recrystallized from ethyl acetate/hexane. Yield: 1.7 g (80%); m.p. 155°-157°C.

A typical coupling cycle for peptide synthesis with Boc-amino acids on a peptide synthesizer (Beckman Model 990) was as follows:

Methylbenzyhydramine (MBHA) resin (1.18 g, 0.85 meq amino groups/g resin) was weighed into the reaction vessel and washed with two portions of chloroform (26 ml each). The resin was prewashed with 22% thioanisole (5 ml)/66% trifluoroacetic acid (TFA) in 14 ml dichloromethane (DCM) for 5 minutes, and then deprotected for 30 minutes with the same thioanisole/TFA mixture. The resin was washed with three portions of chloroform (20 ml each), two portions of 2-propanol (26 ml each) and two portions of DCM (26 ml each). The resin was neutralized with two portions of 12% diisopropylethylamine (DIPEA) (26 ml each), and then washed with four portions of DCM (26 ml each), followed by two portions of 1:1 DCM:dimethylformamide (DMF) (26 ml each). A solution of a Boc-protected amino acid (2.5 mole equivalents) and 1-hydroxybenzotriazole (HOBt) (2.5 mole equivalents) was introduced as a solution in 10 ml DMF, and DCC was added (256 mg in 6 DMF). Coupling was allowed to proceed for three hours,

or overnight. Hindered residues (e.g. backbone N-methyl amino acids) required longer coupling times. The resin was washed with two 26 ml portions of DMF, followed by two 26 ml portions of 2-propanol and then two 26 ml portions of DCM. Completion of coupling was assessed by Kaiser's test (ninhydrin test). If coupling is not complete, a double coupling was performed (i.e. the resin was neutralized as above and the coupling step repeated). When complete coupling is achieved, the cycle was repeated with the next amino acid.

Upon completion of the synthesis, the peptide was cleaved from the resin by treatment with liquid hydrofluoric acid (HF) for 45 minutes at 0°C. The HF was evaporated and the peptide treated with aqueous acetic acid and lyophilized. The crude peptide was then purified by high performance liquid chromatography (HPLC) on a C18 column, eluting with a mixture of acetonitrile and 0.1% TFA in water. Purified fractions (homogeneous by UV and TLC analysis) were combined and lyophilized. Analytical HPLC was used to determine the purity of the final product; peptides synthesized was at least 98% pure.

References

Folkers K. et al.; 1986; "Increased Potency of Antagonists of the Luteinizing Hormone Releasing Hormone Which Have D-3 Pal in Position 6"; Biochem. Biophys. Res. Comm.; 137(2):709-715

Tian, Z.P. et al.; 1994; "Design and synthesis of highly water soluble LHRH antagonists"; Pept.: Chem., Struct. Biol., Proc. Am. Pept. Symp.; 13th; 562-564

Roeske R. W.; US Patent No. 5,843,901; Dec. 1, 1998; Assigned to Advanced Research and Technology Institute, Bloomington, Ind.

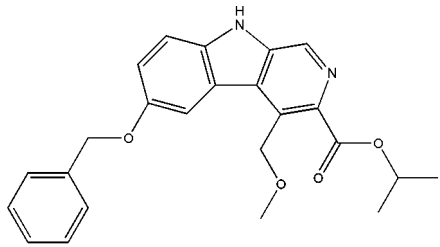
ABECARNIL

Therapeutic Function: Anticonvulsant, Anxiolytic

Chemical Name: 9H-Pyrido[3,4-b]indole-3-carboxylic acid, 4-(methoxymethyl)-6-(phenylmethoxy)-, 1-methylethyl ester

Common Name: Abecarnil; SH 524

Structural Formula:



Chemical Abstracts Registry No.: 111841-85-1

Trade Name	Manufacture	Country	Year Introduced
Abecarnil	Schepa	-	-

Raw Materials

Potassium carbonate
Anisaldehyde
Sodium hydroxide
Hydrochloric acid
Triethylamine
Hydrochloric acid
Glycine isopropyl ester
Paraformaldehyde
tert-Butyl hypochlorite
5-Benzyloxy-3-(1-isopropylamino-2-methoxyethyl)indole

Manufacturing Process

Under nitrogen, 6 g (43.5 millimoles) of finely pulverized potassium carbonate is stirred for 10 min at 95°C in 25 ml of absolute dimethylformamide. Then, while the mixture is hot, 10 g (29.6 mmol) of 5-benzyloxy-3-(1-isopropylamino-2-methoxyethyl)indole is added and the mixture is stirred approximately 10 min at 95°C until the compound has been dissolved. Thereupon, likewise at 95°C, a solution of 34.5 mmol of glycinimine (prepared from anisaldehyde and glycine isopropyl ester) in 25 ml of dimethylformamide is added dropwise in a time period of 30 min. The solution is agitated until the starting indole can no longer be detected in a thin-layer chromatogram. After cooling, the product is filtered off by suction from potassium carbonate and rinsed with toluene. After adding 100 ml of toluene, 200 ml of 1 N hydrochloric acid is added and the mixture stirred for 3 hours at room temperature. The toluene phase is separated, and the aqueous acidic phase is extracted by shaking with 100 ml of toluene. The organic phase is discarded. The acidic phase is cooled to 5°C, combined with 100 ml of toluene, and adjusted to pH 10-12 with 4 N sodium hydroxide solution. After extraction by shaking, the mixture is again extracted by shaking with 100 ml of toluene, and the combined organic phase is washed with 50 ml of water, dried, filtered, and concentrated, thus obtaining 70% 2-amino-3-(5-benzyloxyindol-3-yl)-4-methoxybutyric acid isopropyl ester as an oil.

A solution is prepared from 3.8 g of 2-amino-3-(5-benzyloxyindol-3-yl)-4-methoxybutyric acid isopropyl ester (10 mmol) in 80 ml of xylene and added dropwise to a suspension of 360 mg of paraformaldehyde in 60 ml of xylene heated for 45 min to 100°C. The mixture is then refluxed for 2 hours on a water trap. After concentration, the residue is chromatographed over silica gel with methylene chloride:acetone=1:1 as the eluent, yielding 2.5 g of 6-benzyloxy-4-methoxymethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid isopropyl ester (65% yield as an oil); or a suspension of 2.56 g of paraformaldehyde in 8 ml of water and 0.8 ml of concentrated hydrochloric acid is refluxed at 80°C for 1 hour. One-tenth of the thus-obtained clear solution is added dropwise, after cooling to room temperature, to a solution of 3.8 g (10 mmol) of 2-amino-3-(5-benzyloxyindol-3-yl)-4-methoxybutyric acid isopropyl ester in 500 ml of water and 10 ml of concentrated hydrochloric acid (pH=3). After ½ hour of agitation, an estimate of the amount of amino compound still remaining is made by thin-layer chromatography, and a corresponding quantity of formaldehyde solution is added. Thereupon, the mixture is stirred for another hour and then extracted twice by shaking with 50 ml of toluene, respectively. The organic phase is discarded. The aqueous phase is adjusted, after adding 100 ml of toluene, to a pH of 5.3 with 27%

strength sodium hydroxide solution. After extraction by shaking, the mixture is additionally extracted by shaking twice with 50 ml of toluene; these 3 organic phases are combined, dried over sodium sulfate, filtered, and concentrated, thus obtaining 3.3 g (85%) of 6-benzyloxy-4-methoxymethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid isopropyl ester as an oil.

A solution is prepared from 3.3 g (8.5 mmol) of 6-benzyloxy-4-methoxymethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid isopropyl ester in 150 ml of methylene chloride, combined under argon with 3.9 ml of triethylamine, and cooled to -15°C. At this temperature, a solution of 3.2 ml (25.6 mmol) of t-butyl hypochlorite in 50 ml of methylene chloride is added dropwise without delay to this solution. After the adding step is completed, the mixture is stirred for another 10 min, combined with 2.6 ml of triethylamine, and agitated for 2 hours at room temperature. Subsequently, the mixture is concentrated to one-half thereof and extracted once by shaking with dilute ammonia solution. The organic phase is dried, filtered, and concentrated. The residue is chromatographed over silica gel with methylene chloride:acetone=4:1 as the eluent. Recrystallization from ethyl acetate gives 1.1 g (35% yield) of 6-benzyloxy-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester, m.p. 150-151°C.

References

Biere H., Huth A., Rahtz D. et al.; US Patent No. 5,414,002; May 9, 1995; Assigned to Schering Aktiengesellschaft, Berlin and Bergkamen, Germany

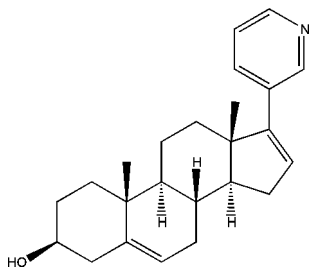
ABIRATERONE

Therapeutic Function: Antiandrogen

Chemical Name: Androsta-5,16-dien-3-ol, 17-(3-pyridinyl)-, (3β)-

Common Name: Abiraterone; CB 7598; Piraterone

Structural Formula:



Chemical Abstracts Registry No.: 154229-19-3

Trade Name	Manufacturer	Country	Year Introduced
Abiraterone	Cougar	-	-

Raw Materials

Diethyl(3-pyridyl)borane
3β-Acetoxyandrosta-5,16-dien-17-yl trifluoromethanesulphonate
Bis(triphenylphosphine)palladium(II) chloride
Sodium carbonate
Sodium hydroxide
Hydrochloric acid

Manufacturing Proces

Diethyl(3-pyridyl)borane (3.38 g, 23 mmol) from Aldrich Chemical Co. Ltd. was added to a stirred solution of 3β-acetoxyandrosta-5,16-dien-17-yl trifluoromethanesulphonate (6.94 g, 15 mmol) in THF (75 ml) containing bis(triphenylphosphine)palladium(II) chloride (0.105 g, 0.15 mmol). An aqueous solution of sodium carbonate (2 M, 30 ml) was then added and the mixture heated, with stirring, by an oil bath at 80°C for 1 h, and allowed to cool. The mixture was partitioned between diethyl ether and water, the ether phase was dried (Na_2CO_3), filtered through a short plug of silica, and concentrated. Chromatography, on elution with light petroleum-diethyl ether (2:1), afforded the 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene (4.95 g, 84%) which crystallised from hexane, m.p. 144-145°C.

To a solution of 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene (4.90 g, 12.5 mmol) in methanol (50 ml) was added an aqueous solution of sodium hydroxide (10% w/v, 10 ml) and the mixture heated, with stirring, on an oil bath at 80°C for 5 min, then allowed to cool. The mixture was poured into water, neutralised with hydrochloric acid (1 M), rebasified with saturated sodium bicarbonate solution, and extracted with hot toluene. The toluene extracts were combined, dried (Na_2CO_3), and concentrated. Chromatography, on elution with toluene-diethyl ether (2:1) afforded the 17-(3-pyridyl)androsta-5,16-dien-3β-ol (3.45 g, 79%) which crystallised from toluene, m.p. 228-229°C.

References

Barrie S.E., Jarman M., Potter G.A., Hardcastle Ian R.; US Patent No. 5,604,213; Feb. 18, 1997; Assigned to British Technology Group Limited (London, GB2)

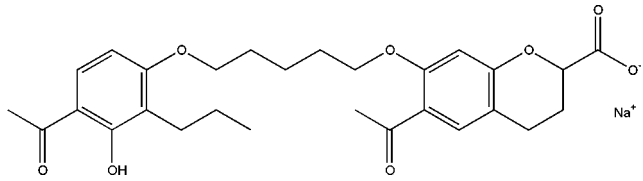
ABLUKAST SODIUM

Therapeutic Function: Antiallergic, Anti-asthmatic

Chemical Name: 2H-1-Benzopyran-2-carboxylic acid, 6-acetyl-7-[[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]oxy]-3,4-dihydro-, sodium salt

Common Name: Ablukast sodium

Structural Formula:



Chemical Abstracts Registry No.: 96565-55-8; 96566-25-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ulpax	Roche	-	-

Raw Materials

Diethyl oxalate	2',4'-Dihydroxyacetophenone
Sodium ethylate	Hydrochloric acid
Palladium on charcoal	Hydrogen
4-Toluenesulfonic acid	Boron trifluoride diethyl etherate
5-Bromo-1-pentanyl acetate	Tetrabutylammonium hydroxide
Acetic acid	Triethylamine
Methanesulfonyl chloride	Tris(3,6-dioxahepyl)amine
Sodium hydroxide	

Manufacturing Process

A solution of 109.8 g (0.75 mol) of diethyl oxalate and 65 g (0.427 mol) of 2',4'-dihydroxyacetophenone in 100 mL of EtOH was added slowly under Ar, with cooling, to a stirred solution of NaOEt (from 40 g of Na and 550 mL of EtOH). The mixture was stirred at 50°C for 3 h, cooled to room temperature, and poured into a separatory funnel containing 500 mL of 2 N HCl. It was extracted with CH_2CH_2 washed with 500 mL of saturated $NaHCO_3$, dried and evaporated to give a red oil, which was dissolved in 250 mL of EtOH and 10 mL of conc. HCl. The mixture was boiled under reflux for 1 h, cooled to ca. 10°C and the product was collected by filtration. It was washed with some EtOH followed by hexane to give 86.0 g (86% yield) of ethyl 7-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylate: m.p. 218-223°C. Crystallization of a portion from hot AcOH gave an analytical sample: m.p. 221-223°C.

A solution of 80 g (0.34 mol) of ethyl 7-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylate in 60 mL of AcOH and 275 mL of THF was hydrogenated over 4.0 g of 10% Pd on charcoal at 45°C and 65 psi. After hydrogen absorption ceased, the catalyst was removed by filtration and the solvents were evaporated under reduced pressure. Crystallization from CCl4 gave 65 g (85%) of ethyl (R,S)-3,4-dihydro-7-hydroxy-2H-1-benzopyran-2-carboxylate: m.p. 80-82°C.

A stirred mixture of 65 g (0.293 mol) of ethyl (R,S)-3,4-dihydro-7-hydroxy-2H-1-benzopyran-2-carboxylate in 650 mL of AcOH, 1.5 mL of acetic anhydride, and 65 mL of $BF_3{\cdot}OEt_2$ was heated at reflux for 18 h and evaporated. To the residue was added 700 mL of water, and the mixture was stirred at room temperature for 1.0 h. The product was collected by filtration

and washed with hexane. It was then dissolved in 900 mL of MeOH, treated with 6.6 g of p-toluenesulfonic acid, boiled under reflux for 18 h, and cooled to 0°C. The product was collected by filtration to give 52 g (70% yield) of ethyl (R,S)-3,4-dihydro-7-hydroxy-2H-1-benzopyran-2-carboxylate: m.p. 140-142°C.

A 1 L, 3-necked, round-bottomed flask equipped with a mechanical stirrer and an Ar bubbler was charged with 37.5 g (0.179 moles) of 5-bromo-1-pentanyl acetate, 350 mL of anhyd. DMSO, 40.7 g (0.163 mol) of ethyl (R,S)-3,4-dihydro-7-hydroxy-2H-1-benzopyran-2-carboxylate, and 51.0 g (0.369 mol) of powdered potassium carbonate. The mixture was stirred at room temperature for 18 h, poured into 1.0 L of water and extracted into EtOAc (2*1 L). The extract was washed with 1 L of brine, dried and evaporated. The residue was dissolved in 200 mL of ether, cooled to 57°C and, with stirring, diluted with petroleum ether. The product was collected by filtration, washed with a little 1:1 ether-petroleum ether (b.p. 40-60°C) and dried to give 60.0 g (97%) of methyl (R,S)-6-acetyl-3,4-dihydro-7-((5-acetoxypentyl)oxy-2H-1-benzopyran-2-carboxylate: m.p.51-53°C.

A solution of 72.08 g (0.19 mol) of 5-bromo-1-pentanyl acetate in 1.4 L of MeOH was treated with 38 mL of a 1.0 molar solution of tetrabutylammonium hydroxide and the mixture was stirred at room temperature for 3.0 h, 3.0 mL of AcOH was added and the solution was evaporated at 35°C. The residue was dissolved in 400 mL of EtOAc and the solution was washed with saturated $NaHCO_3$, brine, dried, and evaporated to give 60.45 g (94% yield) of the intermediate hydroxy ester (an analytical sample may be obtained by crystallization from 70% EtOAc in hexane, m.p. 58-61°C. A stirred solution of 60.25 g of the hydroxyester in 700 mL of EtOAc was cooled to 5°C and treated with 75.5 mL (3 equiv.) of triethylamine and 32.6 mL (2.35 equiv.) of methanesulfonyl chloride. The mixture was stirred at 6°C for 2.0 h, transferred to a separatory funnel and washed sequentially with water, 2 N HCl, and brine. Concentration of the EtOAc to ca. 300 mL and dilution cooled to 0°C and treated with 75.5 mL (3 equiv.) of triethylamine and 32.6 mL (2.35 equiv.) of methanesulfonyl chloride. The mixture was stirred at 6°C for 2.0 h transferred to a separatory funnel and washed sequentially with water, 2 N HCl, and brine. Concentration of the EtOAc to ca. 300 mL and dilution with 250 mL of hexane led to crystallization (0°C, 18 h). The product was collected by filtration and washed with some cold hexane - EtOAc (1:1) to give 66 g (84% yield) of methyl (R,S)-6-acetyl-3,4-dihydro-7-[5-[(methylsufonyl)oxy]pentyloxy]-2H-1-benzopyran-2-carboxylate: m.p. 73-76°C.

A mixture of 66.13 g (0.159 mol) of methyl (R,S)-6-acetyl-3,4-dihydro-7-[5-[(methylsufonyl)oxy]pentyloxy]-2H-1-benzopyran-2-carboxylate, 30.99 g (0.159 mol) of 1-[2,4-dihydroxy-3-propylphenyl)ethanone, 33.07 g (0.239 mol) of pulverized potassium carbonate, 5.16 g (15.9 mmol) of tris(3,6-dioxahepyl)amine in 900 mL of toluene was stirred under Ar at reflux for 6 h and then at room temperature overnight. The mixture was poured into 300 mL of water and the organic phase was separated, washed with brine, dried and evaporated to give 84.3 g of methyl (R,S)-6-acetyl-7-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxilate. Crystallization from MeOH (0°C, 18 h) gave 66 g (81% yield), m.p. 77-80°C.

A stirred solution of 55.82 g (0.109 mol) of methyl (R,S)-6-acetyl-7-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylate in 725 mL of MeOH was treated with 4.45 g (0.111 mol) of NaOH in 20 mL of water and the mixture was stirred at reflux for 1.25 h. It was cooled, concentrated to a volume of ca 360 mL, diluted with 310 mL of ether and left at 0°C overnight. The product was collected by filtration, dried in to give 45.76 g of (R,S)-6-acetyl-7-[[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]oxy]-3,4-dihydro-2H-H-benzopyran-2-carboxylic acid sodium salt (Ablukast) as the monohydrate. A further 12.27 g of product was obtained from the mother liquor to give a total yield of 99%.

References

Manchand P.S., Micheli R.A., Saposnik S.J.; Tetrahedron; 1992; 48, 43, 9391

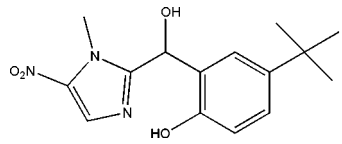
ABUNIDAZOLE

Therapeutic Function: Antiprotozoal

Chemical Name: α-[5-(1,1-Dimethylethyl)-2-hydroxyphenyl]-1-methyl-5-nitro-1H-imidazole-2-methanol

Common Name: Abunidazole; PN 4478846

Structural Formula:



Chemical Abstracts Registry No.: 91017-58-2

Trade Name	Manufacturer	Country	Year Introduced
Abunidazole	ZYF Pharm Chemical	-	-

Raw Materials

p-tert-Butylphenol
Hydrogen chloride
Ethylmagnesium bromide
1-Methyl-5-nitroimidazolyl-2-carboxyaldehyde

Manufacturing Process

150.0 g (1 mol) of p-tert-butylphenol are dissolved in 1200 ml of anhydrous ethyl ether and the thus obtained solution is added to a 10% solution of ethylmagnesium bromide in 1000 ml of anhydrous ether, at room temperature, under stirring.

After having evaporated the ether, 1000 ml of anhydrous benzene are added

and the mixture is distilled, at normal pressure, until its volume is about 2/3 of the original volume. After cooling at room temperature, 1 mol of 1-methyl-5-nitroimidazolyl-2-carboxyaldehyde in 1000 ml of anhydrous benzene is added.

The whole is boiled for 1 h, is cooled to about 10°C and is added with 8% HCl to adjust the pH to 7. Benzene layer is dried and concentrated up to 2/3 of the volume. The 2-(1-methyl-5-nitro)imidazolyl-1-(2-hydroxy-5-tert-butylphenylcarbinol is allowed to crystallize, melting point 158°-160°C; yield 0-60%.

References

Tessitore P.T.; US Patent No. 4,478,846; Oct. 23, 1984

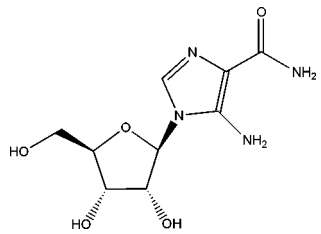
ACADESINE

Therapeutic Function: Cardiotonic, Platelet aggregation inhibitor

Chemical Name: 1H-Imidazole-4-carboxamide, 5-amino-1β-D-ribofuranosyl-

Common Name: Acadesine; AICA riboside; Arasine

Structural Formula:



Chemical Abstracts Registry No.: 2627-69-2

Trade Name	Manufacturer	Country	Year Introduced
AICA	BIOMOL	-	-

Raw Materials

Sodium hydroxide
Methyl iodide
Formic acid
Hydrogen
Ammonium hydroxide
Adenosine 3', 5'-cyclic phosphate N'-oxide
Sodium bicarbonate
Nickel
1,5-Diazabicyclo[5.4.0]undec-5-ene

Manufacturing Process

Adenosine 3', 5'-cyclic phosphate N'-oxide (76.0 g, 0.200 mole) as the

dihydrate was dissolved in a solution of 400 ml DMSO and 31.0 g (0.204 mole) 1,5-diazabicyclo[5.4.0]undec-5-ene. The solution was cooled to 15°C and 40 ml methyl iodide was added with stirring at room temperature. After 30 min, the mixture had gelled; 1.5 L ethanol was added and the solid was thoroughly homogenized by vigorous stirring. The solid was filtered, and the resulting paste was resuspended in 2 L ethanol and homogenized. The product was again filtered, washed with ethanol and ether, and dried, giving 80.4 g of 1-methoxyadenosine 3',5'-cyclic phosphate suitable for further transformation (recrystallization from aqueous methanol with ether).

A solution of 30.0 g 1-methoxyadenosine 3',5'-cyclic phosphate (81.5 mmole), 20.0 g $NaHCO_3$ (238 mmole), and 300 ml H_2O was refluxed 45 mm. The pH of the solution was adjusted to 2.5 with Dowex 50x8 $(H)^+$ while warm, and a water pump vacuum was applied to mixture to remove CO_2. The pH was readjusted to 9-10 with NaOH, and the resin was removed by filtration. The solution was passed onto a column containing 400 ml Dowex 1x2 (formate, 100-200 mesh), and the column was washed well with water. The column was eluted with a gradient of 4 L water in the mixing chamber and 4 L 4 N formic acid in the reservoir. The first major product, coming after about 2 L eluate, was 5-amino-N-methoxy-1-β-D-ribofuranosylimidazole-4-carboxamidine 3',5'-cyclic phosphate, giving 5.4 g (19%) after evaporation of the solvent and trituration of the residue with ethanol (recrystallization from water).

A solution of 5.0 g (14.3 mmoles) 5-amino-N-methoxy-1-β-D-ribofuranosylimidazole-4-carboxamidine 3',5'-cyclic phosphate in 200 ml H_2 preheated to 60°C and containing approximately 5.0 g moist sponge nickel catalyst, was shaken with 2-3 atm. H_2 at 60°C for 2 h. The filtered solution was evaporated to dryness to give 3.75 g of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamidine 3',5'-cyclic phosphate (82%), (recrystallization from water).

A mixture of 4.0 g (12.5 mmole) 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamidine 3',5'-cyclic phosphate and 100 ml conc. NH_4OH was heated in a bomb at 100°C for 16 h, then cooled and evaporated in vacuum. The residue was taken up in 100 ml H_2O and applied to a 2.5x20 cm column of Dowex 1x2 (formate form, 100-200 mesh). After washing well with H_2O the column was eluted with a gradient of 1 L H_2O in the mixing chamber and 1 L 3 N formic acid in the reservoir. Fractions containing the product, appearing near the end of the elution, were evaporated. Trituration of the residue with EtOH gave 2.90 g (68%) of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide 3',5'-cyclic phosphate.

The 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide may be produced by hydrolysis of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide 3',5'-cyclic phosphate with NaOH.

References

Meyer R.B., Shuman D.A.; US Patent No. 3,919,192; Nov. 11, 1975; Assigned: ICN Pharmaceuticals, Irvine, Calif.

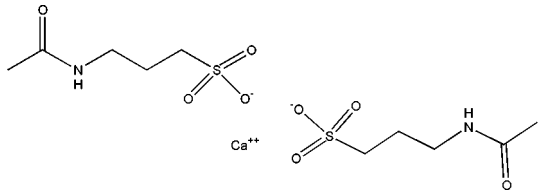
ACAMPROSATE CALCIUM

Therapeutic Function: Psychotropic

Chemical Name: 3-(Acetylamino)-1-propanesulfonic, calsium salt (2:1)

Common Name: Acamprosate; N-Acetylhomotaurine

Structural Formula:



Chemical Abstracts Registry No.: 77337-73-6; 77337-76-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Campral	Merck	-	-
Campral	Forest Pharm	-	-

Raw Materials

Sodium hydroxide	Acetic anhydride
Aminopropanesulfonic acid	Hydrochloric acid

Manufacturing Process

In a 4 liter flask provided with stirring means, a bromine funnel and a thermometer, 17.5% sodium hydroxide solution and aminopropanesulfonic acid (homotaurine) are added.

After complete dissolution, at a temperature of between 25°-40°C, acetic anhydride are added so as not to exceed a temperature of between 30°-40°C. The mixture is then maintained at this temperature by heating for at least 1 h.

The solution is then concentrated in vacuum, the residue is redissolved in 2.5 L of distilled water and the mixture is concentrated again. The residue is then dissolved in 1.6 L of distilled water, filtered, then concentrated almost completely. Drying is terminated in an oven in vacuum. A colorless crystalline powder of 3-acetylaminopropanesulfonate of sodium (sodium N-acetylhomotaurinate) is obtained.

The 3-acetylaminopropanesulfonic acid may be produced by treatment of 3-acetylaminopropanesulfonate of sodium with hydrochloric acid.

In practice it is usually used as calcium salt.

References

Durlach J.P.; US Patent No. 4,355,043; Oct. 19, 1982; Assigned: Les Laboratores Meram, France

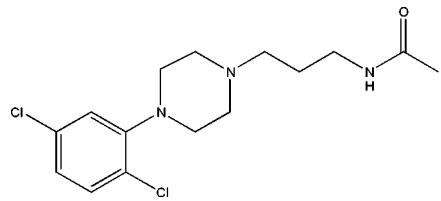
ACAPRAZINE

Therapeutic Function: Adrenergic blocker, Tranquilizer

Chemical Name: Acetamide, N-(3-(4-(2,5-dichlorophenyl)-1-piperazinyl) propyl)-

Common Name: Acaprazine

Structural Formula:



Chemical Abstracts Registry No.: 55485-20-6

Trade Name	Manufacturer	Country	Year Introduced
Acaprazine	ZYF Pharm Chemical	-	-

Raw Materials

Nickel Raney	N-(3-Chloropropyl)phthalimide
Sodium hydroxide	1-(2,5-Dichlorophenyl)piperazine
Sodium carbonate	Hydrogen chloride
Potassium phthalimide	Hydrazine hydrate
4-(m-Chloropheny1)-1-piperazinopropionitrile	1-(3-Chloropropyl)-4-(2,5-dichlorophenyl) piperazine
Acetic anhydride	Chlorosuccinimide
Triethylamine	Hydrogen

Manufacturing Process

2 methods of producing of 1-(3-acetylaminopropyl)-4-(2,5-dichlorophenyl) piperazine:

1. A mixture formed by N-(3-chloropropyl)phthalimide (23.0 g), 1-(2,5-dichlorophenyl)piperazine (24.0 g), anhydrous sodium carbonate (14.0 g) and toluene (130 ml) is boiled under stirring for 30 h. The solution is then cooled, filtered, concentrated to dryness, and the residue is treated with water and ether. The ethereal extract is washed, dried and concentrated to dryness. The

residue is treated with ethyl acetate and transformed into hydrochloride with ethanolic HCl. N-[3-[4-(2,5-Dichlorophenyl)-1-piperazinyl]propyl]phthalimide hydrochloride (30.0 g) is obtained, melting point 233°C (dec.).

N-[3-[4-(2,5-Dichlorophenyl)-1-piperazinyl]propyl]phthalimide (15.0 g) and 99% hydrazinehydrate (2 ml) are heated, under reflux, for 90 min. 5 N HCl (115 ml) is then added and the solution is heated for 30 min under reflux. The solution is cooled, filtered and concentrated to small volume. The residue is diluted with water, made alkaline by means of a solution of NaOH and extracted with CH_2Cl_2. The organic layer is dried, evaporated and distilled under reduced pressure. 7.0 g of 1-(3-aminopropyl)-4-(2,5-dichlorophenyl) piperazine are obtained.

1-(3-Aminopropyl)-4-(2,5-dichlorophenyl)piperazine (50.0 g) is dissolved in CH_2Cl_2, and the solution is heated under reflux. Acetic anhydride (25 ml) dissolved in CH_2Cl_2, (500 ml) is introduced under stirring in about 1 h. The solution is heated for 1 h and is evaporated to dryness in a rotating evaporator. The is treated with H_2O, thus obtaining a solid which is separated, washed and dried at 50°C. This solid is then dissolved in ethyl acetate (about 350 ml), treated with charcoal and crystallized. 1-(3-Acetylaminopropyl)-4-(2,5-dichlorophenyl)piperazine is obtained in an almost quantitative yield, melting point 114°C.

2. Chlorosuccinimide (5.4 g) is added to a solution of 4-(m-chlorophenyl)-1-piperazinopropionitrile (5.0 g) in CH_2Cl_2 (100 ml). The solution is heated for a few hours and, after removal of the solvent, it is chromatographed on an alumina column. The solution is eluted with a 1:1 mixture of cyclohexane and benzene containing 0.3 % of triethylamine. 4-(2,5-Dichlorophenyl)-1-piperazinopropionitrile (2.0 g) is thus obtained.

4-(2,5-Dichlorophenyl)-1-piperazinopropionitrile (20.0 g), acetic anhydride (100 ml), anhydrous sodium sulfate (12.0 g) and a 50% solution of Ni-Raney (6 ml) are hydrogenated at 60.0 pounds per inch at 60°C in a Parr apparatus. After about half an absorption of hydrogen is complete. The reaction mixture is cooled, the is filtered and the solution is concentrated to small volume in a rotating evaporator. The residue is treated with NaOH solution and extracted several times CH_2Cl_2. The organic layer is washed, dried and evaporated. The residue is crystallized from ethyl acetate. 14.0 g of the 1-(3-acetylaminopropyl)-4-(2,5-dichlorophenyl)piperazine are obtained, melting point 114°C.

References

GB Patent No. 1,443,598; July 21, 1976; Assigned: Aziende Chemiche Riunite Angelini Franceso A.C.R.A.F. S.p.A., Italy

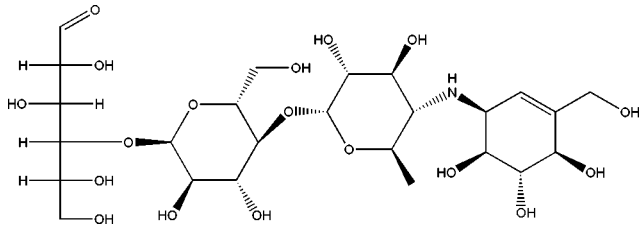
ACARBOSE

Therapeutic Function: Antidiabetic

Chemical Name: D-Glucose, O-4,6-dideoxy-4-(((1S-(1α,4α,5β,6α))-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl)amino)-α-D-glucopyranosyl-(1-4)-O-α-D-glucopyranosyl-(1-4)-

Common Name: Acarbose

Structural Formula:



Chemical Abstracts Registry No.: 56180-94-0

Trade Name	Manufacturer	Country	Year Introduced
Glicobase	Formenti	Italy	-
Glucobay	Bayer Limited	India	-
Glucor	Laboratoires Bayer Pharma	France	-
Glumida	Pensa	Spain	-
Prandase	Yno	-	-
Precose	Bayer	Germany	-
Precose	Cheshire Drugs	-	-
Precose	Allscripts	-	-
Precose	Physicians TC.	-	-

Raw Materials

Microorganisms of family *Actinoplanacease* (by fermentation)
Commercial cation exchanger based on polystyrene with a degree of crosslinking 3-4%
Solution of saccharase inhibitor
Lewatit

Manufacturing Process

The title compound was obtained from a cultural broth of fermenting a microorganism of family Actinoplanaceae in particular of strain genus Actinoplanes, according to DT-OS (German Published Specification) No. 2,347,782.

50 g of cation exchange resin (Lewatit S 1040W) in the H^+ form and 30 g an anion exchanger (Lewatit M 600) in OH form were added to 300 ml of a culture broth with mycelium content of 25% and an inhibitor content of 50 SIU/ml in solution. The mixture was stirred at room temperature for 50 minutes. The solution, containing a sieving nozzle with 0.1 mm slits. For

testing, a sample of filtered broth was centrifuged and was examined for saccharase inhibitor in the supernatant liquor. The solution contained 2.5 SIU/ml, that is to say 5%, of starting activity. This procedure improved the yield of the aminosugar from 20% in the procedure known from DT-OS (German Published Specification) No. 2,347,782, to 50-60%. It has now found that cation exchangers based on styrene, divinylbenzene and methoxymethylmethacrylamide, oxyethyl(meth)acrylic acid amide (ester), dimethylaminoethyl(meth)acrylic acid amide (ester) or oxypropyl(meth)acrylic acid amide(ester) are preferred in industrial separation procedure of acarbose. This exchanger gave a very sharp separation of the individual homologues and impurities. And it has now found the new biosynthesis of acarbose by using of gen engineering methods.

References

Rauenbusch E. et al.; US Patent No. 4,174,439, Nov. 13, 1979, Assigned: Bayer Aktiengesellschaft (Leverkusen, DE)
Lange P.M. et al.; US Patent No. 4,666,776, May 19, 1987, Assigned: Bayer Aktiengesellschaft (Leverkusen, DE)
Deutsches Patent and Markenamt, Offenlegungsschrift DE 100 21 667 A1, 8. 11.2001

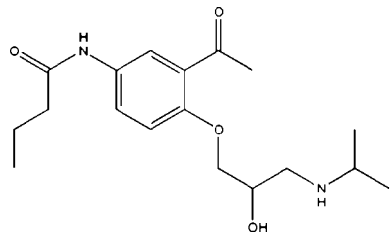
ACEBUTOLOL

Therapeutic Function: beta-Adrenergic blocker

Chemical Name: N-[3-Acetyl-4-[2-hydroxy-3-[(1-methylethyl)-amino] propoxy]phenyl]butanamide

Common Name: 5'-Butyramido-2'-(2-hydroxy-3-isopropylaminoprop-oxy)acetophenone

Structural Formula:



Chemical Abstracts Registry No.: 37517-30-9; 34381-68-5 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Sectral	May and Baker	UK	1975
Sectral	Specia	France	1976
Prent	Bayer	W. Germany	1977

Trade Name	Manufacturer	Country	Year Introduced
Neptall	Rhodia Pharma	W. Germany	1977
Sectral	May and Baker	Switz.	1980
Sectral	Roger Bellon	Italy	1980
Sectral	RBJ Pharma	Italy	1980
Acetanol	Kanebo, Ltd.	Japan	1981
Prent	Bayer	Italy	1981
Acecor	S.P.A.	Italy	-
Diasectral	Rhone Poulenc	-	-
Neptal	Rohm Pharma	-	-
Secradex	May and Baker	UK	-
Sectral	Wyeth	US	-

Raw Materials

Butyramidophenol
Aluminum chloride
Sodium ethoxide
Acetyl chloride
Epichlorohydrin
Isopropylamine

Manufacturing Process

Crude 5'-butyramido-2'-(2,3-epoxypropoxy)acetophenone (16 g), isopropylamine (20 g) and ethanol (100 ml) were heated together under reflux for 4 hours. The reaction mixture was concentrated under reduced pressure and the residual oil was dissolved in N hydrochloric acid. The acid solution was extracted with ethyl acetate, the ethyl acetate layers being discarded. The acidic solution was brought to pH 11 with 2 N aqueous sodium hydroxide solution and then extracted with chloroform. The dried chloroform extracts were concentrated under reduced pressure to give an oil which was crystallized from a mixture of ethanol and diethyl ether to give 5'-butyramido-2'-(2-hydroxy-3-isopropylaminopropoxy)acetophenone (3 g), MP 119-123°C.

Crude 5'-butyramido-2'-(2,3-epoxypropoxy)acetophenone used as starting material was prepared as follows: p-butyramidophenol (58 g; prepared according to Fierz-David and Kuster, Helv. Chim. Acta 1939,2282), acetyl chloride (25.4 g) and benzene (500 ml) were heated together under reflux until a solution formed (12 hours). This solution was cooled and treated with water. The benzene layer was separated and the aqueous layer was again extracted with benzene.

The combined benzene extracts were dried and evaporated to dryness under reduced pressure to give p-butyramidophenyl acetate (38 g) as an off-white solid, MP 102-103°C. A mixture of p-butyramidophenyl acetate (38 g), aluminum chloride (80 g) and 1,1,2,2-tetrachloroethane (250 ml) was heated at 140°C for 3 hours. The reaction mixture was cooled and treated with iced water. The tetrachloroethane layer was separated and the aqueous layer was extracted with chloroform. The combined organic layers were extracted with 2 N aqueous sodium hydroxide and the alkaline solution was acidified to pH 5 with concentrated hydrochloric acid. The acidified solution was extracted with chloroform and the chloroform extract was dried and concentrated under reduced pressure to give 5'-butyramido-2'-hydroxyacetophenone (15.6 g), MP 114-117°C. A solution of 5'-butyramido-2'-hydroxyacetophenone (15.6 g) in

ethanol (100 ml) was added to an ethanolic solution of sodium ethoxide which was prepared from sodium (1.62 g) and ethanol (100 ml). The resulting solution was evaporated to dryness under reduced pressure and dimethylformamide (100 ml) was added to the solid residue. Approximately 10 ml of dimethylformamide was removed by distillation under reduced pressure. Epichlorohydrin (25 ml) was added and the solution was heated at 100°C for 4 hours. The solution was concentrated under reduced pressure to give a residual oil which was treated with water to give a solid. The solid was dissolved in ethanol and the resulting solution was treated with charcoal, filtered and concentrated under reduced pressure to give crude 5'-butyramido-2'-(2,3-epoxypropoxy)acetophenone (16 g), MP 110-116°C.

The crude compound may be purified by recrystallization from ethyl acetate, after treatment with decolorizing charcoal, to give pure 5'-butyramido-2'-(2,3-epoxypropoxy)acetophenone, MP 136-138°C.

References

Merck Index 13
Kleeman and Engel p. 1
PDR p. 1978
OCDS Vol. 2 p. 109 (1980)
DOT 11 (7) p. 264 (1975)
I.N. p. 2
Wooldridge, K.R.H. and Basil, B.; US Patent 3,857,952; Dec. 31,1974; Assigned to May and Baker, Ltd.

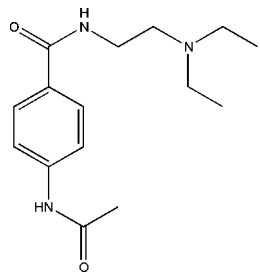
ACECAINIDE

Therapeutic Function: Antiarrhythmic

Chemical Name: Benzamide, 4-(acetylamino)-N-(2-(diethylamino)ethyl)-

Common Name: Acecainide; NAPA

Structural Formula:



Chemical Abstracts Registry No.: 32795-44-1

Trade Name	Manufacturer	Country	Year Introduced
Acecainide	ZYF Pharm Chemical	-	-

Raw Materials

Acetyl chloride
p-Amino-N-(2-diethylaminoethyl)benzamide
Sodium hydroxide

Manufacturing Process

1.0 g of p-amino-N-(2-diethylaminoethyl)benzamide is dissolved in chloroform. A few ice cubes are added to the solution. Acetyl chloride is added dropwise with stirring until no more white precipitate forms; the latter is separated by filtering under suction. The precipitate is washed with cold acetone and dried overnight in a vacuum oven at room temperature. The product is dissolved in a minimum amount of hot isopropanol and allowed to precipitate in the cold. The p-acetamido-N-(2-diethylaminoethyl)benzamide hydrochloride, is recrystallized a second time from hot isopropanol, melting point 190°-193°C.

The free base is obtained from the hydrochloride by dissolving the latter in water, adjusting the pH to greater than 10 with dilute sodium hydroxide, and adding an equal volume of benzene. After shaking in a separatory funnel, the benzene layer is recovered and evaporated to dryness. So the p-acetamido-N-(2-diethylaminoethyl)benzamide is obtained.

References

GB Patent No. 1,319,980; June 13, 1973; Assigned: E.R. Squibb and Sons, Inc., a corporation organized and existing under the laws of the State of Delaware, USA

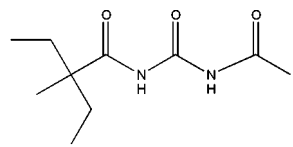
ACECARBROMAL

Therapeutic Function: Sedative, Hypnotic

Chemical Name: Butanamide, N-((acetylamino)carbonyl)-2-bromo-2-ethyl-

Common Name: Acecarbromal; Acetcarbromal; Acetylcarbromal; Sedacetyl

Structural Formula:



Chemical Abstracts Registry No.: 77-66-7

Trade Name	Manufacturer	Country	Year Introduced
Acetylcarbromal	Pfaltz and Bauer	-	-
Afrodor 2000	Farco-Pharma	-	-
Afrodor 2000	Biomenta	-	-
Paxarel	Circle Pharmaceuticals	-	-

Raw Materials

Urea
Bromine
Zinc chloride
Diethylacetic acid anhydride
Acetic anhydride

Manufacturing Process

It was mixed 120 parts of urea and 258 parts of bromodiethylacetylbromide (prepared from diethylacetic acid anhydride and bromine). After 12 hours the mixture was heated for 3 hours at 100°C. The product was mixed with an aqueous solution of sodium bicarbonate and then was filtered. The obtained bromodiethylacetylurea was crystallized from diluted ethanol; melting point 114-118°C. The mixture of 474 parts of bromodiethylacetylurea, 1000 parts of acetic anhydride and 75 parts $ZnCl_2$ was heated at 60°C for 1 hour. The product was stirred with 3000 parts of ice-water and then 1-acetyl-3-(α-bromo-α-ethylbutyryl)urea was filtered; melting point 108-109°C.

References

Merck Index, Monograph number: 18, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
DE Patent 286,760, 1913; Bayer and Co. In Elberfeld
DE Patent 327,129, 1917; Bayer and Co., Leverkusen

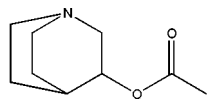
ACECLIDINE

Therapeutic Function: Miotic, Cholinomimetic

Chemical Name: 1-Azabicyclo[2.2.2]octan-3-ol acetate

Common Name: 3-Quinuclidinol acetate

Structural Formula:



Chemical Abstracts Registry No.: 827-61-2; 6109-70-2 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Glacostat	MSD-Chibret	France	1966
Glaunorm	Farmigea	Italy	1969
Glaudin	Sifi	Italy	-

Raw Materials

Methyl isonicotinate
Ethyl bromoacetate
Potassium
Hydrogen

Manufacturing Process

A mixture of 274 g of methyl isonicotinate, 367 g of ethyl bromoacetate and 125 cc of ethyl alcohol was stirred without heating for 4 hours in a flask equipped with a reflux condenser. (The reaction was exothermic and precautions were taken to keep the temperature below 70°C.) The reaction mixture was then left for 15 hours at room temperature.

The reaction product (1-carbethoxymethyl-4-carbornethoxy-pyridinium bromide) was obtained in crystalline form. (It formed prisms melting at 166-169°C after recrystallization from a mixture of isopropanol and acetone.) It was not necessary to isolate it. For the following reduction step, the reaction mixture was brought into solution by the addition of about 1 liter of warm ethyl alcohol. It was then hydrogenated at about 30 atm pressure in the presence of 2 g of platinum oxide. The temperature rose during this reaction to about 40°C. After the calculated amount of hydrogen had been absorbed, the catalyst was filtered off, the solution was concentrated in vacuum, and the residual syrup was dissolved in ice water. Benzene was added and the mixture was made alkaline with an excess of concentrated ice cold potassium carbonate solution. The temperature was kept low by continuous addition of ice, and the benzene layer was separated and dried with sodium sulfate. The dried benzene solution was concentrated in vacuum and the residual oil was distilled in vacuum. BP 30 mm = 175-182°C, n_D^{25}= 1.4613-1.4628. During the reduction, partial alcoholysis occurred, and the product isolated was 1-carbethoxymethyl-4-"carbalkoxy"-piperidine, wherein "carbalkoxy" represents a mixture of carbomethoxy and carbethoxy.

100 g of potassium were pulverized in 200 cc of hot toluene in a heated three-neck flask equipped with an efficient condenser, stirrer and dropping funnel. To the refluxing potassium suspension were added in small portions 229 g of the product of the previous step and about 700 cc of toluene. This addition had to be carried out very cautiously; the onset of the exothermic reaction is sometimes delayed. The addition was finished in about 1 hour. To complete the reaction, the refluxing and stirring were continued for about 4 hours. The reaction mixture was then cooled to about +5°C and about 50 cc isopropanol were added to decompose unreacted potassium. Then 2.5 liters of concentrated hydrochloric acid were added and the mixture was refluxed for 15 hours, and then concentrated in vacuum to dryness. To the residue was added with cooling an excess of 50% potassium hydroxide. Ether was then added and the resulting mixture was filtered through a fritted glass funnel, thus removing the precipitated potassium chloride. The ethereal and aqueous layers were separated, and the aqueous layer was extracted repeatedly with 500 cc portions of ether. The organic solutions were combined, dried over

sodium sulfate and concentrated in vacuum. Aqueous hydrochloric acid was added to the residue until the solution became acid. The mixture was then diluted with distilled water to about 300 cc, heated with decolorizing charcoal, filtered and concentrated in vacuum to dryness. The residue was treated with isopropanol, and the precipitated crystalline product was filtered off. The product was recrystallized from a mixture of water and isopropanol and was identified as 1-azabicyclo[2.2.2]-3-octanone hydrochloride; prisms, MP 311-313°C, with decomposition.

A solution of 50 g of the above ketone-hydrochloride in 30 cc of water was made alkaline by the addition of 30 g of potassium hydroxide. After the alkali was dissolved, 35 g of granular potassium carbonate were added. The free basic ketone was then extracted from the viscous mixture by shaking with 4 portions of hot benzene (300 cc in each portion). The benzene extracts were decanted, filtered over sodium sulfate in order to remove any suspended alkali, and concentrated in vacuum. The residual lszabicyclo[2.2.2]-3-octanone was purified by sublimation (50-70°C/0.5 mm Hg); it can also be purified by recrystallization from petroleum ether. It formed feathery crystals melting at 147-148°C.

The product was reduced as follows:

A solution of 50 g of 1-azabicyclo[2.2.2]-3-octanone hydrochloride in 200 cc of water was hydrogenated at room temperature and 50 atm pressure with 1 g of platinum oxide as catalyst. After the calculated amount of hydrogen had been absorbed, the mixture was filtered and concentrated in vacuum to dryness. The residual product was recrystallized from a mixture of methanol and acetone and formed prisms melting above 300°C. It was identified as 1-azabicyclo[2.2.2]-3-octanol hydrochloride.

A solution of 50 g of 1-azabicyclo[2.2.2]-3-octanol hydrochloride in 30 cc water was made alkaline with 30 g of potassium hydroxide. After the alkali was dissolved 35 g of granular potassium carbonate were added. The free basic alcohol was then extracted from the viscous mixture by shaking with four portions of boiling benzene (300 cc in each portion). The benzene extracts were decanted and filtered over anhydrous sodium sulfate, to remove any suspended alkali. The combined benzene solutions were concentrated in vacuum. The residue was recrystallized from benzene and identified as lszabicyclo[2.2.2]-3-octanol, MP 221-223°C. The product can also be purified by recrystallization from acetone, or by sublimation in vacuum (120°C/20 mm Hg). The alcohol was reacted with acetic anhydride to give the product aceclidine.

References

Kleeman and Engel p. 2
OCDS Vol. 2 p. 295 (1980)
I.N. p. 2
Sternbach, L.H.; US.Patent 2,648,667; Aug. 11,1953; Assigned to Hoffman - La Roche Inc.

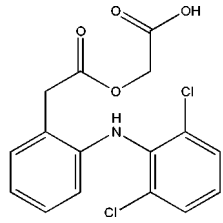
ACECLOFENAC

Therapeutic Function: Analgesic, Antiinflammatory

Chemical Name: Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, carboxymethyl ester

Common Name: Aceclofenac; Locomin

Structural Formula:



Chemical Abstracts Registry No.: 89796-99-6

Trade Name	Manufacturer	Country	Year Introduced
Reservix	Incepta	-	-
Aceclofenac	Xian HaiXin pharmaceutical Co., Ltd.	-	-
Airtal	Almirall	-	-
Kafenac	Almirall	-	-
Zurem	ABIOGEN PHARMA srl	-	-
Beofenac	Almirall	-	-
Bristaflam	Egypt Company Co.	-	-
Bristaflam	BMS Co.	-	-
Berlofen	Elea	-	-
Bristaflam	Bristol	-	-
Biofenac	UCB	-	-
Biofenac	BERAGENA	-	-
Biofenac	EMRA-MED ARZNEIM	-	-
Locomin	UCB	-	-
Proflam	Eurofarma	-	-

Raw Materials

Benzyl bromoacetate Sodium 2-[(2,6-dichlorphenyl)amino]phenylacetate Palladium on carbon Hydrogen

Manufacturing Process

50 g of sodium 2-[(2,6-dichlorphenyl)amino]phenylacetate were dissolved in 300 ml of N,N-dimethylformamide under heating to 50°C, and 44.22 g of benzyl bromoacetate were added thereto. Under these condition stirring was

continued for 9 hours. Upon completion of the reaction, the solvent was removed at reduced pressure, and the sodium salt were precipitated with addition of 400 ml of ether. The solution was then filtered and the ether phase was washed twice time with 100 ml of hexane. The resulting product was crystallized from the hexane/ether and then from acetone/chloroform (1:9) thus obtaining 44.1 g (61%) of benzyl 2-[(2,6-dichlorphenyl)amino]phenylacetoxyacetate in the form of white crystals having a melting point of 67-69°C.

45.28 g of benzyl 2-[(2,6-dichlorphenyl)amino]phenylacetoxyacetate were dissolved in 1500 ml of ethyl acetate, and the resulting solution was mixed with 7 g of Pd/C 10% and then hydrogen ted at atmospheric pressure for 14 hours. The solution was filtered, concentrated and crystallized; thereby obtaining 23.51 g (65%) of 2-[(2,6-dichlorphenyl)amino]phenylacetoxyacetic acid; melting point 149-150°C.

References

Casas A.V.; US Patent No. 4,548,952; Oct. 22, 1985; Assigned to Prodes, S.A., San Justo Desvern, Spain

Schickaneder H., Nikolopoulos A., Murphy T.; WO Patent No. 9,955,660; 1999-11-04; Assigned to Russinsky Ltd (IE), Schickaneder Helmut (IE), Nikolopoulos Aggelos (IE), Murphy Trevor (IE)

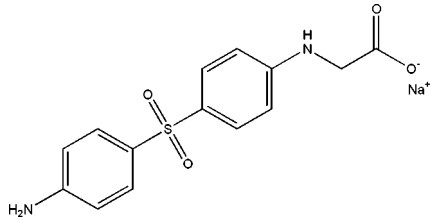
ACEDIASULFONE SODIUM

Therapeutic Function: Antibacterial

Chemical Name: N-p-Sulfanilylphenylglycine sodium

Common Name: Acediasulfone sodium; Glycinodiasulfone sodium

Structural Formula:



Chemical Abstracts Registry No.: 127-60-6; 80-03-5 (Base)

Raw Materials

Methyl chloroacetate
Lithium hydroxide
Sodium hydroxide
4,4'-Diaminodiphenyl sulfone
Hydrochloric acid

Trade Name	Manufacturer	Country	Year Introduced
Solfone	Bracco	-	-

Manufacturing Process

24.8 g of 4,4'-diaminodiphenyl sulfone, 150 g of methyl chloroacetate and 150 ml of ethanol are refluxed together and refluxed for 24 hours. The alcohol and excess methyl chloroacetate are then distilled off on a steam bath under reduced pressure. The residue consisting of the hydrochloride salt of 4-amino-4'-(carbomethoxymethylamino)diphenyl sulfone is mixed with of alcoholic solution containing 2.5 g lithium hydroxide and refluxed for 4 hours on the steam bath. Most of the alcohol is removed by distillation and the residual lithium salt of 4-amino-4'-(carboxymethylamino)diphenyl sulfone taken up water. The solution is filtered and dilute HCl added until no more separation occurs. The 4-amino-4'-(carboxymethylamino)diphenyl sulfone thus obtained is collected and dried.

The sodium salt of 4-amino-4'-(carboxymethylamino)diphenyl sulfone is prepared by dissolving the free acid in an aqueous solution containing one equivalent of sodium hydroxide and evaporating the solution to dryness in vacuo.

References

Merck Index, Monograph number: 21, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Rawlins A.L.; US Patent No. 2,589,211; Mar. 18, 1952; Assigned to Parke, Devis and Co., Detroit, Michigan
Martin H., Habicht E.; US Patent No. 2,751,382; June 19, 1956; Assigned to Cilag Ltd., Schaffhausen, Switzerland

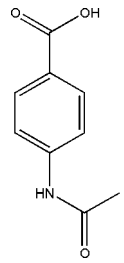
ACEDOBEN

Therapeutic Function: Antiviral

Chemical Name: Benzoic acid, p-acetamido-

Common Name: Acedoben

Structural Formula:



Chemical Abstracts Registry No.: 556-08-1

Trade Name	Manufacturer	Country	Year Introduced
4-Acetamidobenzoic acid	ARIAC	-	-
p-Acetamidobenzoic Acid	Chembay Chemical Co., LTD	-	-
p-Acetamidobenzoic Acid	Sigma-Aldrich	-	-

Raw Materials

Magnesium sulfate
N-p-Tolylacetamide
Hydrochloric acid
Sodium acetate
Potassium permanganate

Manufacturing Process

Into a 2 L, 3-necked flask set in a tub and equipped with a stirrer, an air condenser (drying tube), thermometer, was placed 860 ml of water, 43.0 g of $MgSO_4$ and 43.0 g of sodium acetate and heated on water bath. Into heated solution to 70°C stirring 43.0 g of N-p-tolylacetamide were added. Then 136.0 g of $KMnO_4$ by small portions were added at 75°-80°C. The reaction mixture allow to stand for 6 h and stirring was continue till the solution became colorless. Hot solution was filtered and filtrate treated hydrochloric acid to slightly acidic pH. After that 44.0 g (85%) of p-acetoaminobenzoic acid was obtained as white precipitate, melting point 250°C.

References

Berkengame A.M.; Chemistry and Technology of synthetic drugs; 1935; Moscow

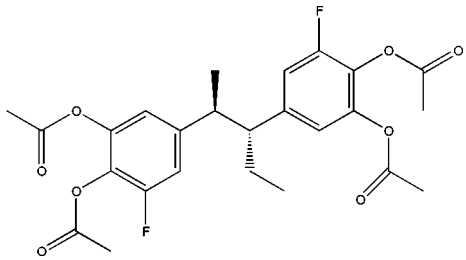
ACEFLURANOL

Therapeutic Function: Antiestrogen

Chemical Name: (1RS,2SR)-4,4'-(1-Ethyl-2-methyl-1,2-ethanediyl)bis[6-fluoro-1,2-benzenediol] tetraacetate

Common Name: Acefluranol; BX 591

Structural Formula:



Chemical Abstracts Registry No.: 80595-73-9

Trade Name	Manufacturer	Country	Year Introduced
Acefluranol	ZYF Pharm Chemical	-	-

Raw Materials

erythro-3,3'-Difluoro-4,4'-dihydroxy-α-ethyl-α'-methylbibenzyl
Pyridine
Acetic anhydride
Aluminum chloride
Sodium hydroxide
Hydrogen peroxide
Sodium borohydride
Hydrochloric acid

Manufacturing Process

4.5 g erythro-3,3'-difluoro-4,4'-dihydroxy-α-ethyl-α'-methylbibenzyl in 30 ml pyridine and 10 ml acetic anhydride were left to stand for 24 h at room temperature, thereafter the reaction mixture was worked up to give a crude product, recrystallisation of which from chloroform-diethyl ether (1:4 v/v) gave 5.5 g erythro-3,3'-difluoro-4,4'-diacetoxy-α-ethyl-α'-methylbibenzyl, melting point 118°-120°C.

5.0 g of the erythro-3,3'-difluoro-4,4'-diacetoxy-α-ethyl-α'-methylbibenzyl were ground with 10.0 g aluminum chloride and the mixture was heated at 150°C for 30 min. After cooling, the mass was added portion-wise to ice, stirred and extracted with chloroform. The chloroform solution was washed with water, dried with anhydrous sodium sulfate and concentrated to half its volume. An equal volume of diethyl ether was added thereto and the solution was treated with charcoal and filtered. The filtrate was evaporated and the residue obtained was crystallized from chloroform-diethyl ether (1:1 v/v) to give 2.6 g erythro-3,3'-diacetyl-4,4'-dihydroxy-5,5'-difluoro-α-ethyl-α'-methylbibenzyl, melting point 194°-196°C.

0.9 g erythro-3,3'-diacetyl-4,4'-dihydroxy-5,5'-difluoro-α-ethyl-α'-methylbibenzyl were suspended in a mixture of 10 ml dioxan and 6 ml 1 N aqueous sodium hydroxide solution. The solution was cooled to 10°C and 0.8 ml 30% hydrogen peroxide added dropwise thereto. The reaction mixture was stirred at 20°C for 1.5 h and then poured into a mixture of dilute hydrochloric acid and ice. The product was extracted with peroxide-free diethyl ether, the extract was evaporated and the residue was crystallized from benzene to give a yellow solid. This was treated in 5 ml ethanol with 2.0 mg sodium borohydride, followed by acidification with hydrochloric acid, rapid extraction with diethyl ether, evaporation of the extract and immediate crystallization from benzene to give 350.0 mg of pure erythro-4,4',5,5'-tetrahydroxy-3,3'-difluoro-α-ethyl-α'-methyldibenzyl, melting point 143°-145°C.

1.0 g erythro-3,3'-difluoro-4,4',5,5'-tetrahydroxy-α-ethyl-α'-methyldibenzyl in a mixture of 10 ml pyridine and 5 ml acetic anhydride was left to stand at 20°C for 20 h and at 60°-80°C for 1 h. The reaction mixture was then poured into a mixture of dilute hydrochloric acid and ice, stirred for several h and filtered. The filtrate was evaporated and the residue was taken up in

chloroform and the chloroform solution was washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulfate and the solvent removed. The gummy residue was taken up with benzene and the benzene solution filtered through a neutral alumina. The benzene was removed from the filtrate to give 1.0 g pure erythro-3,3'-difluoro-4,4',5,5'-tetraacetoxy-α-ethyl-α'-methyldibenzyl; melting point 160°-162°C (crystallised from diethyl ether).

References

Chan R.P.K.; US Patent No. 4,427,697; Jan. 24, 1984; Assigned: Biorex Laboratories Limited, England

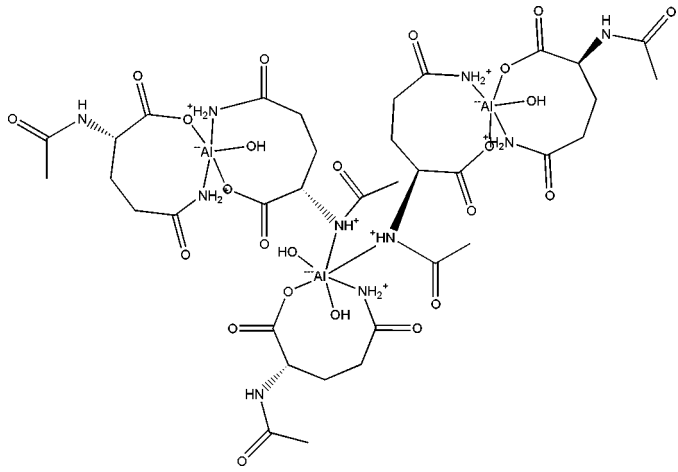
ACEGLUTAMIDE ALUMINUM

Therapeutic Function: Antiulcer

Chemical Name: Pentakis(N^2-acetyl-L-glutaminato)tetrahydroxytrialuminum

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 12607-92-0

Trade Name	Manufacturer	Country	Year Introduced
Glumal	Kyowa Hakko	Japan	1978
Glumal	Liade	Spain	-

Raw Materials

N-Acetyl-L-glutamine
Aluminum isopropoxide

Manufacturing Process

A mixture of 37.6 g of N-acetyl-L-glutamine and 1,000 ml of water is heated to 40°C, and 900 ml of an isopropanol solution containing 40.8 g of aluminum isopropoxide is added to the warm mixture with stirring. The stirring is continued for 10 minutes. The reaction mixture is filtered and the filtrate is concentrated under reduced pressure. Isopropanol is added to the aqueous solution and the salt precipitates in the solution. The precipitates are collected by filtration and upon drying, 48.5 g of the crystalline-like aluminum salt of N-acetyl-L-glutamine are obtained.

References

Merck Index 20
Kleeman and Engel p. 32
DOT 14 (2) p. 54 (1978)
I.N. p. 3
Kagawa, T., Fuji, K., Tanaka, M. and Tanaka, H.; US Patent 3,787,466; Jan. 22,1974; Assigned to Kyowa Hakko Kogyo Co., Ltd.

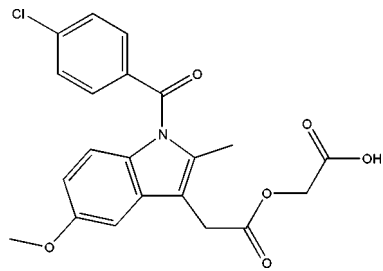
ACEMETACIN

Therapeutic Function: Antiinflammatory

Chemical Name: 1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetoxyacetic acid

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53164-05-9

Trade Name	Manufacturer	Country	Year Introduced
Rantudil	Bayer	W. Germany	1980
Rantudil	Tropon	W. Germany	-

Raw Materials

N-(p-Methoxybenzyl)-p-chlorobenzhydrazide HCl
Benzyl levulinoyloxyacetate
Hydrogen

Manufacturing Process

25.4 g (0.050 mol) of [1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetoxy]-benzyl acetate were dissolved in 400 ml of glacial acetic acid and hydrogenated on 2.0 g of palladium carbon at room temperature. After the absorption of hydrogen had finished (1 hour), the catalyst was filtered off, the filtrate was concentrated by evaporation under vacuum and the compound was caused to crystallize by adding petroleum ether. The compound melted at 149.5-150.5°C (determined on the micro-Kofler bench); the yield was 19.4 g which corresponds to 93% of the theoretical yield.

The starting material for the above step may be prepared as follows: 5 g (0.016 mol) of N^1-(p-methoxyphenyl)-p-chlorobenzhydrazide hydrochloride and 4.75 g (0.018 mol) of benzyl levulinoyloxyacetate were heated in 25 ml of glacial acetic acid for 3 hours at 80°C. The solvent was then evaporated off under vacuum. The residue was taken up in chloroform and the solution was washed neutral by shaking with sodium bicarbonate solution and thereafter with water. After drying the chloroform solution, this was subjected to chromatography on aluminium oxide, the eluate was concentrated by evaporation and the viscous oil remaining as residue was crystallized by adding ether. The compound melted at 94-95°C. The yield was 4.1 g which corresponds to 50.7% of the theoretical yield.

References

Merck Index 21
DFU 2 (7) p.423 (1977)
Kleeman and Engel p. 3
DOT 17 (7) p.279 (1981)
I.N. p. 3
Boltze, K.H., Brendler, O., Dell, H.D. and Jacobi, H.; US Patent 3,910,952; October 7,1945; Assigned to Tropenwerke Dinklage and Co.
Boltze, K.H., Brendler,O., Dell, H.D. and Jacobi, H.; US Patent 3,966,956; June 29,1976; Assigned to Tropenwerke Dinklage and Co.

ACENOCOUMAROL

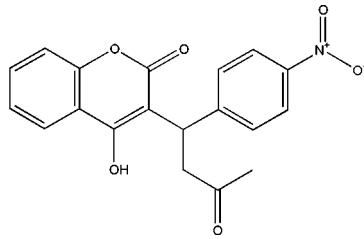
Therapeutic Function: Anticoagulant, Vitamin

Chemical Name: 3-(α-Acetonyl-p-nitrobenzyl)-4-hydroxycoumarin

Common Name: Nicoumalone

Chemical Abstracts Registry No.: 152-72-7

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Sintrom	Geigy	US	1957
Sintrom	Geigy	W. Germany	-
Sintrom	Ciba Geigy	Switz.	-
Sintrom	Ciba Geigy	France	1959
NeoSintrom	Geigy	-	-
Ascumar	Star	Finland	-
Syncumar	EGYT	Hungary	-
Synthrome	Geigy	UK	-
Sintrom	Ciba Geigy	Japan	-

Raw Materials

4-Hydroxycoumarin
Nitrobenzalacetone

Manufacturing Process

16 parts of 4-hydroxycoumarin and 19 parts of 4-nitrobenzalacetoneare thoroughly mixed and heated for 12-14 hours in an oil bath, the temperature of which is between 135°C and 140°C. After cooling, the melt is dissolved in a little acetone. The solution is slowly added to a lye made up from 6 parts of sodium hydroxide in 400 parts of water while stirring and then the mixture is stirred for 30 minutes. A little animal charcoal is then added, the mixture is stirred for a further 15 minutes, 400 parts of water are added and the charcoal and undissolved components are separated by filtration under suction. The clear solution is made acid to Congo red paper with hydrochloric acid and the product which is precipitated is filtered off under suction. 3-[α-(4'-Nitrophenyl)-β-acetylethyl]-4-hydroxycoumarin is obtained. MP 196-199°C.

It should be noted that the process is akin to that for Warfarin except that 4-nitrobenzalacetone replaces benzalacetone as a raw material.

References

Merck Index 23
Kleeman and Engel p. 4
OCDS Vol. 1 p. 331 (1977)
I.N. p.3
Stoll, W. and Litvan, F.; US Patent 2,648,682; August 11, 1953; Assigned to J.R. Geigy A.G., Switzerland.

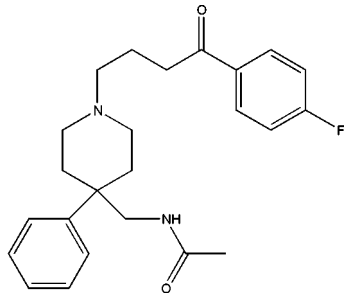
ACEPERONE

Therapeutic Function: Vasodilator, Antihypertensive, Neuroleptic

Chemical Name: Acetamide, N-((1-(4-(4-fluorophenyl)-4-oxobutyl)-4-phenyl-4-piperidinyl)methyl)-

Common Name: Aceperone; Acetabutone

Structural Formula:



Chemical Abstracts Registry No.: 807-31-8

Trade Name	Manufacturer	Country	Year Introduced
Aceperone	ZYF Pharm Chemical	-	-
Aceperone	Vasudha Pharma Chem Limited.	-	-

Raw Materials

1-Benzyl-4-(4-phenyl)-4-(acetaminomethyl)piperidine
Sodium bicarbonate
3-(4-Fluorobenzoyl)propyl bromide
Thiophenol
Sodium hydroxide

Manufacturing Process

A mixture of 1-benzyl-4-(4-phenyl)-4-(acetaminomethyl)piperidine, 3-(4-fluorobenzoyl)propyl bromide, sodium bicarbonate and anhydrous acetone was stirred and heated under reflux. The resulting mixture was filtered while still hot, and the filtrate was concentrated to dryness under reduced pressure. The residue was washed with ether to give 1-benzyl-1-[3-(4-fiuorobenzoyl)propyl]-(4-phenyl-4-acetaminomethyl)piperidinium bromide.

To a stirred mixture of thiophenol and 15% (W/W) aqueous sodium hydroxide was added the 1-benzyl-1-[3-(4-fluorobenzoyl)propyl]-(4-phenyl-4-acetaminomethyl)piperidinium bromide and the mixture was heated to 85°-90°C for 2 h. After cooling, solid matter precipitated was collected by filtration and washed with water to give 1-[3-(4-fluorobenzoyl)propyl]-4-(acetaminomethyl)-4-phenylpiperidine, melting point 111°-112°C.

References

Nakao M. et al.; US Patent No. 3,850,935; Nov. 26, 1974; Assigned: Sumitomo Chemical Company, Limited, Osaka, Japan

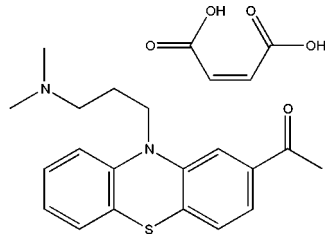
ACEPROMAZINE MALEATE

Therapeutic Function: Neuroleptic, Antiemetic

Chemical Name: Ethanone, 1-(10-(3-(dimethylamino)propyl)-10H-phenothiazin-2-yl)-, maleate (1:1)

Common Name: Acepromazine maleate; Acetopramazine maleate; Notensil

Structural Formula:



Chemical Abstracts Registry No.: 3598-37-6; 61-00-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Sedaject	Bayer Korea Co.	-	-
Anatran	Ayerst	-	-
Sedalin	Chassot	-	-

Raw Materials

3-Acetylphenothiazine
Phosgene
γ-Dimethylaminopropyl alcohol

Manufacturing Process

120 g 3-acetylphenothiazine (0.479 mol) are heated to the boil in 1.2 L xylene and a rapid stream of phosgene then passed in for a period of 12 hours. The solvent is then removed by distillation and the residue taken up in 1 L benzene. The benzene solution is heated to the boil and 112 g of γ-dimethylaminopropyl alcohol (1.09 mol) are added within a period of 15 min and the reaction mixture boiled for a further 2 hours. After cooling, the precipitated hydrochloride of the γ-dimethylaminopropyl alcohol washed with benzene and the combined benzene solutions rapidly washed with water in order to remove excess basic alcohol. The material is dried over potash and the hydrochloride precipitated by means of ethereal hydrochloric acid. The

hydrochloride may also be precipitated by passing in gaseous hydrogen chloride. After recrystallisation from isopropanol, 157 g (78% of theory) of γ-dimethylaminopropyl 3-acetylphenothiazine-10-carboxylate are obtained. The hydrochloride melts at 212°C.

In practice it is usually used as maleate salt.

References

Hoerlein U. et al,; DE Patent No. 1,049,865; Assigned to Farbenfabriken Bayer Aktiengesellschaft, Leverkusen-Bayerwerk
GB Patent No. 808,050; Jan. 28,1959; BAYER AG

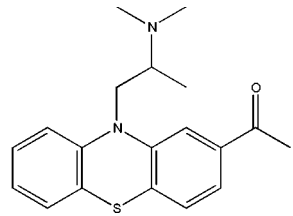
ACEPROMETAZINE

Therapeutic Function: Neuroleptic, Antitussive

Chemical Name: Ethanone, 1-(10-(2-(dimethylamino)propyl)-10H-phenothiazin-2-yl)-

Common Name: Aceprometazine

Structural Formula:



Chemical Abstracts Registry No.: 13461-01-3

Trade Name	Manufacturer	Country	Year Introduced
Aceprometazine	ZYF Pharm Chemical	-	-

Raw Materials

2-Acetylphenothiazine
1-Dimethylamino-2-chloropropane
Sodium hydride

Manufacturing Process

In a 1 liter flask, equipped with stirrer, thermometer and nitrogen inlet, 241.0 g of 2-acetylphenothiazine (1 mole) is dissolved in 300 ml of dry dimethylformamide. When the 2-acetylphenothiazine is almost completely soluble, to this solution is added 275 ml of a 4 N solution of 1-dimethylamino-2-chloropropane in toluene.

The mixture is heated to 50°C and 26.0 g (1.08 moles) of sodium hydride is added portion-wise, maintaining the temperature at 50°-60°C. The addition should take about 1 h. The reaction is allowed to stir for 3 h at 50°-60°C. Any excess hydride is destroyed by the cautious addition of 10 ml methanol, and the reaction mix is poured into 800 ml of 20% acetic acid.

The toluene layer is separated and extracted with 150 ml of 20% acetic acid, and discarded. The acid solutions are combined and washed once with toluene. The toluene is discarded. Fresh toluene (200 ml) is added and caustic solution is added with cooling and stirring until the pH is 9 or above. The toluene layer is separated. The aqueous layer is extracted once more with 75 ml of toluene and discarded. The toluene extracts are combined, given a small water wash, and concentrated. The residue is distilled yielding 10-[2-(dimethylamino)propyl]-2-acetylphenothiazine.

References

Kantor M.L., Tubis S.; US Patent No. 3,100,772; August 13, 1963; Assigned: America Home Products Corporation, New York, N.Y.

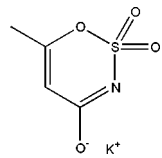
ACESULFAME POTASSIUM

Therapeutic Function: Pharmaceutic aid

Chemical Name: 6-Methyl-1,2,3-oxathiazin-4(3H)-one 2,2-dioxide potassium salt

Common Name: Acetylfame K, Acetylfame potassium

Structural Formula:



Chemical Abstracts Registry No.: 55589-62-3; 33665-90-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Acesulfame Potassium	Hoechst	-	-
Acesulfame K	Wuzhou international Co., Ltd.	-	-
Acesulfame Potassium	Zhang Peng International	-	-
Acesulfame K	AroKor Holdings Inc.	-	-
Acesulphame K	Acroyali Holdings Qingdao Co., Ltd.	-	-

Trade Name	Manufacturer	Country	Year Introduced
Acesulfame K	Zhangjiagang Hope Chemicals Co., Ltd.	-	-
VitaSweet Ace K	VitaSweet	-	-

Raw Materials

Dimethylethylamine
Sulfamic acid
Sulfur trioxide

Manufacturing Process

80 g (1.096 mol) of dimethylethylamine were added drop-wise, with cooling, to 80 g (0.825 mol) of sulfamic acid suspended in 500 ml of glacial acetic acid. When dissolution was complete, 80 ml (1.038 mol) of diketene were added, while cooling at 25°-35°C. After 16 hours, the mixture was evaporated and the residue was stirred with acetone, whereupon crystallization of dimethylethylammonium acetoacetamide-N-sulfonate took place. Yield: 110 g (43%), melting point 73°-75°C.

12.7 g (50 mmol) of dimethylethylammonium acetoacetamide-N-sulfonate in 110 ml of methylene chloride were added drop-wise to 8 ml (200 mmol) of liquid SO3 in 100 ml of CH_2Cl_2 at -30°C, stirring vigorously, within 60 minutes. 30 minutes later, 50 ml of ethyl acetate and 50 g of ice were added to the solution. The organic phase was separated off, and the aqueous phase was extracted twice more with ethyl acetate. The combined organic phases were dried over sodium sulfate, evaporated and the residue was dissolved in methanol. On neutralization of the solution with methanolic KOH, the potassium salt of 6-methyl-3,4-dihydro-1,2,3-oxathiazin-4-one 2,2-dioxide precipitated out. Yield: 7.3 g (73%). The product was detected by thinlayer chromatography; the structure of it was confirmed with IR spectrum.

References

Clauss K. et al.; US Patent No. 5,103,046; April 7, 1992; Assigned to Hoechst Aktiengesellschaft Frankfurt am Main, DE)

ACETAMINOPHEN

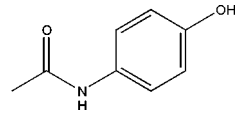
Therapeutic Function: Analgesic, Antipyretic

Chemical Name: N-(4-Hydroxyphenyl)acetamide

Common Name: Paracetamol; Acetyl-p-aminophenol; APAP

Chemical Abstracts Registry No.: 103-90-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Trigesic	Squibb	US	1950
Apamide	Ames	US	1952
Nebs	Norwich Eaton	US	1955
Tylenol	McNeil	US	1955
Febrolin	Tilden Yates	US	1957
Tempra	Mead Johnson	US	1957
Fendon	Am. Pharm.	US	1958
Amdil	Breon	US	1958
Lyteca	Westerfield	US	1962
Menalgesia	Clapp	US	1963
Dial-Agesic	Borden	US	1968
Tenlap	Dow	US	1970
SK-APAP	SK and F	US	1971
Valadol Tablets	Squibb	US	1971
Tapar	Parke Davis	US	1974
Cen-Apap	Central	US	1974
Acephen	G and W	US	1978
St. Joseph Aspirin	St. Joseph	US	1982
Panadol	Glenbrook	US	1983
Pain and Fever	Lederle	US	-
Accu-Tap	Accu-Med	US	-
Actamin	Buffington	US	-
Am inofen	Dover	US	-
Anuphen	Comatic	US	-
Dapa	Ferndale	US	-
Datril	Bristol-Myers	US	-
Dirox	Winthrop	US	-
Dolanex	Lannett	US	-
Febrogesic	First Texas	US	-
Halenol	Halsey	US	-
Hedex	Winthrop	US	-
Homoolan	Winthrop	US	-
Injectapap	Johnson and Johnson	US	-
Korum	Geneva	US	-
Metalid	Philips Roxane	US	-
Minotal	Carnrick	US	-

Trade Name	Manufacturer	Country	Year Introduced
Neopap	Webcon	US	-
Neotrend	Bristol-Myers	US	-
Nilprin	AVP	US	-
Panamax	Winthrop	US	-
Panodil	Winthrop	US	-
Parten	Parmed	US	-
Phenaphen	Robins	US	-
Phendex	Mallard	US	-
Phrenilin	Carnrick	US	-
Prompt	Delree	US	-
Proval	Reid-Provident	US	-
Robigesic	Robins	US	-
Valorin	Otis Clapp	US	-
Abrol	Rekah	Israel	-
Abrolet	Rekah	Israel	-
Acamol	Ikapharm	Israel	-
Acetalgin	Streuli	Switz.	-
Aldolor	Novis	Israel	-
Alpiny	SS Pharmaceutical	Japan	-
Alvedon	Draco	Sweden	-
Anaflon	Duphar	UK	-
Anhiba	Hokuriku	Japan	-
APA/Aparacet	Arcana	Austria	-
Apiretal	Ern	Spain	-
Arasol	Horner	Canada	-
Benmyo	Heilmittelwerke Wien	Austria	-
Ben-U-Ron	Benechemie	W. Germany	-
Calpol	Calmic	UK	-
Campain	Winthrop	Canada	-
Ceetamol	Protea	Australia	-
Cetadol	Rybar	UK	-
Chemcetaphen	Chemo-Drug	Canada	-
Dipramat Infantil	Byk Gulden	W. Germany	-
Dolamin	Nyal	Australia	-
Doliprane	Bottu	France	-
Dolprone	Siegfried	W. Germany	-
Dymadon	Calmic	UK	-
Efferalgan	UPSA	France	-
Enelfa	Dolorgiet	W. Germany	-
Exdol	Merck-Frosst	Canada	-
Febrilix	Boots	UK	-

Trade Name	Manufacturer	Country	Year Introduced
Finimal	Mepros	Netherlands	-
Finimal	Pharmaton	Switz.	-
Gelocatil	Gelos	Spain	-
Ildamol	Rekah	Israel	-
Kinder-Finiweh	Cesmopharma	Netherlands	-
Kratofin	Kwizda	Austria	-
Labamol	Vitamed	Israel	-
Langesic	Boots	UK	-
Letamol	Letap	Switz.	-
Momentum	Much	W. Germany	-
Myalgin	Allied Labs	UK	-
Napional	Pharma Import	Austria	-
Nealgyl	Bottu	France	-
Nevral	Lepetit	Italy	-
Pacemo	Alpinapharm	Switz.	-
Pacet	Rekah	Israel	-
Painex	A.L.	Norway	-
Pamol	Marshalls Pharm.	UK	-
Panacete	Prosana	Australia	-
Panadol	Sterwin Espanola	Spain	-
Panadon	Isis	Yugoslavia	-
Panasorb	Winthrop	UK	-
Panasorb	Bayer	W. Germany	-
Panok	B.M. Labs	UK	-
Pantalgin	UCB	Belgium	-
Paracet	Zdravlje	Yugoslavia	-
Paracet	Weifa	Norway	-
Paralgin	ICN	Canada	-
Paramol	Duncan Flockhart	UK	-
Paramolan	Trima	Israel	-
Parasin	Adams	Australia	-
Paraspen	Fisons	UK	-
Para-Suppo	Orion	Finland	-
Parmol	Knoll	Australia	-
Parol	Atabay	Turkey	-
Pasolind	Stada	W. Germany	-
PCM	Napp	UK	-
Pediaphen	Ross	Canada	-
Phenipirin	Aksu	Turkey	-
Pinex	A.L.	Norway	-

Trade Name	Manufacturer	Country	Year Introduced
Puernol	Formenti	Italy	-
Pyrinazin	Yamanouchi	Japan	-
Pyrital	Medica	Finland	-
Reliv	ACO	Sweden	-
Rivalgyl	Rivopharm	Switz.	-
Rounox	Rougier	Canada	-
Servigesic	Servipharm	Switz.	-
Setamol	Pharmacia	Sweden	-
Setol	Dif-Dogu	Turkey	-
Supramol	Sam-On	Israel	-
Tabalgin	Bayer	W. Germany	-
Tachipirina	Angelini	Italy	-
Temperal	Prodes	Spain	-
Trenodin	Fresenius	W. Germany	-
Tymol	Reckitt and Colman	W. Germany	-
Veralydon	Lelong	France	

Raw Materials

Nitrobenzene
Acetic anhydride

Manufacturing Process

About 250 ml of a reaction mixture obtained by the electrolytic reduction of nitrobenzene in sulfuric acid solution and containing about 23 grams of p-aminophenol by assay is neutralized while at a temperature of 60°C to 65°C, to a pH of 4.5 with calcium carbonate. The calcium sulfate precipitate which forms is filtered off, the precipitate washed with hot water at about 65°C and the filtrate and wash water then combined. The solution is then extracted twice with 25 ml portions of benzene and the aqueous phase is treated with 0.5 part by weight, for each part of p-aminophenol present, of activated carbon and the latter filtered off. The activated carbon is regenerated by treatment with hot dilute caustic followed by a hot dilute acid wash, and reused a minimum of three times.

To the filtrate obtained, there are then added about 0.2 gram of sodium hydrosulfite or sodium sulfite and 15.0 grams of anhydrous sodium acetate in about 27 grams of acetic anhydride at 40°C. The reaction mixture formed is cooled to 8°C to 10°C with stirring and held at this temperature for 60 minutes. A crystalline precipitate of about 27 grams of N-acetyl-p-aminophenol is obtained melting at 169-171°C. This is equivalent to a yield of 85%.

In lieu of utilizing calcium carbonate as the neutralizing agent, calcium hydroxide, barium hydroxide, barium chloride or other alkaline earth metal salt or hydroxide forming an insoluble sulfate may be employed.

References

Merck Index 39
Kleeman and Engel p. 684
PDR p. Many References
OCDS Vol. 1 p. 111 (1977)
DOT 16 (2) p. 59 (1980)
I.N. p. 728
REM p. 1111
Wilbert,G. and De Angelis, J.; US Patent 2,998,450; August 29, 1961; Assigned to Warner-Lambert Pharmaceutical Company

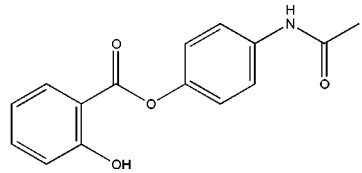
ACETAMINOSALOL

Therapeutic Function: Analgesic, Antineuralgic, Antirheumatic, Antipyretic

Chemical Name: 2-Hydroxybenzoic acid 4-(acetylamino)phenyl ester

Common Name: Acetamidosalol; Acetaminosal; Acetylparaminosalol; Acetaminosalol; Phenetsal

Structural Formula:



Chemical Abstracts Registry No.: 118-57-0

Trade Name	Manufacturer	Country	Year Introduced
Acetaminosal	ZYF Pharm Chemical	-	-

Raw Materials

N-Acetyl-p-aminophenol
Acetyl salicylic chloride
Sodium hydroxide
Acid chloride

Manufacturing Process

2 Methods of producing of acetyl salicylic acid ester of N-acetyl-p-aminophenol:

1. 65.0 g of N-acetyl-p-aminophenol were slurried with 400 ml of water and cooled to 10°C. 125 ml of 20% sodium hydroxide were slowly added to the mixture with stirring, the temperature being maintained 10°-15°C. To the solution obtained, 75.0 g of acetyl salicylic chloride were added with vigorous stirring over a period of 0.5 h, the solution being maintained at a temperature

of about 10°C. Towards the end of the reaction the pH was checked and adjusted to greater than 10 by the addition of a small amount of 20% sodium hydroxide. After all the acid chloride had been added, vigorous stirring was continued for 0.5 h during which time the crude product separated out. The acetyl salicylic acid ester of N-acetyl-p-aminophenol was filtered off, washed thoroughly with water and recrystallised from ethanol.

2. 65.0 g of sodium N-acetyl-p-aminophenol were slurried with 500.0 g of dry benzene and 80.0 g of acetyl salicylic chloride added. The mixture was heated under reflux for 4 h and filtered hot. The excess benzene was removed under vacuum and the crude acetyl salicylic acid ester of N-acetyl-p-aminophenol crystallized from ethanol.

References

Robertson A.; US Patent No. 3,431,293; March 4, 1969; Assigned: Sterling Drug Inc., New York, N.Y.

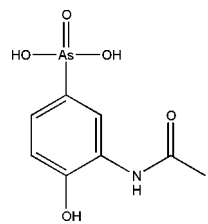
ACETARSOL

Therapeutic Function: Antiprotozoal, Tonic

Chemical Name: Arsonic acid, (3-(acetylamino)-4-hydroxyphenyl)-

Common Name: Acetarsol; Acetarsone; Osarsol(um)

Structural Formula:



Chemical Abstracts Registry No.: 97-44-9

Trade Name	Manufacturer	Country	Year Introduced
Acetarsol	Cyklo Pharma Chem Pvt. Ltd.	-	-
Acetarsol	Nizhpharm	-	-
Fluoryl	AFI	-	-
Gynoplix	Theraplix	-	-
Laryngarsol	Sanofi-Synthelabo	-	-
Nilacid	Sanofi-Synthelabo	-	-
Orarsan	Boots	-	-
Osarbon	Nizhpharm	-	-

Trade Name	Manufacturer	Country	Year Introduced
Pallicid	Wander	-	-
Spirocid	Hoechst	-	-
Stovarsol	Abbott	-	-

Raw Materials

4-Chloroaniline
Hydrogen chloride
Sodium hydroxide
Sodium thiosulfate
Sodium nitrite
Sodium arsenite
Nitric acid/Sulfuric acid
Acetic anhydride

Manufacturing Process

1 part of 4-chloroaniline is dissolved with 2 parts of concentrated hydrochloric acid (specific gravity 1.16) and 10 parts of water, and diazotised in the usual manner. 3 parts of sodium arsenite are introduced into the diazo solution thus obtained, the sodium arsenite being dissolved in 5 parts of water and 1 part of 96% ethanol. The solution is heated slowly to 70°C. When evolution of nitrogene ceased, it is filtered from separated oil and the addition of hydrochloric acid precipitates the 4-chlorophenylarsonic acid, which crystallizes out in the form of white needles.

By action HNO_3/H_2SO_4 on 4-chlorophenylarsonic acid is obtained 4-chloro-3-nitrophenylarsonic acid which is converted at 100°C with 33% aqueous solution of sodium hydroxide to 4-hydroxy-3-nitrophenylarsonic acid. After reduction of NO_2 group of 4-hydroxy-3-nitrophenylarsonic acid by the action of $Na_2S_2O_3$ or Fe/NaOH is obtained 3-amino-4-hydroxyphenylarsonic acid. From 3-amino-4-hydroxyphenylarsonic acid and acetic anhydride is prepared N-acetyl-4-hydroxy-m-arsanilic acid.

References

Bart H.; GB Patent No. 568; Jan. 9, 1911
GB Patent No. 5595; 06.03.1911; Assigned to Farbwerke vorm. Meister, Lucius, and Bruning, Hoechst, Germany

ACETAZOLAMIDE

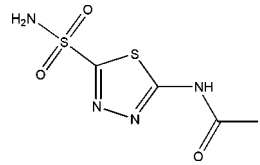
Therapeutic Function: Carbonic anhydrase inhibitor, Diuretic, Antiglaucoma

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

Common Name: -

Chemical Abstracts Registry No.: 59-66-5

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Diamox	Lederle	US	1953
Hydrazole	Softcon Products	US	1975
Acetamide	Nessa	Spain	-
Acetamox	Santen	Japan	-
Acetazolam	ICN	Canada	-
Acetazolamide Chibret	Chibret	France	-
Albox	Kwizda	Austria	-
Atenezol	Tsuruhara	Japan	-
Defiltran	Jouveinal	France	-
Diazomid	Dif-Dogu	Turkey	-
Diamox	Theraplix	France	-
Didoc	Sawai	Japan	-
Diluran	Spofa	Czechoslovakia	-
Diuramid	Polfa	Poland	-
Dirureticum-Holzinger	Holzinger	Austria	-
Diuriwas	Wassermann	Italy	-
Donmox	Hona	Japan	-
Edemox	Wassermann	Spain	-
Glauconox	Llorens	Spain	-
Glaupax	Erco	Denmark	-
Glaupax	Baeschlin	W. Germany	-
Gleupax	Dispersa	Switz.	-
Inidrase	Omikron-Gagliardi	Italy	-
Nephramid	Chemiek	E. Germany	-
Oedemin	Astra	Sweden	-
Renamid	Pliva	Yugoslavia	-
Uramox	Taro	Israel	-
Zohnox	Konto	Japan	-

Raw Materials

Hydrazine hydrate
Ammonium thiocyanate
Acetic anhydride
Chlorine
Ammonia
Bromine

Manufacturing Process

According to REM, hydrazine hydrate is reacted with 2 mols of ammonium thiocyanate to produce 1,2-bis(thiocarbamoyl)hydrazine which by loss of ammonia and rearrangement produces 5-amino-2-mercapto-1,3,4-thiadiazole. That compound is acetyled with acetic anhydride.

Then, as described in US Patent 2,554,816, the 2-acetylamido-5-mercapto-1,3,4-thiadiazole is converted to the sulfonyl chloride by passing chlorine gas into a cooled (5-10°C) solution in 33% acetic acid (66 parts to 4 parts of mercapto compound) used as a reaction medium. Chlorine treatment is continued for two hours. The crude product can be dried and purified by recrystallization from ethylene chloride. The pure compound is a white crystalline solid, MP 194°C, with decomposition, when heated rapidly. The crude damp sulfonyl chloride is converted to the sulfonamide by addition to a large excess of liquid ammonia. The product is purified by recrystallization from water. The pure compound is a white, crystalline solid, MP 259°C, with decomposition. The yield of sulfonamide was 85% of theory based on mercapto compound.

An alternative process is described in US Patent 2,980,679 as follows. 15 grams of finely powdered 2-acetylamino-1,3,4-thiadiazole-5-mercaptain are suspended in 200 ml of water containing 4 grams of potassium bromide. From 0.5 to 1 gram of ferric chloride are subsequently added. The mass is energetically stirred and 52 grams of liquid bromide are added by increments for about 45 minutes, while keeping the reaction temperature below 10°C, and, preferably, at 4-8°C by employing a cooling bath. Stirring is continued for a further 10 minutes, then the 2-acetylamino-1,3,4-thiadiazole-5-sulfobromide is collected on a funnel equipped with a porous diaphragm, thoroughly washed with cold water and finally subjected to amidation with liquid ammonia. The reaction mixture is allowed to stand for a certain period, then the ammonia is evaporated, after which the residue is taken up with diluted ammonia and, after decolorizing with carbon, the sulfonamide is precipitated with hydrochloric acid. The yield of crude sulfonamide obtained with this process, with respect to the starting mercapto compound is abut 84%. If the amidation is carried out with 33% aqueous ammonia, the yield is slightly lower.

References

Merck Index 45
Kleeman and Engel p. 6
PDR pp. 830, 1008, 1606
OCDS Vol. 1 p. 249 (1977)
I.N. p. 5
REM p.936
Clapp, J.W. and Roblin, R.O., Jr.; US Patent 2,554,816; May 29, 1951; Assigned to Americar Cyanamid Company
Gianfranco, P.; US Patent 2,980,679; April 18, 1961; Assigned to Omikron-Gagliardi Societa di Fatto, Italy

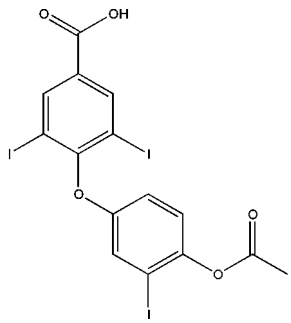
ACETIROMATE

Therapeutic Function: Antihyperlipidemic

Chemical Name: Benzoic acid, 4-(4-hydroxy-3-iodophenoxy)-3,5-diiodo-, acetate

Common Name: Acetiromate; Adecol

Structural Formula:



Chemical Abstracts Registry No.: 2260-08-4

Trade Name	Manufacturer	Country	Year Introduced
Acetiromate	ZYF Pharm Chemical	-	-

Raw Materials

3,5-Diiodo-4-(3-iodo-4-hydroxyphenoxy)benzoic acid
Acetic anhydride

Manufacturing Process

To 3 parts of 3,5-diiodo-4-(3-iodo-4-hydroxyphenoxy)benzoic acid 10 parts of acetic acid anhydride was added and mixture was heated on oil bath for some hours. In the result of this reaction amorphous precipitate was obtained. After recrystallization from glacial acetic acid 2.4 parts of 3,5-diiodo-4-(3-iodo-4-acetoxyphenoxy)benzoic acid were obtained.

References

Fr. Patent No. M1610; Dec. 10, 1962; Assigned: Takeda Chemical Industries, LTD

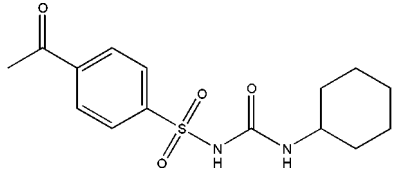
ACETOHEXAMIDE

Therapeutic Function: Hypoglycemic

Chemical Name: 1-[(p-Acetylphenyl)sulfonyl]-3-cyclohexylurea

Common Name: Cyclamide

Structural Formula:



Chemical Abstracts Registry No.: 968-81-0

Trade Name	Manufacturer	Country	Year Introduced
Dymelor	Lilly	US	1964
Dimelin	Shionogi	Japan	-
Dimelor	Lilly	UK	-
Gamadiabet	Salvat	Spain	-
Metaglucina	Perga	Spain	-
Ordimel	Lilly	Spain	-

Raw Materials

Sodium nitrite
Hydrogen chloride
Ammonia
p-Aminoacetophenone
Sulfur dioxide
Cyclohexyl isocyanate

Manufacturing Process

Preparation of p-Acetylbenzenesulfonamide: 100 grams of p-aminoacetophenone were dissolved in a solvent mixture containing 165 ml of 12 N hydrochloric acid and 165 ml of glacial acetic acid. The mixture was cooled with stirring to about 0°C. A solution containing 56.2 grams of sodium nitrite and 175 ml of water was added dropwise with stirring to the acidic solution while maintaining the temperature below 5°C.

After the addition had been completed, the acidic solution containing p-acetylphenyldiazonium chloride formed in the above reaction was added dropwise with stirring to a mixture of 530 ml of glacial acetic acid and 530 ml of benzene which had been previously cooled, and the cooled solution saturated with sulfur dioxide and to which had been added 34 g of cupric chloride dihydrate. After the addition had been completed, the reaction mixture was stirred at about 40°C for three hours, and was then poured into 3,000 ml of an ice-water mixture.

The benzene layer containing p-acetylbenzenesulfonyl chloride formed in the above reaction was separated, and the acidic aqueous phase was extracted twice with 250 ml portions of benzene. The benzene layers were combined, the combined extracts were filtered, and the benzene was evaporated from the resulting filtrate in vacuum.

The solid residue comprising p-acetylbenzenesulfonyl chloride was dissolved in 100 ml of dioxane, and the solution was added to 200 ml of 14% aqueous ammonium hydroxide. The resulting solution was stirred overnight at ambient room temperature. The p-acetylbenzenesulfonamide thus prepared was collected by filtration. Recrystallization of the filter cake from aqueous ethanol yielded purified p-acetylbenzenesulfonamide melting at about 176°C to 179°C.

Preparation of N-p-Acetylphenylsulfonyl-N'-Cyclohexylurea: A reaction mixture consisting of 32.7 grams of p-acetylbenzenesulfonamide and 64 grams of anhydrous potassium carbonate in 350 ml of anhydrous acetone was stirred at refluxing temperature for about 1% hours, thus forming the potassium salt of p-acetylbenzenesulfonamide. 30.9 grams of cyclohexylisocyanate were added dropwise to the reaction mixture. Refluxing and stirring were continued during the course of the addition and for an additional 16 hours.

The acetone was removed by evaporation in vacuum, and about 750 ml of water were added to dissolve the resulting residue. The solution was filtered. The potassium salt of N-p-acetylphenylsulfonyl-N'-cyclohexylurea formed in the above reaction, being water-soluble, passed into the filtrate. Acidification of the filtrate with 6 N aqueous hydrochloric acid caused the precipitation of N-p-acetylphenylsulfonyl-N'-cyclohexylurea which was collected by filtration. Recrystallization of the filter cake from 90% aqueous ethanol yielded purified N-p-acetylphenylsulfonyl-N'-cyclohexylurea melting at about 188-190°C.

References

Merck Index 53
Kleeman and Engel p. 7
PDR p. 1049
OCDS Vol. 1 p. 138 (1977)
I.N. p. 6
REM p.976
Sigal, M.V., Jr. and Van Arendonk, A.M.; US Patent 3,320,312; May 16, 1967; Assigned to Eli Lilly and Company.

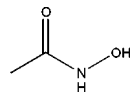
ACETOHYDROXAMIC ACID

Therapeutic Function: Urease inhibitor

Chemical Name: Acetamide, N-hydroxy-

Common Name: Acetohydroxamic acid; Uronefrex

Structural Formula:



Chemical Abstracts Registry No.: 546-88-3

Trade Name	Manufacturer	Country	Year Introduced
Lithostat	Mission Pharmacal Co.	-	-
Uronefrex	Robert	-	-

Raw Materials

Hydroxylamine
Acetamide
Nitrohydroxylamine
Ethyl acetic acid ether
Acetaldehyde

Manufacturing Process

3 Methods of producing of acetohydroxamic acid:

1. Ethyl acetic acid ether was treated with hydroxylamine and acetohydroxamic acid was obtained.

2. Acetohydroxamic acid was obtained in the result of reaction of acetamide with hydroxylamine.

3. Acetohydroxamic acid was obtained by treatment of acetaldehyde with nitrohydroxylamine.

References

Karrer P.; Lehrbuch der organischen chemie; Stuttgart; 1959; 1216 s.

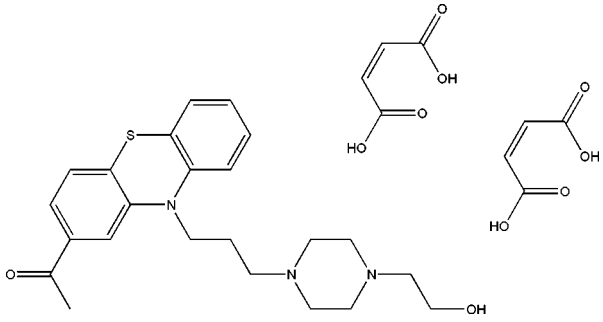
ACETOPHENAZINE DIMALEATE

Therapeutic Function: Tranquilizer

Chemical Name: 10-[3-[4-(2-Hydroxyethyl)-1-piperazinyl]propyl] phenothiazin-2-yl methyl ketone maleate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 5714-00-1; 2751-68-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Tindal	Schering	US	1961

Raw Materials

2-Acetylphenothiazine
Sodium amide
1-Bromo-3-chloropropane
Maleic acid
1-(2-Hydroxyethyl)piperazine

Manufacturing Process

The requisite intermediate, 10-(3-chloropropyl)-2-acetylphenothiazineis prepared as follows: To a suspension of sodium amide (from 3 grams of sodium) in 300 ml of liquid ammonia is added 30 grams of 2-acetylphenothiazine. After stirring for one hour, there is added 19 grams of 1-bromo-3-chloropropane. The ammonia is allowed to evaporate and the residue is diluted with 200 ml of water. The mixture is extracted with ether and the ether solution is dried over anhydrous sodium sulfate, filtered and concentrated.

The residue consists of crude 10-(3-chloropropy1)-2-acetylphenothiazine as a viscous oil and is used in the next step without further purification. The crude base obtained from the reaction of 10-(3-chloropropyl)-2-acetylphenothiazine with 1-(2-hydroxyethyl)piperazine is purified by conversion to its dimaleate salt, MP 167-168.5°C from ethanol.

References

Merck Index 64
Kleeman and Engel p. 7
OCDS Vol. 1 p. 383 (1977)
I.N. p. 6
REM p. 1086
Sherlock, M.H. and Sperber, N.; US Patent 2,985,654; May 23, 1961; Assigned to Schering Corporation, Bloomfield, N.J.., a corporation of a New Jersey

ACETOXOLONE ALUMINUM SALT

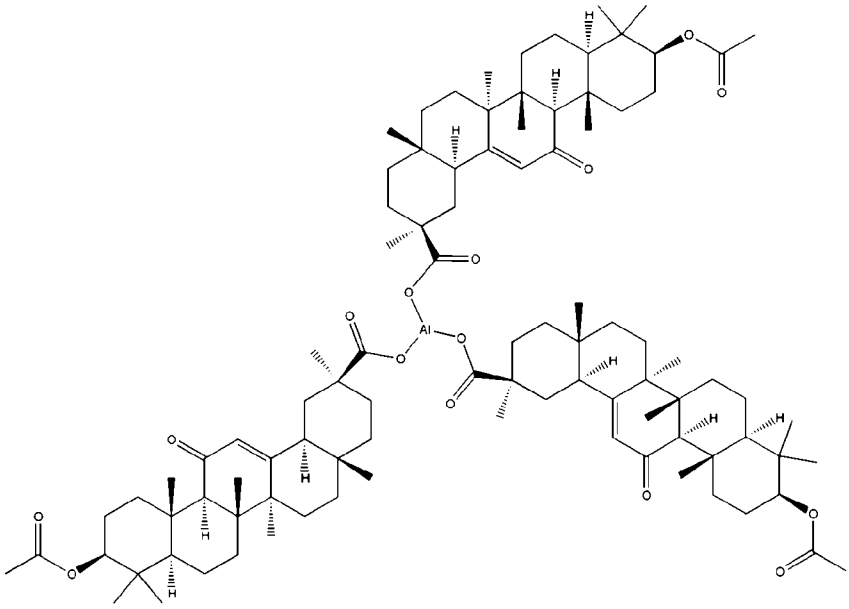
Therapeutic Function: Antiulcer

Chemical Name: 3-(Acetyloxy)-11-oxoolean-12-en-29-oic acid aluminum salt

Common Name: -

Chemical Abstracts Registry No.: 6277-14-1 (Base)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Oriens	Inverni Beffa	Italy	1981

Raw Materials

3-Acetyl-18β-glycyrrhetinic acid
Aluminum alcoholate

Manufacturing Process

The salts of 3-acetyl-18β-glycyrrhetinic acid can be prepared by reaction between 3-acetyl-18β-glycyrrhetinic acid and an aluminum alcoholate. Preferably lower alcoholates are used, i.e., alcoholates in which the alkoxy group or groups have from one to four carbon atoms. The salification reaction may be carried out at room temperature or at an elevated temperature in conventional fashion, preferably in the presence of organic solvents. As organic solvents may be used alcohols, ethers, ketones, chlorinated solvents (methylene chloride, chloroform) ethyl acetate, etc.

References

Merck Index 70
Bonati, A.; US Patent 3,764,618; October 9,1973; Assigned to Dott. Inverni and Della Befia S.P.A.

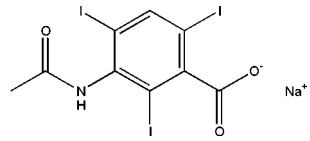
ACETRIZOATE SODIUM

Therapeutic Function: Diagnostic aid (radiopaque medium)

Chemical Name: 3-(Acetylamino)-2,4,6-triiodobenzoic acid sodium salt

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 129-63-5

Trade Name	Manufacturer	Country	Year Introduced
Urokon Sodium	Mallinckrodt Inc.	US	1950
Thixokon	Mallinckrodt Inc.	US	1957
Cystokon	Mallinckrodt Inc.	US	1964
Pyelokon-R	Mallinckrodt Inc.	US	-
Salpix	Ortho	US	-
Diaginol	May and Baker	UK	-
Diaginol	Banyu	Japan	-
Vasurix	Guerbet	France	-
Fortombrin	Dagra	Netherlands	-
Iodopaque	Labaz	Switz.	-
Triurol	Lundbeck	Denmark	-

Raw Materials

3-Amino-2,4,6-triiodobenzoic acid
Acetic anhydride
Sodium hydroxide

Manufacturing Process

3-Amino-2,4,6-triiodobenzoic acid (51.5 g) was mixed with 125 ml of acetic anhydride containing 2 drops of concentrated sulfuric acid and refluxed for thirty minutes. The mixture was allowed to cool slightly, and then was poured into 600 ml of water at room temperature and stirred until crystallization was complete. The mixed anhydride of 3-acetylamino-2,4,6-triiodobenzoic acid with acetic acid thus prepared was then separated by filtration and washed with water. Without drying, the solid was suspended in 600 ml of water and hydrolyzed with a slight excess of ammonium hydroxide. It was necessary to warm the mixture slightly and stir it for about one-half hour in order to dissolve all the solid. The solution was then treated with activated carbon, filtered and precipitated with an excess of hydrochloric acid, filtered, washed and dried at 70°C. The yield was 51.5 g of 3-acetylamino-2,4,6-triiodobenzoic

acid which melted at 276.6-278.2°C with decomposition when placed in the melting block at 260°C and heated at the rate of 3°C per minute. Due to decomposition, the melting point varied from about 269-280°C, depending upon the rate of heating and other conditions.

3-Acetylamino-2,4,6-triiodobenzoic acid (28 g) was dissolved in a little over 50 ml of 1 N sodium hydroxide in a round-bottom flask. The pH was adjusted to slightly over 7 and the solution was evaporated on a steam bath under reduced pressure. After the residue became solid, it was further dried overnight in a vacuum desiccator containing calcium chloride. The salt weighed 31.2 g, theory being 29.0 g, indicating that the product contains about 7% water of crystallization when dried under these conditions. The finished salt was scraped from the flask and ground.

References

Merck Index 73
Kleeman and Engel p. 8
I.N. p.7
Wallingford, V.H.; US Patent 2,611,786; September 23, 1952; Assigned to Mallinckrodt Chemical Works

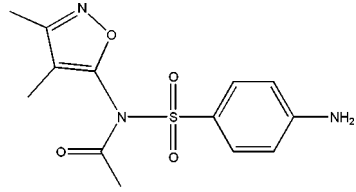
ACETYL SULFISOXAZOLE

Therapeutic Function: Antimicrobial

Chemical Name: N-[(4-Aminophenyl)sulfonyl]-N-(3,4-dimethyl-5-isoxazolyl) sulfanilamide

Common Name: Acetylsulfafurazol

Structural Formula:



Chemical Abstracts Registry No.: 80-74-0

Trade Name	Manufacturer	Country	Year Introduced
Gantrisin Acetyl	Roche	US	1954
Lipo-Gantrisin Acetyl	Roche	US	1954
Pediazole	Ross	US	-

Raw Materials

Sulfisoxazole
Acetic anhydride

Manufacturing Process

267 grams (1 mol) of sulfisoxazole were suspended in 400 ml of acetone and 79 grams (1 mol) of dry pyridine at 20-25°C in a round-bottom flask equipped with a stirrer and thermometer. 132 grams (1 mol) of acetic anhydride were added within 3 minutes with stirring. The sulfisoxazole dissolved in the mixture and a clear solution resulted. The temperature rose to 39-40°C. After stirring for several minutes, the product started to crystallize as a white crystalline mush. The temperature rose to 42-43°C maintained itself at this temperature for 15-30 minutes, and then started to drop. Stirring was continued for 5 hours and the mixture was then allowed to stand for 10 hours. One liter of 2.5-3.0% ice-cold aqueous ammonia and some fresh ice were then added while stirring and the crystals were filtered without delay. The crystals were washed on the filter with 1 liter of ice-cold 1% ammonia and then with 1 liter of water. The material on the filter was well pressed off, washed with 200-300 ml of alcohol and dried at 70°C to constant weight. The N-monoacetyl sulfisoxazole melted at 193-194°C and showed a positive Bratton-Marshall reaction and a positive Hucknall-Turfat reaction.

The product is in the form of colorless crystals which are somewhat water repellent. It is insoluble in alkali but is saponified upon standing in alkaline suspension (3% ammonia). It is soluble in strong acids (20-36% HCl or 10 N H_2SO_4) and is rapidly saponified upon standing.

References

Merck Index 104
Kleeman and Engel p. 13
PDR pp. 1487, 1558
I.N. p. 10
Hoffer, Max; US Patent 2,721,200; October 18, 1955; Assigned to Hoffmann-La Roche Inc.

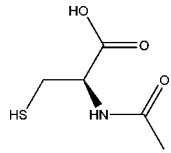
ACETYLCYSTEINE

Therapeutic Function: Expectorant

Chemical Name: N-Acetyl-L-cysteine

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 616-91-1

Trade Name	Manufacturer	Country	Year Introduced
Mucomyst	Mead Johnson	US	-
Acetein	Senju	Japan	-
Airbron	BDH	UK	-
Broncholysin	Spofa	Czechoslovakia	-
Brunac	Bruschettini	Italy	-
Fabrol	Ciba	-	-
Fluimucetin	Zambon	Italy	-
Fluimucetin	Inpharzam	Belgium	-
Fluimucil	Zambon	Italy	-
Inspir	Vitrum	Sweden	-
Mucolyticum	Lappe	W. Germany	-
Mucosolvin	VEB Berlin Chemie	E. Germany	-
NAC	Mead Johnson	-	-
Parvolex	Duncan Flockhart	UK	-
Mucomist	Bristol	Italy	-
Mucisol	Deca	Italy	-
Rinofluimucil	Inpharzam	W. Germany	-
A.R.B.	Tokyo Tanabe	Japan	-
Mucofilin	Eisai	Japan	-

Raw Materials

L-Cysteine HCl
Acetic anhydride

Manufacturing Process

To a suspension of 35.2 grams (0.2 mol) of L-cysteine hydrochloride monohydrate stirred in a reaction vessel containing 87 ml of 91% aqueous tetrahydrofuran under a nitrogen atmosphere there is added 54.4 grams (0.4 mol) of sodium acetate trihydrate. The mixture is stirred for 20 minutes at room temperature to insure neutralization of the hydrochloride salt resulting in the formation of a suspension of equimolar amounts of cysteine and sodium acetate.

The mixture is then chilled to 3-6°C by external cooling and 20 ml (20.8 grams, 0.21 mol) of acetic anhydride is added thereto in dropwise fashion with cooling in the above range. The resulting mobile suspension is stirred for 6 hours at room temperature, allowed to stand overnight, and finally heated at reflux (72°C) for 4 hours. The resulting suspension of sodium N-acetyl-L-cysteinate is then neutralized by treatment at 5-10°C with 8 grams of hydrogen chloride. Resulting sodium chloride is removed by filtration and the product is isolated by distilling the solvent from the filtrate in vacuum and crystallizing the residue from 35 ml of water, yield 26.3 grams (80.6%) of N-acetylcysteine as a white solid, MP 109-110°C.

References

Merck Index 82
Kleeman and Engel p. 8

PDR p. 1126
DOT 16 (2) p. 42 (1980)
I.N. p. 8
REM p. 867
Martin, T.A. and Waller, C.W.; US Patent 3,184,505; May 18, 1965; Assigned to Mead Johnson and Company.

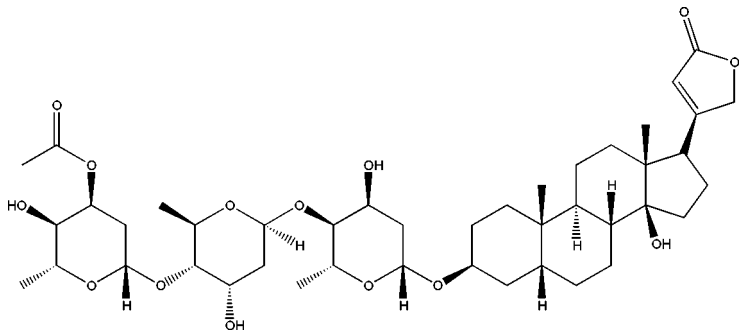
ACETYLDIGITOXIN

Therapeutic Function: Cardiotonic

Chemical Name: Card-20(22)-enolide, 3-((O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1.4)-O-2,6-dideoxy-beta-D-ribo-hexopyranosyl-(1.4)-2,6-dideoxy-β-D-ribo-hexopyranosyl)oxy)-14-hydroxy-, monoacetate, (3β,5β)-

Common Name: Digitoxin monoacetate

Structural Formula:



Chemical Abstracts Registry No.: 1111-39-3

Trade Name	Manufacturer	Country	Year Introduced
Acylanid	Sandoz	US	1954
Acygoxine	Sandoz	France	1972
Acylanide	Sandoz	France	1954
Acylanid	Sandoz	Italy	1966
Sandolanid	Sandoz	W. Germany	1968

Raw Materials

Digitalis Ferruginea Leaves

Manufacturing Process

Acetyldigitoxin-α can be obtained from acetyldigitoxin-β by heating it in an

anhydrous or aqueous organic solvent at neutral, weakly acid or weakly alkaline pH, i.e., at a pH range from about 3.5 to about 8.

The acetylidigitoxin-β used for this purpose is a cardiac glycoside which can be obtained either by splitting off the glucose residue from lanatoside A, or by extraction of the leaves of *Digitalis ferrugines*. It is composed of the aglycone digitoxigenin and 3 molecules of digitoxose, to one of which an acetyl group is attached. Acetyldigitoxin-α, obtained from acetyldigitoxin-β by rearrangement, differs from the latter in the position of the acetyl group.

The process may be carried out, for example, in the following manner: A solution of acetyldigitoxin-β in a suitable solvent, such as methanol, is boiled under reflux and then diluted with water. The unchanged acetyldigitoxin-β, which crystallizes out first, is filtered off and can again be submitted to the same process. On concentrating the filtrate, acetyldigitoxin-α separates out in crystalline form and after filtering off and recrystallizing is obtained in a pure state. The acetyldigitoxin-α crystallizes from aqueous methanol in platelets melting at 217-221°C.

References

Merck Index 83
Kleeman and Engel p. 9
I.N. p.8
Stoll, A. and Kreis, W.; US Patent 2,776,963; January 8, 1957; Assigned to Sandoz, AG, Switzerland.

β-ACETYLDIGOXIN

Therapeutic Function: Cardiotonic

Chemical Name: Card-20(22)-enolide, 3-((O-4-O-acetyl-2,6-dideoxy-beta-d-ribo-hexopyranosyl-(1.4)-O-2,6-dideoxy-beta-d-ribo-hexopyranosyl-(1.4)-2,6-dideoxy-beta-d-ribo-hexopyranosyl)oxy)-12,14-dihydroxy-, (3β,5β,12β)-

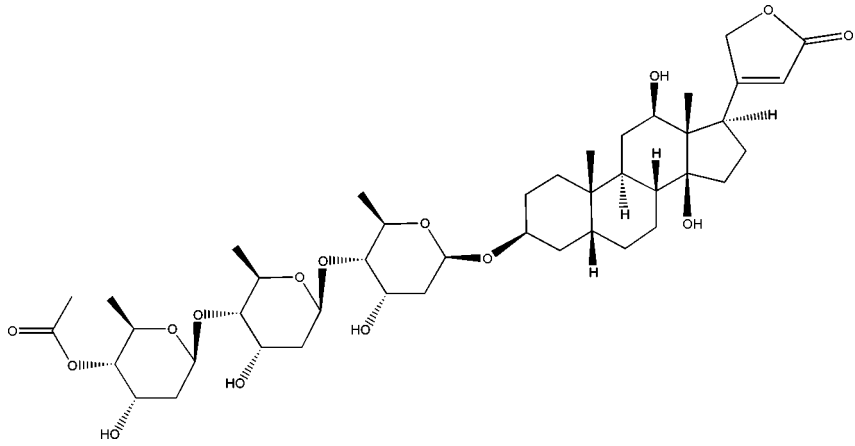
Common Name: beta-Acetyldigoxin; Betagoxinum

Chemical Abstracts Registry No.: 5355-48-6

Trade Name	Manufacturer	Country	Year Introduced
Novodigal	Asta Medica Arzneimittel	-	-
Novodigal	Lilly	-	-
Digoxin	Didier	-	-
Digoxin	Elkins-Sinn	-	-
Digoxin	Roxane	-	-
Digoxin	Wyeth-Ayerst	-	-

Trade Name	Manufacturer	Country	Year Introduced
Lanoxin	GlaxoSmithKline	-	-
Digitek	Bertek	-	-
Digoxin	Novartis	-	-
Corotal	Rosch and Handel	-	-

Structural Formula:



Raw Materials

Crude partial acetylated digoxin	Digoxin
Dicyclohexylcarbodiimide	Acetic acid

Manufacturing Process

Dried crude product of the partial acetylation of digoxin (42 g) prepared from digitalis - is dissolved under reflux in acetone (480 ml) and n-hexane (2400 ml) is added to the solution with stirring. Fine crystals, which begin to separate immediately, are left at room temperature for 5 hours, then they are filtered with suction, washed with n-hexane and dried in vacuum at 40°C, yielding 32 g of crude β-acetyldigoxin (product 1). Product 1 (31 g) is dissolved under reflux in chloroform (500 ml) and toluene (2500 ml) is added thereto with stirring. The crystals, which separate after standing for 6 hours at room temperature, are filtered, washed with toluene and ether and dried in vacuum yielding 29 g of β-acetyldigoxin (product 2). MP: 249°-251°C.

The filtrate, which results from the separation of product 1, is evaparated to dryness in vacuum. The residue, which mainly contains unreacted digoxin, is purified by recrystallization from pyridine/ether/water (3.5:5:40) and repeatedly acetylated. It can then be recycled to produce more β-acetyldigoxin. The filtrate resulting from the separation of product 2 is evaporated to dryness. The resulting residue contains the di- and polyacetyl derivatives of digoxin, which are deacetylated to digoxin in a known manner

and later is returned to a further acetylation process and can then be recycled to produce more β-acetyldigoxin.

Beta-Acetyldigoxin may be prepared from digoxin, acetic acid and dicyclohexylcarbodiimide using the last one as a condensing agent.

References

Pelan B. et al.; G.B. Patent No. 2,000,145 A; June 22, 1977
Haberland G., Arzneim.Forsh. 15, 481 (1965)

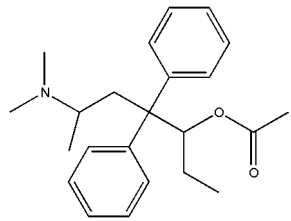
ACETYLMETHADOL

Therapeutic Function: Narcotic analgesic

Chemical Name: Benzeneethanol, β-(2-(dimethylamino)propyl)-α-ethyl-β-phenyl-, acetate (ester)

Common Name: Acemethadone; Acetyldimepheptanol; Acetylmethadol; Amidolacetat; Dimepheptanolacetat; Methadyl acetate; Race-Acetylmethadol

Structural Formula:



Chemical Abstracts Registry No.: 509-74-0

Trade Name	Manufacturer	Country	Year Introduced
Acetylmethadol	National Inst. for Drug Abuse	-	-
ORLAAM	Roxane Laboratories, Inc.	-	-

Raw Materials

Vinyl propionate	1-Dimethylamino-2-propanol
Novozym 435	Thionyl chloride
Sodium hydroxide	Diphenylacetonitrile
Dibenzo-18-crown-6	Hydrogen chloride
Sodium borohydride	Ethyl magnesium bromide

Acetyl chloride
Cerium (III) chloride heptahydrate

Manufacturing Process

Racemic 1-dimethylamino-2-propanol (100.0 g, 0.97 mol) was stirred with vinyl propionate (63.6 ml, 0.58 mol) at 40°C and Novozym 435 (5.0 g) was added. The reaction was stirred slowly for 75 h and after this time TLC (10% methanol/dichloromethane-visualize $KMnO_4$ solution) indicated that the reaction had gone to at least 50% conversion. The enzyme was removed by filtration and the filtrate was distilled at reduced pressure. S-(+)-1-Dimethylamino-2-propanol was obtained as a colourless oil (31.6 g, 64%), boil point 35°C.

A solution of thionyl chloride (37 ml, 0.48 mol) in chloroform (20 ml) was added slowly, with stirring, to a cooled (ice/water) solution of S-(+)-1-dimethylamino-2-propanol (30.6 g, 0.32 mol) in chloroform (85 ml). When the addition was complete a precipitate formed. The mixture was allowed to warm to room temperature over 30 min and then heated to reflux for a further 30 min. The precipitate redissolved on heating but then the product crystallized out from the boiling solvent as it formed. More chloroform (20 ml) was needed to maintain the stirring. The cooled mixture was diluted with ether and filtered. The 45.0 g (96%) of crude product was isolated. This was recrystallised from 2-propanol as in the other series to give 30.9 g (65%) of R-(-)-1-dimethylamino-2-chloropropane, melting point 192°-193°C.

A 50% w/v solution of sodium hydroxide in water (12.5 ml, 0.32 mol) was added to a mechanically stirred suspension of diphenylacetonitrile (15.0 g,0.08 mol) and dibenzo-18-crown-6 (0.5 g, cat.) in dimethylsulphoxide (12.5 ml). The color rapidly deepened to an orange/brown. R-(-)-1-Dimethylamino-2-chloropropane (30.0 g, 0.095 mol) was added in portions over 30 min, this caused the temperature to rise to 30°C. After the addition was complete the mixture was warmed to 45°-50°C (water bath) and stirred for a further hour. The reaction mixture was then allowed to cool to room temperature and was poured into ice/water (250 ml) and extracted with ethyl acetate (3 times 150 ml). The combined extracts were dried ($MgSO_4$) and filtered and evaporated down to -100 ml. The product was extracted into 1N HCl (100 ml+50 ml) and this was back washed with ethyl acetate. The aqueous was basified with 2 M sodium hydroxide and extracted into ethyl acetate (3 times 100 ml). The extracts were washed with brine (70 ml), dried ($MgSO_4$), and evaporated down to a yellow oil. This was chilled and triturated with cold hexane (50 ml) to give a white solid which was collected by filtration and washed thoroughly with a further portion of cold hexane (100 ml). 14.65 g (33%) of S-(+)-2,2-diphenyl-4-dimethylaminopentanenitrile were obtained, melting point 100°-101°C (recrystallised from hexane).

All apparatus was dried and the reaction was carried out under an inert atmosphere of argon. A solution of S-(+)-2,2-diphenyl-4-dimethylaminopentanenitrile (10.0 g, 0.018 mol) in toluene (15 ml) was added to a stirred solution of 3 M ethyl magnesium bromide in ether (10.7 ml, 0.03 mol). The ether was removed under reduced pressure and the remaining solution heated at reflux (135°-140°C) for 3 h. The solution went slightly cloudy but there was no significant precipitation. After cooling to room temperature 2 N HCl (30 ml) was added with care and then stirring was

continued at 135°-140°C for a further 30 min. The two phases were allowed to separate and cool to room temperature. After scratching the sides of the flask a solid started to crystallise from the aqueous phase. The flask was cooled to complete crystallisation and the white solid was collected by filtration. This solid was recrystallised from water to yield 6.6 g (53%) of S-(+)-methadone hydrochloride (6-dimethylamino-4,4-diphenyl-3-heptanone hydrochloride) were obtained, melting point 240°-241°C.

S-(+)-Methadone hydrochloride (600.0 mg,1.74 mmol) was dissolved in ethanol (10 ml) and the solution was stirred whilst sodium borohydride (3.47 mmol) was added portion-wise over a period of 5 min. When the addition was complete a spatula end of cerium (III) chloride heptahydrate was added. The resultant solution was allowed to stir at room temperature for 30 min then the ethanol was removed under reduced pressure. The residue was portioned between diethyl ether (40 ml) and water (40 ml). The aqueous layer was extracted with more diethyl ether (2 times 20 ml) and then the combined organics were washed with brine (40 ml) and dried ($MgSO_4$). The ether was removed under reduced pressure to leave 435.0 mg, (80%) of 6-dimethylamino-4,4-diphenyl-3-heptanol.

6-Dimethylamino-4,4-diphenyl-3-heptanol (435.0 mg, 1.40 mmol) dissolved in ethyl acetate (10 ml) was treated with acetyl chloride (183.0 mg, 2.33 mmol). The mixture was refluxed for 2 h. After allowing the solution to cool to room temperature the solvent was removed under reduced pressure to leave a white foam, this crystallised from ethyl acetate to give 6-dimethylamino-4,4-diphenyl-3-acetoxyheptane hydrochloride (levo-α-acetyl methadol hydrochloride) (420.0 mg, 79%).

The 6-dimethylamino-4,4-diphenyl-3-acetoxyheptane may be produced by treatment of the 6-dimethylamino-4,4-diphenyl-3-acetoxyheptane hydrochloride with sodium hydroxide.

References

Scheinmann F. et al.; US Patent No. 6,143,933; Nov. 7, 2000; Assigned: Salford Ultrafine Chemicals and Research Ltd., United Kingdom

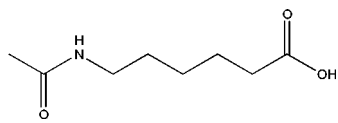
ACEXAMIC ACID

Therapeutic Function: Antifibrinolytic

Chemical Name: Hexanoic acid, 6-(acetylamino)-

Common Name: Acexamic acid; Plastesol

Structural Formula:



Chemical Abstracts Registry No.: 57-08-9

Trade Name	Manufacturer	Country	Year Introduced
Acexamic acid	Flamma	-	-
Acide Acexamicum	ZYF Pharm Chemical	-	-
Plastenan	Sanofi Winthrop	-	-

Raw Materials

Calcium hydroxide
Acetylcaprolactame
Hydrogen chloride

Manufacturing Process

400 L of demineralized water, 5.0 kg of calcium hydroxide, and 155.0 kg (1000 moles) of acetyl-caprolactame are introduced under stirring and at a temperature of about 25°C into a 1000 L stainless double walled reactor.

The temperature is raised to 30°C. 75.0 kg of calcium hydroxide are introduced stepwise in the form of successive amounts of 2.0 kg each in the medium, under stirring and at a temperature adjusted and maintained 25°-30°C through external cooling, in a manner such that the time required to introduce into the reactor the whole amount of calcium hydroxide approximates 1.5 h. When the stirring is stopped, the pH is about 7.5-7.8.

The obtained mixture is stirred continuously at a temperature of 30°C during 14 h. At the end of this operation the pH is again adjusted at a value 7.5-7.8.

The hydrolysate is filtered on a 60 x 60 pressfilter comprising 6 compartments and equipped with fabrics of the polyester known under the designation TERGAL which have been previously coated with a suspension of a cellulose commercialized under the trademark SOLKA FLOX BW20. The duration of filtration is of 1.5 h. 580 L of the filtrate are recovered and subjected to a concentration under reduced pressure in an evaporator the volume of which is of 750 L, at a distillation temperature ranging from 45°-50°C under a reduced pressure of 10-15 Torr.

The operation is ran until concentration of the solution to 280 L, the concentrated solution being then left standing. The crystallisation is already considerable 2 h after the end of the operation of concentration. Crystallisation is ended after 16-24 h.

The crystals are centrifuged at a speed of 700 revolutions/minute. The centrifuged crystals of calcium acexamate are washed twice on the centrifuge with 20 l of acetone. 107.0 kg of crystals are obtained, which are dried under vacuum at 40°C. The 96.0 kg of dry calcium acexamate obtained are ground and sifted.

Acexamic acid may be produced by treatment of the calcium acexamate with HCl.

References

Goulay J.; US Patent No. 3,974,215; Aug. 10, 1976; Assigned: Choay S.A., Paris, France

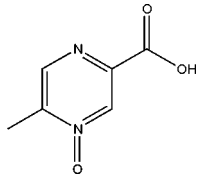
ACIPIMOX

Therapeutic Function: Antihyperlipidemic

Chemical Name: 2-Pyrazinecarboxylic acid, 5-methyl-, 4-oxide

Common Name: Acipimox; Zopinox

Structural Formula:



Chemical Abstracts Registry No.: 51037-30-0

Trade Name	Manufacturer	Country	Year Introduced
Olbetam	Pfizer	-	-
Nedios	Byk Pharmaceuticals	-	-
Olbemox	Pharmacia	-	-
Olbemox	Pfizer	-	-

Raw Materials

Ethyl chloroformate
Ammonia
Hydrogen peroxide
Hydrochloric acid
2-Carboxy-5-methylpyazine
Acetic acid
Sodium hydroxide

Manufacturing Process

2-Carboxy-5-methylpyazine (9.7 g) in dry dioxan (114 ml) and tributylamine (17.7 ml) was treated with ethyl chloroformate (7.5 ml), keeping the temperature at 0-5°C. After 10 min, dioxan (190 ml) saturated with ammonia was added. The mixture was stirred for 3 h at room temperature, then dioxin was distilled off, and the residue was taken up tin saturated aqueous sodium bicarbonate (20 ml). The mixture was filtered and the product washed with water to give 2-carbamoyl-5-methylpyrazine (9.2 g), melting point 204°-206°C.

This 2-carbamoyl-5-methylpyrazine (7.0 g) in glacial acetic acid (30 ml) and 35% (w/v) hydrogen peroxide (20 ml) was heated with stirring at 70°C for 7 h. The reaction mixture was cooled, the product which separated was filtered and washed with water to give 2-carbamoyl-5-methylpyrazine-4-oxide (5.5 g), melting point 206°-208°C.

2-Carbamoyl-5-methylpyrazine 4-oxide (5.0 g) was added to 10% by weight sodium hydroxide (50 ml) and then refluxed for 30 min. The reaction mixture was acidified with dilute hydrochloric acid and extracted in a continuous extractor with ethyl acetate. The ethyl acetate extract was concentrated to small volume and gave, after filtration 2-carboxy-5-methylpyrazine 4-oxide (3.2 g), melting point 178°-180°C.

References

GB Patent No. 1,361,967; July 31, 1974; Assigned: CARLO ERBA SPA an Italian body corporate of Via Carlo Imbonati 24, 20159 Milan, Italy

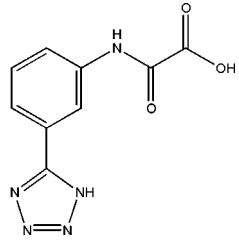
ACITAZANOLAST

Therapeutic Function: Anti-asthmatic, Antiallergic, Bronchodilator

Chemical Name: Acetic acid, oxo-((3-(1H-tetrazol-5-yl)phenyl)amino)-

Common Name: Acitazanolast; Azitanolast; Zepenolast

Structural Formula:



Chemical Abstracts Registry No.: 114607-46-4

Trade Name	Manufacturer	Country	Year Introduced
Zepelin	Kowa	-	-
Zepelin	Wakamoto	-	-

Raw Materials

3-(1H-Tetrazol-5-yl)aniline
Oxalyl chloride
Hydrochloric acid
Triethylamine
Sodium hydroxide

Manufacturing Process

2 Methods of preparation of 3-(1H-tetrazol-5-yl)oxanilic acid:

1. 5.0 g of 3-(1H-tetrazol-5-yl)aniline was dissolved in 25 ml of N,N-dimethylformamide, followed by adding 5.68 g of triethylamine. Then, 5.64 g of ether oxalyl chloride was dropwise added to the solution while cooling in ice water. After completion of the dropwise addition, the reaction temperature was slowly raised up to room temperature and the reaction was continued for 15 h. After the reaction was completed, the reaction mixture was poured into 100 ml of ice water and crystals separated out from the solution was filtered off to obtain 8.3 g of ethyl 3-(1H-tetrazol-5-yl)oxanilate (yield 94.1%), melting point 192°-l93°C (recrystallized from acetone/n-hexane).

The ethyl 3-(1H-tetrazol-5-yl)oxanilate (5.0 g), was dissolved in 35 ml of ethanol and 100 ml of 0.5 N sodium hydroxide was dropwise added thereto under water cooling. After the dropwise addition, the reaction temperature was slowly raised up to room temperature and under such condition, the reaction was carried out for 3 h. This solution was dropwise added to 70 ml of 4 N hydrochloric acid at room temperature. Thereafter, the solution was stirred for 1 h and crystals separated out from the solution was filtered off. The resultant crystals were washed with water and 3.9 g of 3-(1H-tetrazol-5-yl)oxanilic acid was recovered (yield 87.4%), melting point 241°-243°C (dec. recrystallized from isopropyl).

2. Oxalyl chloride (12.0 g) was dissolved in 50 ml of anhydrous dimethoxyethane. To this solution a solution of 3-(1H-tetrazol-5-yl)aniline (5.0 g) in 250 ml of anhydrous dimethoxyethane was dropwise added over 3 h at room temperature while stirring. Insolubles were removed by filtering the solution, then 50 ml of water was gradually added to the reaction mixture under ice cooling and stirring was continued for 1 h at room temperature. Then, 500 ml of ethyl acetate was added thereto to carry out extraction, the extract was washed with water, dried over anhydrous sodium sulfate and then the solvent was distilled off to obtain 5.4 g of the 3-(1H-tetrazol-5- yl)oxanilic acid (yield 74.8%), melting point 241°-243°C (dec. recrystallized from isopropyl).

References

Sawaki S. et al.; US Patent No. 4,795,754; Jan. 3, 1989Assigned: Wakamoto Pharmaceutical Co., Ltd., Tokyo, Japan

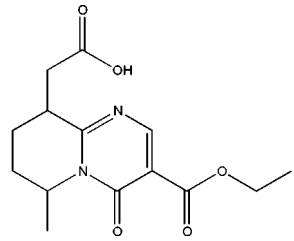
ACITEMATE

Therapeutic Function: Platelet aggregation inhibitor, Antihyperlipidemic

Chemical Name: 3-(Ethoxycarbonyl)-6,7,8,9-tetrahydro-6-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-9-acetic acid

Common Name: Acitemate; Vapedrine

Structural Formula:



Chemical Abstracts Registry No.: 64405-40-9

Trade Name	Manufacturer	Country	Year Introduced
Acitemate	Onbio Inc.	-	-

Raw Materials

3-Ethoxycarbonyl-7-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2a]pyrimidine
Palladium on carbon
Glyoxylic acid monohydrate
Hydrogen

Manufacturing Process

23.6 g of 3-ethoxycarbonyl-7-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2a]pyrimidine and 10.0 g of glyoxylic acid monohydrate are reacted and the obtained 3-ethoxycarbonyl-7-methyl-9-carboxy(hydroxymethyl)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2a]pyrimidine is heated in 150 ml ethanol under stirring for 3 h. After cooling the crystals are filtered off and recrystallized from ethanol. Thus 3-ethoxycarbonyl-7-methyl-9-(carboxymethylene)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2a]pyrimidine melting point 110°-112°C, is obtained (yield: 51%).

55.6 g of 3-ethoxycarbonyl-9-(carboxymethylene)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2a]pyrimidine are hydrogenated in 500 ml of ethanol in the presence of 20.0 g of 9% by weight Pd/C catalyst containing metal. When 1 mole of hydrogen has been used up, the catalyst is removed from the reaction mixture by filtration and the solution is evaporated under reduced pressure. The 3-ethoxycarbonyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-9-acetic acid is obtained (yield: 57%), melting point 156°-157°C (recrystallized from ethanol).

References

Hermecz I. et al.; US Patent No. 4,123,533; Oct. 31, 1978; Assigned: Chinoin Gyogyazer es Vegyeszeti Termekek Gyara R.T., Budapest, Hungary

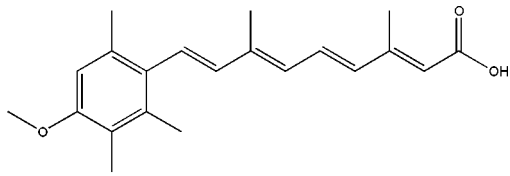
ACITRETIN

Therapeutic Function: Antipsoriatic

Chemical Name: 2,4,6,8-Nonatetraenoic acid, 3,7-dimethyl-9-(4-methoxy-2,3,6-trimethyl-phenyl)-, (all-E)

Common Name: Acitretin; Etretin

Structural Formula:



Chemical Abstracts Registry No.: 56079-83-9

Trade Name	Manufacturer	Country	Year Introduced
Acitretin	Roche	-	-
Neotigason	Roche Pty Limited	Australia	-
Neotigason	Roche	-	-
Soriatane	Roche Pharmaceuticals	-	-

Raw Materials

5-(4-Methoxy-2,3,6-trimethylphenyl)-3-methylpenta-2,4-diene-1-triphenylphosphonium bromide
3-Formylcrotonic acid butyl ester
Sodium hydride

Manufacturing Process

228 g of 5-(4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide was added under nitrogen to 910 ml of dimethylformamide and treated at 5-10°C within 20 min. with 17.5 g of a suspension of sodium hydride (about 50% by weight) in mineral oil. The mixture was stirred for 1 hour at about 10°C, then 61.8 g of 3-formylcrotonic acid butyl ester was added dropwise at 5-8°C, a mixture was heated for 2 hours at 65°C, subsequently introduced into 8 L of ice-water, then was added 300 g of sodium chloride, and the mixture thoroughly extracted with a total 18 L of hexane. The extract was washed 5 times with 1 L of methanol/water (6:4 parts by volume) each time and 2 times with 1.5 L water each time, dried over sodium sulphate and evaporated under reduced pressure to leave 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester, m.p. 80-81°C.

125.8 g of this ester was introduced into 2 L of abs. ethanol and treated with a solution of 125.6 g of hydroxide in 195 ml of water. The mixture was heated

to boiling under nitrogen gassing for 30 minutes, then cooled, introduced into 10 L of ice-water and, after the addition of about 240 ml of conc. hydrochloric acid (pH 2-4), thoroughly extracted with total 9 L methylene chloride. Extract is washed with about 6 L water to neutrality, dried over calcium chloride and evaporated under reduced pressure. The residue is taken up in 700 ml of hexane. The precipitated 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid melts at 228-230°C.

References

W. Bollang, R. Ruegg, G. Ryser, US Patent No. 4,105,681, Aug. 8, 1978

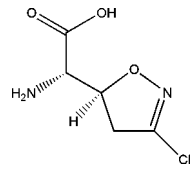
ACIVICIN

Therapeutic Function: Antineoplastic

Chemical Name: 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (S-(R*,R*))-

Common Name: Acivicin; NSC-163501

Structural Formula:



Chemical Abstracts Registry No.: 42228-92-2

Trade Name	Manufacturer	Country	Year Introduced
Acivicin	ZYF Pharm Chemical	-	-
LKT-A0934-M010	LKT Laboratories, Inc.	-	-

Raw Materials

cis-2-Buten-1,4-dio
Trichloroacetonitrile
Dibromoformaldoxime
Monotrichloroacetimidate
tert-Butyl benzene
Bromonitrile oxide

Manufacturing Process

Starting from commercial, cis-2-buten-1,4-diol, the monotrichloroacetimidate was obtained as a colorless liquid (60%, b.p. 88°-102°C/0.2 mm Hg) by treatment with trichloroacetonitrile (1 equivalent) in tetrahydrofuran at -23°C in the presence of catalytic amount of sodium. Monotrichloroacetimidate upon refluxing in tert-butyl benzene for about 1 hour underwent, smoothly,

rearrangement to afford the vinylglycine synton (84%, MP: 30°C). The treatment of the last compound with bromonitrile oxide (3 equiv.) generated in situ from dibromoformaldoxime in ethyl acetate containing excess of $KHCO_3$ and trace amounts of water afforded 3:2 mixture of cycloadducts threo- and erythro-N-[1-(3-bromo-4,5-dihydroisoxazol-5-yl)-2-hydroxyethyl]-2,2,2-trichloroacetamide. The undesired threo- isomer (MP: 164°-165°C) was quantitatively removed from the mixture by fractional crystallization from chloroform. The erythro-isomer (oil) was refluxed with methanolic-HCl for 1 hour to give the chloro-alchohol (50%, syrup), which upon Jones oxidation (with $H_2Cr_2O_7$/acetone) followed by deprotection of trichloroacetyl group ($Ba(OH)_2/H_2O$, H_3^+O) afforded racemic acivicin (66 %). The synthetic, racemic antibiotic was spectrally (UV, ^1H NMR) indistinguishable from natural product, prepared from fermentation broth of Stretomyces sviceus.

References

Vyas D.M., Chiang Y. and Doyle T.W.; Tetrahedron Letters, vol. 25, No 5, p.p. 487-490; 1984

Mrtin D.G., Duchamp D.J. and Chidester C.G.; Tetrahedron Letters, No 27, p.p. 2549-2552, 1973

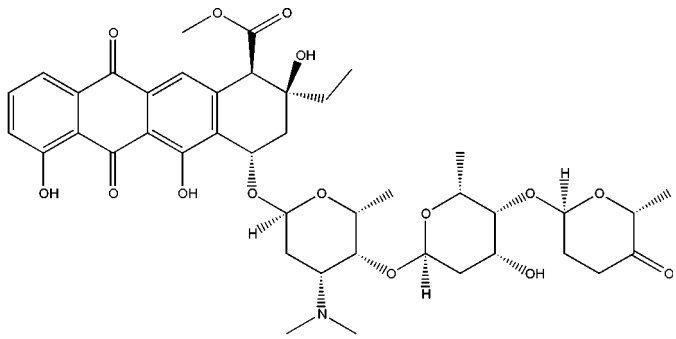
ACLARUBICIN

Therapeutic Function: Antitumor, Antibiotic

Chemical Name: Aclacinomycin A

Common Name: Aclacinomycin A

Structural Formula:



Chemical Abstracts Registry No.: 57576-44-0

Trade Name	Manufacturer	Country	Year Introduced
Aclacinon	Yamanouchi	Japan	1981
Aclacinomycine	Roger Bellon	France	1981

Raw Materials

Carbohydrates

Manufacturing Process

An aqueous medium having the following composition was prepared:

	Percent
Potato starch	1
Glucose	1
Prorich	1.5
KH_2PO_4	0.1
	Percent
K_2HPO_4	0.1
$MgSO_4 \cdot 7H_2O$	0.1
NaCl	0.3
Minerals*	0.125
Silicone (KM75)	0.05
pH	7.0

*2.8 g $CuSO_4 \cdot 5H_2O$, 0.4 g $FeSO_4 \cdot 7H_2O$, 3.2 g $MnCl_2 \cdot 4H_2O$, 0.8 g $ZnSO_4 \cdot 7H_2O$ in 500 ml water

100 ml of this medium was sterilized at 120°C for 15 min in a 500 ml Sakaguchi-shaking flask which was inoculated from an agar slant culture of Streptomyces galilaeus MA144-M1 by platinum loop. Incubation proceeded for 48 hr at 28°C on a reciprocal shaker. 10 L of the previously sterilized medium in a 20 L stainless steel jar fermenter were aseptically inoculated with 200 ml of the above seed cultures. Fermentation was carried out at 28°C for 32 hours with agitation (240 rpm) and aeration (5 L/min). The cultured broth obtained was adjusted to pH 4.5, mixed with an adsorbent siliceous earth material and filtered from the mycelium. The filtrate and cake obtained thereby were extracted separately. The cake was suspended in acetone (3 L/kg wet cake), stirred for 2 hr and filtered, and the cake was further extracted with acetone once again. The extracts thus obtained were evaporated to one-tenth volume in vacuum. The culture filtrate was adjusted to pH 6.8 and extracted twice with one-third volume of ethyl acetate, and the ethyl acetate extracts were concentrated to one-tenth volume in vacuum.

Twenty grams of the resulting oily substances were mixed with 20 grams of silicic acid (Mallinckrodt Chemical Co.), applied to a column 40 cm in length and 4.5 cm in diameter filled with silicic acid, and eluted with a benzene-acetone-methanol mixture. The initial eluate which eluted with a 1:1:0 mixture was discarded and the active fractions eluted with 1:3:0 and 1:3:0.3 mixtures were collected and concentrated to dryness in vacuum. 11.5 g of this crude substance was then dissolved in a small amount of ethyl acetate and applied to the same silicic acid column as above. After discarding the initial eluates by the 1:1 and 2:1 benzene-acetone mixtures, aclacinomycin B fractions were first eluted with the above mixtures of 1:3 and 1:5 ratio, and aclacinomycin A fractions were then eluted with the 1:5:0.5 and 1:5:1

benzene-acetone-methanol mixtures. The eluates were dried over anhydrous sodium sulfate and concentrated to dryness in vacuum. 4.8 g of crude aclacinomycin A and 3.5 g of aclacinomycin B were obtained as yellow powder.

2.0 g of crude aclacinomycin A obtained as above were dissolved in a small amount of chloroform, applied to a column 20 cm in length and 20 cm in diameter filled with 30 g of silicic acid. After eluting off the pigments containing aglycone and aclacinomycin B and other impurities with chloroform and 1.5% methanol-containing chloroform, aclacinomycin A fractions were eluted with 2% methanol-containing chloroform, and concentrated to dryness in vacuum. 53 mg of yellow powder of aclacinomycin A was obtained. Its melting point was 129°C to 135°C.

References

DFU2 (3) 171 (1978) (as Aclacinomycin A)
DOT 18 (10) 517 (1982)
I.N. p.42 (1984)
Umezawa, H., Takeuchi, T., Hamada, M., Takamatsu, A. and Oki, T.; US Patent 3,988,315; October 26, 1976; Assigned to Zaidan Hojin Biseibutsu Kagaku Kenkyu Kai

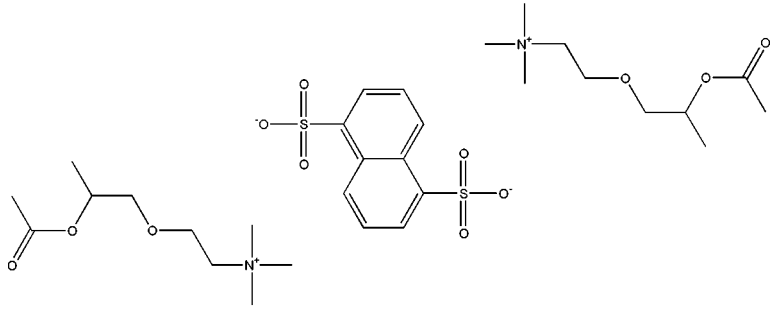
ACLATONIUM NAPADISYLATE

Therapeutic Function: Cholinergic

Chemical Name: 2-[2-(Acetyloxy)-1-oxopropoxy]-N,N,N-trimethylethan-aminium 1,5-naphthalenedisulfonate (2:1)

Common Name: Bis[acetoxy-methyl acetic acid trimethylammoniumethyl ester]-naphthalene-1,5-disulfonate

Structural Formula:



Chemical Abstracts Registry No.: 55077-30-0

Trade Name	Manufacturer	Country	Year Introduced
Abovis	Toyama	Japan	1981

Raw Materials

Bis(choline)-naphthalene-1,5-disulfonate
Lactic acid anhydride diacetate

Manufacturing Process

5.2 g of bis(choline)-naphthalene-1,5-disulfonate was suspended in 30 ml of acetonitrile, and 10 g of lactic acid anhydride diacetate was added thereto. This mixture was refluxed for 3 hours. The resulting reaction mixture was allowed to stand at room temperature while cooling to precipitate the desired product crystals, which were collected by filtration. 5.5 g (76% yield) of the desired product having a melting point of 189°C to 191°C were obtained.

References

Merck Index 110
DFU 7 (4) 227 (1982)
DOT 19 (1) 8 (1983)
I.N.p.42
Miura, K., Takagawa, N., Suzuki, Y. and Matsumoto, Y.; US Patent 3,903,137; September 2, 1975; Assigned to Toyama Chemical Co., Ltd.

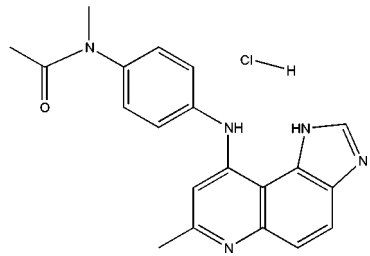
ACODAZOLE HYDROCHLORIDE

Therapeutic Function: Antineoplastic

Chemical Name: Acetamide, N-methyl-N-(4-((7-methyl-1H-imidazo[4,5-f]quinolin-9-yl)amino)phenyl)-, hydrochloride

Common Name: Acodazole hydrochloride; NSC-305884

Structural Formula:



Chemical Abstracts Registry No.: 55435-65-9; 79152-85-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Acodazole Hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

Acetic anhydride	N-Methyl-p-nitroaniline
Hydrogen	Nickel Raney
5-Nitrobenzimidazole	Palladium on carbon
Ethyl acetoacetate	Calcium sulfate
Acetic acid	$POCl_3$
Sodium hydroxide	Dowtherm®

Manufacturing Process

An 82.0 g (0.5 mole) of 5-nitrobenzimidazole in 900 ml of ethanol was reduced over 4.0 g of 5% Pd/C catalyst containing 50% H_2O. After filtration of the catalyst, 65.0 g (0.5 mole) of ethyl acetoacetate, 20.0 g of anhydrous calcium sulfate, and 0.5 ml of HOAc was added. After filtration, the solution was concentrated in vacuo till a solid remained. The product was filtered and washed with fresh ethanol and air-dried. The yield of ethyl 3-(5-benzimidazolylamino)crotonate was 84.0 g (69%), melting point 160°-162°C.

40.0 g of ethyl 3-(5-benzimidazolylamino)crotonate was added to 80 ml of boiling Dowtherm® and the boiling was continued for 5 min. The product separated upon cooling. The product was filtered, washed with Dowtherm® and then acetone and air-dried. The yield of 7-methyl-9-imidazo[4,5-f]quinolinol was 29.0 g (91%), melting point 345°-347°C.

Into a 22 L, 4-necked flask set in a tub and equipped with a stirrer, an air condenser (drying tube), thermometer, and dropping funnel was placed $POCl_3$ (4590 ml). The 7-methyl-9-imidazo[4,5-f]quinolinol (1062.0 g, 5.33 moles) was added with no heating effect noted. Dimethylformamide (4690 ml) was added dropwise over a 2.5 h period at a rate to control the temperature below 85°C. The resulting viscous solution was allowed to stand overnight at room temperature and then added cautiously to ice to a total volume of ca. 50 L. The resulting solution was then adjusted to a pH of 7 to 8 by the addition of NaOH pellets (9771.0 g). More ice was added as needed to keep the temperature below 45°C. The resulting precipitate was collected by filtration, washed well by stirring in water (3x20 L) and dried at 60°C to yield 1107.0 g (95.5%) of 9-chloro-7-methylimidazo[4,5-f]quinolone.

To 500 ml of acetic anhydride was added portionwise, 100.0 g (0.658) of N-methyl-p-nitroaniline. Following the addition, the solution was heated on a steam bath for 2 h, then stirred overnight at room temperature. The white precipitate of the N-methyl-4-nitroacetanilide was collected by filtration, washed with ether and air-dried to give 53.0 g, melting point 153°-156°C. The filtrate was concentrated in vacuum to give another 61.0 g, melting point 150°-154°C.

A mixture of 114.0 g (0.587 m) of N-methyl-4-nitroacetanilide and 800 ml of ethanol was shaken with hydrogen over one teaspoon of Raney active nickel catalyst in water. A pressure drop of 127 psi was recorded (calc. 118 psi). The catalyst was removed by filtration and the ethanol filtrate refluxed overnight with 127.0 g (0.587 m) of the 9-chloro-7-methylimidazo[4,5-f]quinolone. The mixture was chilled, filtered, washed with ether and air-dried to give 75.5 g of 9-[p-(N-methylacetamido)anilino]-7-methyl-1-H-imidazo[4,5-f]quinoline

hydrochloride sesquihydrate, melting point 315°-318°C (recrystallized from 4,000 ml of MeOH).

By treatment of 9-p-(N-methylacetamido)anilino-7-methyl-1H-imidazo[4,5-f]quinolone hydrochloride sesquihydrate with NaOH may be produced the 9-p-(N-methylacetamido)anilino-7-methyl-1H-imidazo[4,5-f]quinolone.

References

Spencer C.F., Snyder H.R.; US Patent No. 3,878,206; April 15, 1975; Assigned: Morton-Norwich Products, Inc., Norwich, N.Y.

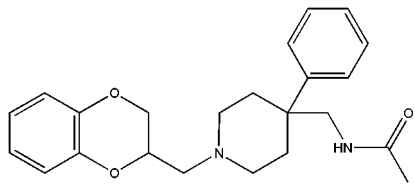
ACOXATRINE

Therapeutic Function: Vasodilator, Antihypertensive

Chemical Name: Acetamide, N-((1-(1,4-benzodioxan-2-ylmethyl)-4-phenyl-4-piperidyl)methyl)-

Common Name: Acetoxatrine; Acoxatrine

Structural Formula:



Chemical Abstracts Registry No.: 748-44-7

Trade Name	Manufacturer	Country	Year Introduced
Acoxatrine	ZYF Pharm Chemical	-	-

Raw Materials

Lithium aluminum hydride
Acetyl chloride
DL-1-Cyano-4-phenyl-piperidine
Sodium hydroxide

Manufacturing Process

To a solution of 11.5 parts lithium aluminum hydride in 100 parts tetrahydrofurane is added dropwise a solution of 94 parts DL-1-cyano-4-phenyl-piperidine in 240 parts tetrahydrofurane, at a temperature of about 45°C. After the addition is complete, the reaction mixture is stirred first at the same temperature for 3 h and 30 min and then refluxed for 1 h. The whole is decomposed by successive addition of 12 parts water, 9 parts sodium

hydroxide 20% and 50 parts water. The mixture is filtered from inorganic matter. The filter-cake is washed with tetrahydrofurane and the combined filtrates are evaporated. The oily residue is dissolved in 240 parts 2-propanol and to this solution are added about 60 parts concentrated hydrochloric acid. After keeping at room temperature, the precipitated salt is filtered off, washed with 2-propanol and dried, yielding DL-4-(amino-methyl)-1-[1,4-benzodioxanyl)methyl]-4-phenylpiperidine dihydrochloride; melting point 272°-278°C as a white amorphous powder.

From 4.1 parts DL-4-(aminomethyl)-1-[2-(1,4-benzodioxanyl)methyl]-4-phenylpiperidine dihydrochloride, the free base is liberated in the usual manner and extracted with chloroform. The organic layer is separated, dried and evaporated. The DL-4-(aminomethyl)-1-[2-(1,4-benzodioxanyl)methyl]-4-phenylpiperidine obtained is dissolved in 128 parts anhydrous chloroform. This solution is cooled to 5°C and there is added dropwise a solution of 1.6 parts acetylchloride in 7 parts anhydrous chloroform (exothermic reaction). The reaction mixture is stirred over night at room temperature and then alkalized with about 25 parts sodium hydroxide 20% at a temperature of 20°C. The aqueous layer is separated and extracted twice with chloroform. The combined organic layers are washed with water, dried over magnesium sulfate, filtered and evaporated. The oily residue is dissolved in a mixture of 40 parts acetone and 20 parts diisopropyl ether and evaporated again. The solid residue is triturated in diisopropylether, yielding DL-4-(N-acetylaminomethyl)-1-[2-(1,4-benzodioxanyl)-methyl]-4-phenylpiperidine; melting point 140°-141.1°C, as a white microcrystalline powder.

References

Janssen P.A.J.; US Patent No. 3,166,561; January 19, 1965; Assigned: Research Laboratorium Dr. C. Janssen N.V., a corporation of Belgium

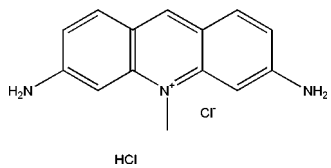
ACRIFLAVINE HYDROCHLORIDE

Therapeutic Function: Antiseptic, Topical antibacterial

Chemical Name: Acridinium, 3,6-diamino-10-methyl-, chloride, monohydrochloride, mixture with 3,6-acridinediamine hydrochloride

Common Name: Acid acriflavine; Acriflavin; Acriflavinium chloride; Euflavin; Flavacridinum; Xanthacridinum

Structural Formula:



Chemical Abstracts Registry No.: 6034-59-9; 837-73-0 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Acriflavine hydrochloride	ABCR GmbH and Co. KG	-	-
Acriflavine hydrochloride	Advance Scientific and Chemical, Inc.	-	-
Acriflavine hydrochloride	Spectrum Chemicals and Laboratory Products, Inc.	-	-
Acriflavine hydrochloride	Ruger Chemical Co., Inc.	-	-
Acriflavine hydrochloride	AppliChem	-	-
Acriflavine hydrochloride	Amend Drug and Chemical Company	-	-
Acriflavine hydrochloride	CCA (Changzhou) Biochemical Co., Ltd.	-	-
Acridina	Fatro	-	-
Acriflavin	Koi	-	-
Acriflavin	Vipor Chemicals Pvt.Ltd.	-	-
Acriflavin	Advance Scientific and Chemical, Inc.	-	-
Acriflavin	C. Krieger + Co. Nachf. GmbH + Co.	-	-
Acriflavin	Exim-Pharm International	-	-
Acriflavin	Hasco-Lek	-	-
Acriflavin	Dr Zdrowie SA	-	-
Acriflavin	Rasfer Internacional, S.A.	-	-
Acriflavin	Trannspharma, Sas	-	-
Acriflavin	Mediplus International	-	-
Acriflavin	Unical (Ceylon) Limited	-	-
Acriflavin	Olita Scientific Works	-	-
Acriflavin	Hygea SA; Polska Grupa Aptekarska	-	-
Acriflavin	Internatio NV	-	-
Acrinol	Pasteur	-	-
Burnol	Boots Company PLC	-	-
Diacrid	Sidroga AG	-	-
Euflavin	Macsen Laboratories	-	-
Gonacrine	May and Baker	-	-
Panflavin	Chinosolfabrik	-	-
Trypaflavin	Zoolek	-	-

Raw Materials

4,4-Diaminodiphenylmethane
Nitric acid
Hydrochloric acid
Tin
Ferric chloride
Acetanhydride
4-Toluolsulfomethyl ether

Manufacturing Process

4,4-Diaminodiphenylmethane reacted with HNO_3 and as a result of this reaction 4,4-diamino-2,2-dinitro-diphenylmethane was obtained.

By reducing of 4,4-diamino-2,2-dinitro-diphenylmethane with HCl and Sn, 2,2,4,4-tetraaminodiphenylmethane was produced, which at heating to 150°C gave 3,6-diamino-9,10-dihydroacridine.

The 3,6-diamino-9,10-dihydroacridine by oxidation with $FeCl_3$ was converted to 3,6-diaminoacridine.

3,6-Diaminoacridine was reacted with acetanhydride and 3,6-bis-(acetylamino)-acridine was produced.

3,6-Bis-(acetylamino)-acridine was methylated by p-toluolsulfomethyl ether and 3,6-bis-(acetylamino)-10-methylacridinumtosylate was produced.

Then the 3,6-bis-(acetylamino)-10-methylacridinumtosylate was converted to 3,6-diamino-10-methylacridinum chloride (acriflavinum chloride) by reaction with hydrochloric acid.

References

Kleemann A., Engel J.; Pharmazeutische Wirkstoffe, GeorgThieme Verlag Stuttgart, New York, 1982

ACRISORCIN

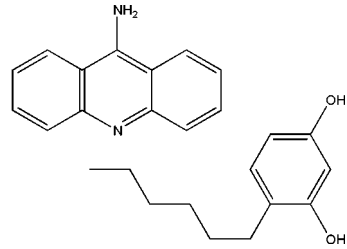
Therapeutic Function: Antifungal, Anthelmintic

Chemical Name: 1,3-Benzenediol, 4-hexyl-, compd. with 9-acridinamine (1:1)

Common Name: Acrisorcin; Akrinol; Aminacrine hexylresorcinate

Chemical Abstracts Registry No.: 7527-91-5

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Aminacrine hexylresorcinate	ZYF Pharm Chemical	-	-

Raw Materials

4-Hexylresorcinol
Hydrochloric acid
Potassium hydroxide
9-Aminoacridine

Manufacturing Process

4-Hexylresorcinol 194.0 g is added to a solution composed of 56.1 g potassium hydroxide in 1.5 L of water with stirring, and the mixture heated to about 40°C to effect complete solution. The pH of this solution is 12. A second solution of 9-aminoacridine hydrochloride is prepared as follows: 2 L of water containing 83 ml of concentrated hydrochloric acid are heated with stirring to about 80°C. Slowly 194.0 g of 9-aminoacridine are added. Heating is continued until a clear solution is obtained. About 2 ml of additional concentrated hydrochloric acid are added in small increments until the solution is slightly acid (pH of about 6). The 4-hexyl resorcinol solution is now slowly added under rapid agitation to the 9-aminoacridine hydrochloride solution. A copious precipitate is formed which, upon :stirring and continued addition of the 4-hexylresorcinol solution, becomes a creamy yellow slurry. At the end of the addition, the pH is 7-8 (indicator paper). The slurry is stirred while heated for an additional 15 min and then rapidly filtered on a 15 cm Buchner funnel. The product thus obtained is washed thoroughly, using about 1 L of cold water, to give a very pale yellow color in the last wash. The compound is then pressed dry and then oven-dried for 2-3 h at 50°C. The resultant product, 9-aminoacridine 4-hexyl resorcinolate, has a melting point of 189°-190°C.

References

Seneca H.; US Patent No. 3,122,553; Feb. 25, 1964; Assigned: Bansen, Inc., New York, N.Y., a corporation of New York

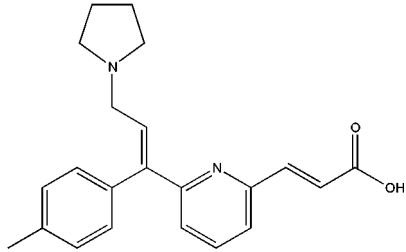
ACRIVASTINE

Therapeutic Function: Antihistaminic

Chemical Name: 2-Propenoic acid, 3-(6-(1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl)-2-pyridinyl)-, (E,E)-

Common Name: Acrivastine; Semprex

Structural Formula:



Chemical Abstracts Registry No.: 87848-99-5

Trade Name	Manufacturer	Country	Year Introduced
Acrivastine	ZYF Pharm Chemical	-	-
Semprex Cap.	Glaxo Wellcom-Misr Co.	-	-
Benadryl	Warner-Lambert	-	-
Benadryl	Pfizer	-	-

Raw Materials

Sulfuric acid	Triphenyl-2-pyrrolidinoethylphosphonium bromide
Butyl lithium	2,6-Dibromopyridine
4-Tolunitrile	Hydrochloric acid
Sodium carbonate	4-Toluenesulfonic acid
Ammonia	Sodium hydride
Sodium hydroxide	Triethyl phosphonoacetate

Manufacturing Process

Butyl lithium (50 ml, 1.65 mol in hexane) was added under nitrogen to a stirred suspension of 2,6-dibromopyridine (19.5 g) in dry ether (200 ml) at -50°C. After 0.75 h a solution of 4-tolunitrile (10.0 g) in ether (50 ml) was added; stirring was continued at -50°C for 3 h. The mixture was allowed to warm to -30°C and treated with hydrochloric acid (200 ml, 2 mol). The precipitated solid was collected, washed with water to give the 2-bromo-6-(4-toluoyl)pyridine as colourless needles (12.2 g), melting point 97°-98°C (recrystallized from aqueous ethanol).

A mixture of 2-bromo-6-(4-toluoyl)pyridine (200.0 g), ethylene glycol (85 ml), p-toluenesulphonic acid (32.0 g) and benzene (11 ml) was boiled under a Dean/Stark trap until water collection had become very slow (about 20 ml collected in 16 h).

The cooled solution was poured into ice/water containing sodium carbonate (100.0 g) with stirring. The benzene layer was separated, washed with water, dried with sodium sulfate and evaporated to about 500 ml. Cooling gave a

first crop of 2-(6-bromo-2-pyridyl)-2-(4-tolyl)-1,3-dioxolan, melting point 113°-114°C (170.0 g). Dilution with petroleum ether gave a second crop, melting point 109°-112°C (34.0 g). The residue after evaporation (31.0 g) was recycled.

A solution of 2-(6-bromo-2-pyridyl)-2-(4-tolyl)-1,3-dioxolan, vide supra, (70.0 g) in dry toluene (800 ml) was added dropwise during 5 h to a stirred solution of butyl lithium (1.6 mol in hexane, 200 ml) and toluene (200 ml) at -65° to -72°C under nitrogen. After a further 30 min at -70°C, dry dimethylformamide (40 ml) was added during 35 min. Stirring continued overnight at -70° to -60°C. Hydrochloric acid (2 N, 400 ml) was added, allowing the temperature to rise to about -10°C. After 30 min, 2 N ammonia (ca. 90 ml) was added to pH 7-8. The toluene layer was separated and the aqueous phase was extracted with ether. The combined organic liquids were washed with ice/water, dried ($MgSO_4$) and evaporated in vacuum below 50°C. The aldehyde, 2-(6-formyl-2-pyridyl)-2-(4-tolyl)-1,3-dioxolan, (63.9 g) crystallized on keeping at 3°C, melting point 52-63°C.

The 2-(6-formyl-2-pyridyl)-2-(4-tolyl)-1,3-dioxolan (2.5 g) was dissolved in 1,2-dimethoxyethane (10 ml) and added to a solution of the phosphonate carbanion produced from triethyl phosphonoacetate (2.0 g) and sodium hydride (0.22 g) in the same solvent. The mixture was stirred for 2 h, diluted with ether (25 ml) and treated with hydrochloric acid (5 ml, 2 mol). The organic phase was separated, washed with water, dried, and evaporated. The resulting oil was dissolved in ethanol (20 ml) containing concentrated hydrochloric acid (3 ml) and water (3 ml). After heating on the steam bath for 10 min, the solution was diluted with ice water, rendered alkaline with sodium bicarbonate solution, and extracted with ether. Evaporation gave 1.0 g ((E)-3-(6-(4-toluoyl)-2-pyridyl)acrylate as colourless platelets, melting point 108°-111°C (crystallized from cyclohexane).

Butyl lithium (10 ml, 1.64 mol in hexane) was added under nitrogen to a stirred suspension of triphenyl-2-pyrrolidinoethylphosphonium bromide (7.2 g) in dry toluene (75 ml). After 0.5 h, ((E)-3-(6-(4-toluoyl)-2-pyridyl)acrylate, vide supra, (4.8 g) in toluene (50 ml) was added. The suspension, initially orange, became deep purple, then slowly faded to yellow during 2 h heating at 75°C. The cooled solution was diluted with ether (150 ml) and treated with hydrochloric acid (50 ml, 2 mol). The aqueous phase was separated, washed with ether, and basified with potassium carbonate (ice) and extracted with ether. The mixture of isomeric esters obtained by evaporation was dissolved in ethanol (100 ml) containing sodium hydroxide solution (20 ml, 1 mol) and partially evaporated on the steam bath under reduced pressure for 5 min. The residual aqueous solution was neutralized with sulfuric acid (20 ml, 0.5 mol) and evaporated to dryness. The solid residue was extracted with hot isopropanol (3x50 ml) and the extracts were concentrated until crystallization commenced. The (E)-3-(6-(3-pyrrolidino-1-(4-tolyl)prop-1-(E)-enyl)-2-pyridyl)acrylic acid, melting point 222°C (dec. recrystallization from isopropanol) was obtained.

References

Coker G.G., Findlay J.W.A.; EU Patent No. 0,085,959; Feb. 3, 1983; Assigned: The Wellcome Foundation Limited 183-193 Euston Road, London NW1 2BP(GB)

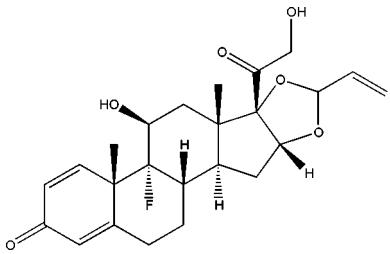
ACROCINONIDE

Therapeutic Function: Antiinflammatory, Antiallergic

Chemical Name: (11β,16α)-9-Fluoro-11,21-dihydroxy-16,17-[2-propenylidenebis(oxy)]pregna-1,4-diene-3,20-dione

Common Name: Acrocinonide

Structural Formula:



Chemical Abstracts Registry No.: 28971-58-6

Trade Name	Manufacturer	Country	Year Introduced
Acrocinonide	Onbio Inc.	-	-

Raw Materials

9-Fluoro-11β,16α,17,21-tetra-hydroxy-pregna-1,4-diene-3,20-dione
Perchloric acid
Sodium bicarbonate
Acrolein

Manufacturing Process

A suspension of 1.0 g of 9-fluoro-11β,16α,17,21-tetra-hydroxy-pregna-1,4-diene-3,20-dione in a mixture of 35 ml of dioxan, 15 ml of acrolein and 0.1 ml of perchloric acid was stirred for 3 h at room temperature. The clear solution thus obtained was poured into an aqueous saturated solution of sodium bicarbonate. The mixture was extracted twice with benzene, and the benzenic extract was concentrated to a small volume. The resulting crystals were collected and the 9-fluoro-11β,21-dihydroxy-16α,17-(2-propenylidenedioxy)-pregna-1,4-diene-3,20-dione was obtained as white crystals, melting point 200°-205°C.

References

GB Patent No. 1,292,269; Oct. 11, 1972; Assigned: ROUSSEL-UCLAF SOCIETE ANONYME, a body corporate organized under the laws of France, of 35 Boulevard des Invalides, Paris 7e, France

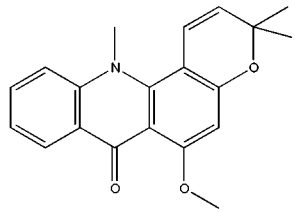
ACRONINE

Therapeutic Function: Antineoplastic

Chemical Name: 7H-Pyrano[2,3-c]acridin-7-one, 3,12-dihydro-6-methoxy-3,3,12-trimethyl-

Common Name: Acronine; Acronycine; NSC-403169

Structural Formula:



Chemical Abstracts Registry No.: 7008-42-6

Trade Name	Manufacturer	Country	Year Introduced
Acronine	ZYF Pharm Chemical	-	-

Raw Materials

2-Nitrobenzoyl chloride
3-Chloro-3-methylbutyne
Sodium hydride
3,5-Dimethoxyphenol
Zinc
Methyl iodide

Manufacturing Process

The acridone alkaloids constitute a small group of natural products found exclusively in the Rutaceae family of higher plants. A sustained interest in this field has been due to the reported activity of acronycine a constituent of Acronnychia baueri and Vepris amphody as an anti-tumor agent.

There are different methods of the synthetic preparation of acronycine (W. M. Bandaranayake et al., J. Chem. Soc. Perkin 1, 998 (1968); J. Hlubucek et al.; Aust. J. Chem. 23, 1881 (1970). One of them is described below. Friedel-Crafts condensation between 2-nitrobenzoyl chloride and 3,5-dimethoxyphenol.

2-Nitrobenzoyl chloride (12 g) and $AlCl_3$, (anhyd., 13 g) were dissolved in dry ether (50 ml) and this mixture added to a solution of 3.5-dimethoxyphenol (5 g) in dry ether 150 ml) at 0°C and the final mixture stirred at 0°C for 3 hours, brought to 20°C and stirred for a further 3 h. Diluted HCl and ice were added and the product extracted with EtOAc (3x50 ml), this extract was washed with aq. $NaHCO_3$, water, dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield a dark red oil. This oil was treated with 2 M aq. NaOH. (100 ml) for 1 h., acidified with diluted HCl and re-extracted with

EtOAc which gave, after a similar work up, a paled red oil (5.0 g). Thin layer chromatography (TLC) showed three components one of which was the starting phenol. Column chromatography (150 g silica gel) and elution with benzene:petrol ether 40°-60°C (1:1) followed by increasing polarity of solvents (benzene through chloroform to chloroform:ether (4:1) gave 59 fractions. Fractions 1-12 were combined to gave a solid, which crystallized from benzene to give 4,6-dimethoxy-2-hydroxy-2-nitrobenzophenone, MP: 198°-199°C. Fractions 13-21 were discarded. Fractions 22-42 were combined (0.3 g), crystallized from benzene and the product added to that obtained from fractions 43-59 which crystallized from benzene to give 2,6-dimethoxy-7-hydroxy-2-nitrobenzophenone (0.5 g) MP: 175°-177°C.

Condensation of 3-chloro-3-methylbutyne with 2,6-dimethoxy-7-hydroxy-2-nitrobenzophenone:

A solution of the above benzophenone (2 g) and excess 3-chloro-3-methylbutyne (4.5 g) in dry DMF (60 ml) containing anhydrous K_2CO_3 (4 g) and dry KI (2 g) was stirred and heated at 65°C for 14 hours (under N_2). The mixture was cooled, diluted with water, acidified, extracted with chloroform (3x50 ml) and the extract was worked up in the usual way (including a NaOH wash) to give an oil, which was redissolved in DMF (20 ml) and heated at 130°C, under N_2, for 7 h whence most of the starting material had disappeared. The solvent was removed under reduced pressure to give a product (0.62 g) which was purified by preparative layer chromatography on silica gel to give 6-(2-nitrobehzoyl)-5,7-dimethoxy-2,2-dimethylchromene (0.22 g) which crystallized from EtOH, MP: 92°-93°C.

6-(2-Aminobenzoyl)-5,7-dimethoxy-2,2-dimethylchromene (0.2 g) was dissolved in EtOH (30 ml) containing water (5 ml) and ammonium chloride (1 g) and Zn mossy (1.5 g) was added in portions and the mixture stirred at room temperature for 5 days. The solution was filtered, evaporated to dryness under reduced pressure and the residue dissolved in EtOAc (25 ml) and worked up in the usual way to give a solid (0.19 g). It crystallised from EtOH with MP: 123°-126°C.

Cyclization of aminodimethylchromenylbenzophenone: 6-(2-aminobenzoyl)-5,7-dimethoxy-2,2-dimethylchromene (0.12 g) was dissolved in DMSO (8 ml) and NaH (0.06 g) added, the mixture was stirred for 6 days at room temperature. A further addition of NaH (0.06 g) was made and the solution heated to 50°C for 0.5 h whence it was poured into water, extracted with EtOAc and worked up in the usual way to give a crude mixture (0.11 g; components). Separation of this mixture on plate (silica gel:benzene:EtOAc, 10:4) gave band 1 (R_f 0.45: 38 mg) identified as starting material. Band 2 (R_f 0.32: 42 mg; 43%) which crystallized from ethylacetate as des-N-methylisoacronycine, MP: 293°-295°C. Band 3 (R_f 0.10; 29 mg, 29%) crystallized from ethyl acetate as des-N-methylacronycine. MP: 237°-240°C.

Des-N-methylacronycine (14 mg) was dissolved in dry acetone (10 ml), anhydrous K_2CO_3 (1 g), and MeI (2 ml) added and the mixture refluxed for 11 hours. The solution was filtered and the solvents evaporated to give a solid (12 mg) which after purification on TLC, gave acronycine which crystallized from aqueous MeOH, MP: 171°-173°C. This product showed identical U.V. and R_f characterization when compared with acronycine and had an accurate mass

measurement of 321.1368. $C_{20}H_{19}NO_3$, required: 321.1364. UV and ^1H NMR spectrum confirmed the structures of all described compounds.

References

Adams Joyce H. et al.; Tetrahedro,n v.37, pp 209-217, 1981
Coker G.G., Findlay J.W.A.; EU Patent No. 0,085,959; Feb. 3, 1983; Assigned: The Wellcome Foundation Limited 183-193 Euston Road, London NW1 2BP(GB)

ACTAPLANIN

Therapeutic Function: Growth stimulant

Chemical Name: See structure

Common Name: -

Structural Formula: Complex of glycopeptide antibiotics produced by Actinoplanes missourinesis

Chemical Abstracts Registry No.: 37305-75-2

Trade Name	Manufacturer	Country	Year Introduced
Actaplanin	Onbio Inc.	-	-

Raw Materials

Potassium chloride
Ferric sulfate
Agar
Hydrochloric acid
Dextrin
Yeast extract
Dextrose
Peptone
Corn steep liquor
Sulfuric acid
Actinoplanes sp
Magnesium sulfate heptahydrate
Yeast
Pre-cooked oatmeal
Glucose
Soybean meal
Calcium carbonate
Dextrin
Molasses, beet sugar
Betaine
Potassium phosphate dibasic

Manufacturing Process

The microorganism used for the production of antibiotic Actaplanin (A-4696) has been identified as a strain of a species of Actinoplanes of the family Actinoplanaceae. The Actinoplanaceae are a new family of microorganisms of the order Actinomycetales, having been first described by Dr. John N. Couch, Jour. Elisha Mitchell Sci. Soc., 65, 315-318 (1949).

The Actinoplanes sp. useful for the production of A-4696 was isolated from a sample of soil obtained from the Cascade mountain area in the state of

Washington.

Mycelial fragments of Actinoplanes sp., strain ATCC 23342 were inoculated on a nutrient agar slant having the following composition (g): pre-cooked oatmeal 60.0; yeast 2.5; K_2HPO_4 1.0; dried distiller's solubles 5.0; Czapek's mineral stock 5.0 ml; agar 25.0; water, deionized 1 L; Czapek's mineral stock has the following composition (g): KCl 100.0; $MgSO_4 \cdot 7H_2O$ 100.0; $FeSO_4 \cdot 7H_2O$ 2.0; (dissolve in 2 ml conc. HCl); deionized water 1 L.

The slant was inoculated with ATCC 23342 and incubated for 6 days at 30°C. The culture does not normally sporulate on this medium, and it is necessary to macerate the mycelial mat with a flattened, sharpened, inoculating needle in order to increase the number of potential growth centers. The macerated mature culture was covered with sterile distilled water and scraped carefully with a sterile rod to obtain a mycelial suspension.

The suspension thus obtained was used to inoculate 100 ml of a sterile vegetative medium having the following composition (g): glucose 5.0; dextrin 20.0; soybean meal 5.0; yeast extract 2.5; calcium carbonate 1.0; tap water 1 L.

The inoculated vegetative medium was grown for 48 h at 30° on a rotary shaker operating at 250 rpm. 10 ml of the incubated vegetative medium was inoculated into 100 ml of a sterile "bump" medium of the same composition as given next above. The thus inoculated "bump" medium was incubated for 24 h at 30°C with constant shaking on a rotary shaker operating at 250 rpm.

0.4 ml of the incubated "bump" medium was inoculated into 100 ml portions of a production medium of the composition shown below contained in 500 ml. Erlenmeyer flasks, and sterilized at 120°C for 30 min (g): dextrose 1.0; dextrin 3.0; peptone 1.5; soybean meal 0.5; $MgSO_4 \cdot 7H_2O$ 0.2; molasses, beet sugar 1.5; corn steep liquor 0.5; betaine 0.1; K_2HPO_4 0.05; deionized water q.s. 25 L.

The pH of the medium was adjusted to 7.5 with 5 N sodium hydroxide solution before sterilization. After sterilization the pH was approximately 6.9. The production fermentation was shaken for about 96 h at a temperature of 30°C on a rotary shaker operating at 250 rpm. The pH at the end of the fermentation cycle was about 7.2.

The preparation of the inoculum proceeded through the incubation of the "bump" medium detailed above 25 L of a production medium as outlined above, with 0.02% Dow Corning antifoam added, was sterilized by autoclaving at 120°C for 30 min and charged into a 40 L fermentation tank. 100 ml of incubated "bump" medium was inoculated into the sterile production medium. The inoculated production medium contained in the 40 L tank was allowed to ferment for 4 days at 30°C. The fermentation was aerated with sterile air in an amount of about 0.5 volume of air per volume of culture medium per minute. The fermenting production medium was agitated with a mixer utilizing an impeller of a proper size and turning at an appropriate rpm to insure adequate mixing of air with the medium. The pH of the culture medium gradually increased from an initial level of about 6.9-7.2 as the fermentation proceeded.

The whole broth obtained from an A-4696 fermentation, was filtered with the aid of a commercial filter aid. The filtrate was set aside. The mycelial cake was washed with 32 L of water and the wash water set aside. The mycelial cake was then suspended in an additional 32 L of water and the pH of the mixture adjusted to pH 10.5 with 5 N sodium hydroxide solution. The mycelial cake water suspension was stirred for 45 min and the mixture was filtered. This filtrate and the water wash were combined with the original filtrate from the fermentation broth and the pH of combined filtrates was adjusted to pH 4.0 with H_2SO_4. The acidified combined filtrates was passed through a carbon column utilizing 1.0 kg of activated carbon, (Pittsburgh, 12x40). The activated carbon column was washed until the effluent was colorless. The A-4696 activity was adsorbed on the carbon column. The A-4696 activity was eluted from the carbon column utilizing a 1% H_2SO_4 solution in acetone: H_2O (1:1). 2 L of the acidified acetone-water solution was sufficient to elute the A-4696 activity from the carbon column. The eluate containing the A-4696 activity as treated with a saturated barium hydroxide solution, in order to form a precipitate of barium sulfate, thus removing the sulfate ions from the solution. The mixture was filtered and the barium sulfate precipitate was discarded. The filtrate containing the A-4696 activity was concentrated under vacuum to dryness. The resulting residue comprising the A-4696 activity amounted to approximately 80.0 g.

References

Hamill R.L. et al.; US Patent No. 3,952,092; April 20, 1976; Assigned: Eli Lilly and Company, Indianapolis, Ind.

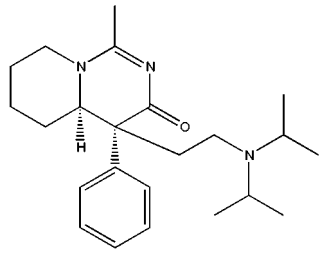
ACTISOMIDE

Therapeutic Function: Cardiac depressant

Chemical Name: 3H-Pyrido[1,2-c]pyrimidin-3-one, 4-(2-(bis(1-methylethyl) amino)ethyl)-4,4a,5,6,7,8-hexahydro-1-methyl-4-phenyl-, cis-(+-)-

Common Name: Actisomide; Dizactamide

Structural Formula:



Chemical Abstracts Registry No.: 96914-39-5

Trade Name	Manufacturer	Country	Year Introduced
Dizactamide	ZYF Pharm Chemical	-	-

Raw Materials

Platinum oxide
N,N-Dimethylacetamide dimethylacetal
4-Diisopropylamino-2-phenyl-2-pyridin-2-yl-butyramide
Lithium aluminum hydride

Manufacturing Process

Hydrogenation of 4-diisopropylamino-2-phenyl-2-pyridin-2-yl-butyramide over platinum oxide catalyst reduced the pyridine ring to a piperidine to give 4-diisopropylamino-2-phenyl-2-piperidin-2-yl-butyramide as a white solid, MP: 107°-108°C. Structure was confirmed by proton, carbon-13-NMR spectra and by elemental analysis.

2-(1-Acetylpiperidin-2-yl)-4-diisopropylamino-2-phenylbutyramide was prepared by acetylation of above product with N,N-dimethylacetamide dimethylacetal by heating at 80°C for about 14 hours. The acetamide melted at 191°-192°C. The treatment of that intermediate with lithium aluminum hydride led the newly introduced acetyl group to condense with the adjacent amide nitrogen. There was thus obtained 4-(2-diisopropylaminoethyl)-1-methyl-4-phenyl-4,4a,5,6,7,8-hexahydropyrido[1,2-c]pyrimidin-3-one, the new anti-arrhythmic agent actisomide, MP: 70°-75°C. Its structure was confirmed by proton NMR and infrared spectra and by elemental analysis.

References

Adelstein G.W., Chorvat R.J.; EP Patent No. 0,104,647; Sept. 27, 1983
Lednicer D., The Organic Chemistry of Drug Synthesis; v. 5; pp. 149-150; 1995; Wiley and Sons Inc.

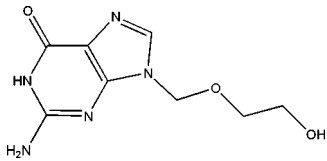
ACYCLOVIR

Therapeutic Function: Antiviral

Chemical Name: 2-Amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one

Common Name: Acycloguanosine; 9-(2-Hydroxyethoxymethyl)guanine

Structural Formula:



Chemical Abstracts Registry No.: 59277-89-3

Trade Name	Manufacturer	Country	Year Introduced
Zovirax	Burroughs-Wellcome	UK	1981
Zovirax	Burroughs-Wellcome	US	1982
Zovirax	Burroughs-Wellcome	Switz.	1982
Zovirax	Burroughs-Wellcome	W. Germany	1983
Zovirax	Burroughs-Wellcome	Sweden	1983
Zovirax	Burroughs-Wellcome	France	1983

Raw Materials

Sodium nitrite
2-Chloro-9-(2-hydroxyethoxymethyl)adenine
Ammonia

Manufacturing Process

Solid sodium nitrite (0.97 g) was added at room temperature with stirring over a period of one hour to a solution of 2-chloro-9-(2-hydroxyethoxymethyl)adenine (0.5 g) in glacial acetic acid (10 ml). The reaction mixture was stirred for an additional 4½ hours. The white solid was removed by filtration, washed with cold acetic acid and then well triturated with cold water to remove the sodium acetate present. The solid product was retained. The combined acetic acid filtrate and wash was evaporated at reduced pressure and 40°C bath temperature and the residual oil triturated with cold water. The resulting solid material was combined with the previously isolated solid and the combined solids dried and recrystallized from ethanol to give 2-chloro-9-(2-hydroxyethoxymethyl)-hypoxanthine (0.25 g), MP>310°C. Elemental analysis and NMR spectrum were consistent with this structure.

A mixture of 2-chloro-9-(2-hydroxyethoxymethyl)-hypoxanthine (0.375 g) and methanol (80 ml) saturated with anhydrous ammonia was heated in a bomb at 125°C for 5 hours. The bomb was cooled in an ice bath and the reaction mixture removed. Solvent and excess ammonia were removed under reduced pressure at 50°C. After the residue was triturated with cold water to remove the ammonium chloride formed, the remaining solid was dried and then recrystallized from methanol to give pure 9-(2-hydroxyethoxymethyl) guanine (0.24 g), MP 256.5-257°C.

References

Merck Index 140
DFU 4 (11) 842 (1979)
Kleeman and Engel p. 14
PDR p. 773
OCDS Vol. 3 p. 229
DOT 18 (2) 52 (1982)
REM p. 1231
Schaeffer, H.J.; US Patent 4,199,574; April 22, 1980; Assigned to Burroughs-Wellcome Co.

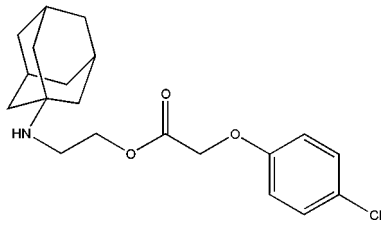
ADAFENOXATE

Therapeutic Function: Nootropic, Psychostimulant

Chemical Name: 2-(1-Adamantylamino)ethyl (p-chlorophenoxy)acetate

Common Name: Adafenoxate

Structural Formula:



Chemical Abstracts Registry No.: 82168-26-1

Trade Name	Manufacturer	Country	Year Introduced
Adafenoxate	Laboratorios Wassermann	-	-

Raw Materials

1-Aminoadamantine-2-ethanol
p-Chlorophenoxyacetyl chloride
p-Chlorophenoxyacetic acid

Manufacturing Process

Preparation of the p-chlorophenoxyacetate of 1-aminoadamantine-2-ethanol, starting from a p-chlorophenoxyacetic acid halide:

22 g (0.11 mol) of 1-aminoadamantine-2-ethanol dissolved in 250 ml of benzene are poured into a 500 ml flask fitted with a mechanical stirrer, using a decanting funnel. 23 g (0.11 m) of p-chlorophenoxyacetyl chloride are added in drops while stirring, the mixture then being stirred for 30 minutes. 120 ml of a 10% solution of sodium carbonate is then added, and the resulting mixture is stirred for 10 minutes. The organic phase is decanted, and the benzene is then removed by distillation. The residue is crystallized with petroleum ether. This yields 37 g (93%) of a white solid.

Preparation of the p-chlorophenoxyacetate of 1-aminoadamantine-2-ethanol, starting from p-chlorophenoxyacetic acid:

In a 1 liter flask, provided with a Dean-Stark separator tube and reflux refrigerant, a mixture of 20.5 g (0.011 m) of p-chlorophenoxyacetic acid, 22 g (0.11 m) of 1-aminoadamantine-2-ethanol, 98 g of conc. sulfuric acid and 700 ml of toluene is heated to boiling point over a period of 24 hours. At the end

of this period, the mixture is treated with an aqueous solution of 5% sodium carbonate to an alkali pH, and is then washed with water. The mixture is then dried on anhydrous sodium sulphate, and the toluene is removed by distillation at reduced pressure. The crude product so obtained is crystallized with petroleum ether. The yield is 35.2 g (88%) of a white solid.

Preparation of the chlorhydrate of p-chlorophenoxyacetate of 1-aminoadamantine-2-ethanol:

A solution of 60 g (0.16 m) of p-chlorophenoxyacetate of 1-aminoadamantine-2-ethanol in 300 ml of ether is subjected to the passage of HCl gas until the precipitation of a solid product is completed. It is left to cool in a refrigerator over a period of 6 hours and it is then filtered. The resulting solid is recrystallized with a mixture of ether and methanol. 61 g (92%) of the product are obtained.

References

Andreoli R.R. et al; US Patent No. 4,476,319; Oct. 9, 1984; Assigned to Sociedad Espanola de Espacialides Formaco-Terapeuticas S.A., Barselona, Spain

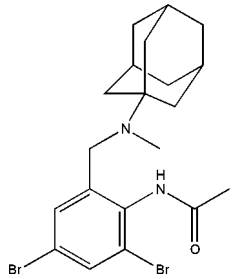
ADAMEXINE

Therapeutic Function: Mucolytic

Chemical Name: Acetamide, N-(2,4-dibromo-6-((methyltricyclo [3.3.1.13,7]dec-1-ylamino)methyl)phenyl)-

Common Name: Adamexine; Broncostyl

Structural Formula:



Chemical Abstracts Registry No.: 54785-02-3

Trade Name	Manufacturer	Country	Year Introduced
Adamexine	ZYF Pharm Chemical	-	-
Broncostyl	Robert	-	-

Raw Materials

2-Bromomemtyl-4,6-dibromo-N,N,diacetylaniline
N-Methyladamantyl

Manufacturing Process

4.3 g 2-brommemtyl-4,6-dibromo-N,N-diacetylaniline and 1.65 g N-methyladamantyl amine in 100 ml of absolute ethanol were heated to reflux for 8 hours. The ethanol was removed and a residue was washed with some times with ether. The resulting hard mass was refluxed with 150 ml 2 N HCl for 2 hours. The obtained product was cooled and stood for 10-12 hours at 4°C in a refrigerator. The crystalline 2-(N-(1-adamantyl)-N-methylaminomethyl-4',6'-dibromacetanilid hydrochloride (adamexine) was filtered off and thoroughly washed with distilled water. It was recrystallized from a mixture glacial acetic acid/water 2:1 (v/v) to give a white crystalline powder, melting at 250°-254°C. The hydrochloride is better for a pharmaceutical composition because of solubility in water. The free base may be prepared by adding of an equivalent of any basic compound (NaOH, $NaHCO_3$ and so on).

References

B.D. Patent No. 2,436,909; July 31, 1974; Ferrer Internacional, S. A. Barcelona (Spain)

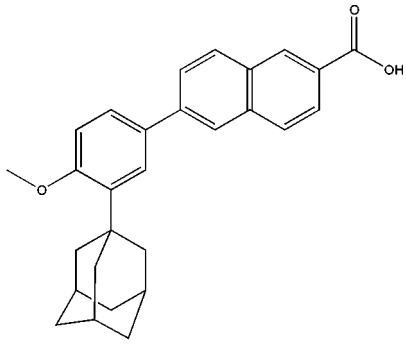
ADAPALENE

Therapeutic Function: Antiacne

Chemical Name: 2-Naphthalenecarboxylic acid, 6-(4-methoxy-3-tricyclo (3.3.1.13,7))dec-1-ylphenyl)-

Common Name: Adapalene

Structural Formula:



Chemical Abstracts Registry No.: 106685-40-9

Trade Name	Manufacturer	Country	Year Introduced
Adaferin	Laboratoires Galderma	France	-
Adapalene	Laboratoires Galderma	France	-
Differin	Laboratoires Galderma	France	-

Raw Materials

4-Bromophenol
1-Adamantanol
Sodium hydride
Methyl iodide
Dibromoethane
Zinc chloride
Nickel chloride/1,2-(diphenylphosphino)ethane-complex

Manufacturing Process

Preparation of 6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoic acid consist of 4 steps.

1. 2-(1-Adamantyl)-4-bromophenol.

34.6 g (200 mmol) of p-bromophenol and 30.4 g (200 mmol) of 1-adamantanol are dissolved in 100 ml of dichloromethane. To the resulting solution there are slowly added 10 ml of concentrated sulfuric acid. The mixture is stirred for 8 hours at ambient temperature, poured into water, neutralized with sodium bicarbonate, extracted with methylehe chloride, dried and evaporated. After recrystallization in isooctane 52.8 g of the expected product are obtained. Yield - 86%. MP: 140°-141°C.

2. 2-(1-Adamantyl)-4-bromoanisole.

To suspension of sodium hydride (80% in oil, 4.32 g, 144 mmol) in 50 ml of THF, there are slowly added while maintaining the temperature at 20°C, 36.8 g (120 mmol) of 2-(1-adamantyl)-4-bromophenol. The mixture is stirred for 1 hour at ambient temperature at which point 9 ml of methyl iodide are added. The mixture is then stirred for 2 hours at 20°C, poured into water, extracted with ether, dried and evaporated. The product is purified by passage through a silica column (10x30), eluting with a mixture of hexane (90%) and dichloromethane (10%). On evaporation, 26.2 g of a white solid are obtained. Yield - 68%. MP: 138°-139°C.

3. Methyl ester of 6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoic acid.

To a suspension of magnesium (1.64 g, 67.5 mmol in 30 ml of THF, there is added a solution of 1.4 g (4.5 mmol) of 2-(1-adamantyl)-4-bromoanisole and 0.39 ml of dibromoethane in 10 ml of THF. The mixture is stirred until the reaction is initiated and then there is slowly added a solution of (40.8 mmol) of 2-(1-adamantyl)-4-bromoanisole in 90 ml of THF. The mixture is refluxed for 2 hours, and then cooled to 20°C. After that 6.2 g (45 mmol) of anhydrous $ZnCl_2$ are added. The mixture is stirred for 1 hour at 20°C at which point 7.95 g (30 mmol) of methyl 6-bromo-2-naphthoate are added followed by addition of 300 g of $NiCl_2$/1,2-(diphenylphosphino)ethane-complex as the catalyst. The mixture is stirred again for 2 hours at 20°C, poured into water, extracted with CH_2Cl_2 dried and evaporated. The product is isolated by column

chromatography, eluting with a mixture of heptane (70%) and dichloromethane (30%) and then recrystallized in ethyl acetate. 12.2 g of the expected product are obtained. Yield - 78%. MP: 222°-223°C.

4. 6-(3-(1-Adamantyl)-4-methoxyphenyl)-2-naphthoic acid.

10.5 g of the ester obtained above (step 3) are treated with a solution of soda in methanol (200 ml, 4.2 N). The mixture is heated at reflux for 48 hours. The solvents are evaporated and the resulting residue is taken up in water and acidified with concentrated HCl. The solid is filtered and dried under vacuum over phosphoric anhydride. The resulting white solid is recrystallized in a mixture of THF and ethyl acetate. 8.2 g of expected product are obtained. Yield - 81%. MP: 325°-327°C.

References

Shroot B. et al.; US Patent No. 4,940,696; July 10, 1990; Assigned to Centre International de Recherches Dermatologioues (CIRD), Valbonne, France

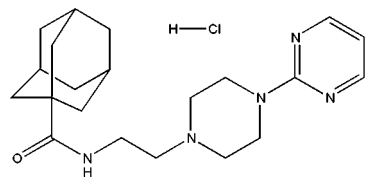
ADATANSERIN HYDROCHLORIDE

Therapeutic Function: Anxiolyticá Antidepressant

Chemical Name: Tricyclo[3.3.1.13,7]decane-1-carboxamide, N-(2-(4-(2-pyrimidinyl)-1-piperazinyl)ethyl)-, hydrochloride

Common Name: Adatanserin hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 144966-96-1; 127266-56-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
WY-50324	Centre de Recherche Pierre Fabre	-	-
Adatanserin hydrochloride	ESTEVE QUIMICA SA	-	-

Raw Materials

[4-(2-Pyrimidinyl)piperazino]ethylamine
Triethylamine
Adamantane-1-carboxylic acid chloride

Manufacturing Process

To a stirred solution of [4-(2-pyrimidinyl)piperazino]ethylamine (2.0 g, 0.01 mol) in 50 ml of methylene chloride, adamantane-1-carboxylic acid chloride (3.6 g, 0.018 mol) and triethylamine (2.9 g, 0.015 mol) were added. Stirring was continued at room temperature overnight. The methylene chloride solution was washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The remaining residue was subjected to preparative HPLC. The residue was dissolved in ethyl acetate (10 ml) and subjected to flash chromatography using a 9 inch column of silica gel and ethyl acetate as the eluent. The N-[2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]tricyclo[3.3.1.1(3,7)]
decane-1-carboxamide was separated.

In practice it is usually used as hydrochloride.

References

Abou Gharbia M. A.-M. et al.; GB Patent No. 2,218,988A; Oct. 29, 1989

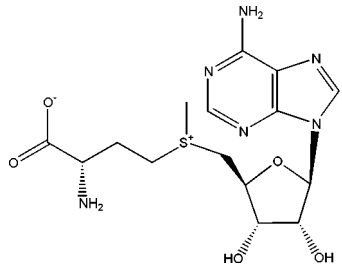
ADEMETIONINE

Therapeutic Function: Metabolic, Antiinflammatory

Chemical Name: S-Adenosyl-DL-methionine

Common Name: Ademethionium; Ademetionine; Adenosylmethionine

Structural Formula:



Chemical Abstracts Registry No.: 29908-03-0

Trade Name	Manufacturer	Country	Year Introduced
Donamet	Ravizza	-	-
Geptral	Knoll	-	-
Gumbaral	AWD.Pharma	-	-
Gumbaral	Asta Pharma AWD	-	-
Legend	Fidia	-	-

Trade Name	Manufacturer	Country	Year Introduced
S-Amet parenteral	Europharma	-	-
Transmetil	Knoll	-	-
Twin	San Carlo	-	-
FO-1501	Sampl-Gibipharma	-	-
Samyr	Knoll	-	-

Raw Materials

Glucose
Polypeptone
Yeast extract
Sucrose
Urea
Methionine, L-
Boric acid
Potassium iodide
Acetic acid
Sulfuric acid
Potassium phosphate monobasic
Magnesium sulfate heptahydrate
Calcium chloride dihydrate
Zinc sulfate heptahydrate
Ferric sulfate heptahydrate
Copper sulfate pentahydrate
Cobalt(II) chloride hexahydrate
Perchloric acid
Potassium hydrocarbonate

Manufacturing Process

S-Adenosyl methionine (SAM) is produced is prepared by cultivating of Saccharomyces cerevisiae.

One loopful of each of the microorganism strains (IFO 2342, IFO 2343, IFO 2345, IFO 2346, IFO 2347) was inoculated in 10 ml of a heat-sterilized culture medium adjusted to pH 6.0 and composed of 5.0 g/dl of glucose, 0.5 g/dl of polypeptone, 0.4 g/dl of KH_2PO_4, 0.4 g/dl of K_2HPO_4, 0.02 g/dl of $MgSO_4 \cdot 7H_2O$ and 0.2 g/dl of yeast extract, and cultivated with shaking at 28°C for 24 h.

1 L of a culture medium adjusted to pH 6.0 and composed of 10.0 g/dl of sucrose, 1.0 g/dl of yeast extract, 0.4 g/dl of K_2HPO_4, 0.01 g/dl of $MgSO_4 \cdot 7H_2O$, 1.5 g/dl of urea (separately sterilized), 0.75 g/dl of L-methionine, 0.02 g/dl of $CaCl_2 \cdot 2H_2O$, 0.25 mg/dl of $ZnSO_4 \cdot 7H_2O$, 0.25 mg/dl of $FeSO_4 \cdot 7H_2O$, 125.0 mg/dl of $MnSO_4 \cdot 6H_2O$, 2.0 μg/dl of $CuSO_4 \cdot 5H_2O$, 2.0 μg/dl of H_3BO_3, 0.2 μg/dl of $CoCl_2 \cdot 6H_2O$ and 1.0 μg/dl of KI was put in a 2-liter fermentor and sterilized. Then, 5 ml of the seed culture broth prepared as above was inoculated in the culture medium and cultivated at 28°C for 72 h with aeration and agitation.

After the cultivation, the microbial cells were collected by centrifugal separation, washed once with physiological saline, suspended in 100 ml of 1.5 N perchloric acid, and shaken at room temperature for 1 h. The suspension was then centrifuged to remove the microbial cells, and the resulting liquid was adjusted to pH 4.5 by adding potassium hydrogen carbonate. The resulting precipitate of potassium perchlorate was removed by centrifugal separation to give an extract containing SAM. The amount of SAM in the extract was determined, and the amount of SAM based on the dry cells.

The extract in an amount of 0.2 g as SAM was passed through a column filled with 50 ml of Amberlite IRC-50 (H^+ form), a weakly acidic cation exchange resin, to cause adsorption of SAM. 0.005 N acetic acid was passed through the column to wash it until the absorbance at 260 nm of the eluate becames less than 0.1. Thus, impurities were removed. Then, 0.1 N sulfuric acid was passed through the column, and SAM was eluted until the absorbance at 260 nm of the eluate becames less than 0.05. The eluate was treated with Amberlite IRA 900 resin (OH- form) to adjust its pH to 3.0, and then lyophilized to obtain SAM sulfate. The SAM based may be produced from SAM sulfate by treatment with potassium hydrogen carbonate. The purity of SAM was measured by cellulose thin-layer chromatography, paper chromatography and high-performance liquid chromatography. The yield of SAM based on the dry cells: IFO 2343-12.1%; IFO 2346-18.8%; IFO 2347-16.7%.

References

Shiozaki S. et al.; US Patent No. 4,562,149; Dec. 31, 1985; Assigned: Nippon Zeon Co., Ltd., Tokyo, Japan

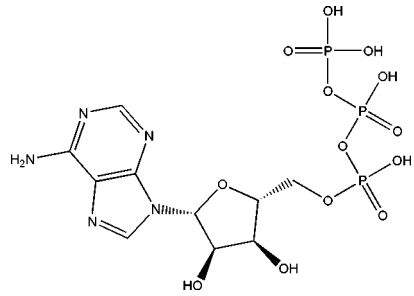
ADENOSINE TRIPHOSPHATE

Therapeutic Function: Coenzyme, Vasodilator

Chemical Name: Adenosine 5'-(tetrahydrogen triphosphate)

Common Name: ATP; Triphosadenine

Structural Formula:



Chemical Abstracts Registry No.: 56-65-5

Trade Name	Manufacturer	Country	Year Introduced
Atepodin	Medix	Spain	-
Atriphos	Biochimica	Switz.	-
Estriadin	Boizot	Spain	-
Striadyne	Auclair	France	-
Triphosphodine	I.C.I.	UK	-

Raw Materials

1,3-Dicyclohexylguanidinium adenosine 5'-phosphoramidate
Bis-Triethylammonium pyrophosphate

Manufacturing Process

With a solution of 0.29 part by weight of well dried 1,3-dicyclohexylguanidinium adenosine 5'-phosphoramidate in 5 parts by volume of ortho-chlorophenol is admixed a solution of 0.95 part by weight of bis-triethylammonium pyrophosphate in a mixed solvent composed of 1 part by volume of ortho-chlorophenol and 2 parts by volume of acetonitrile. The mixture is left standing at 20°C for 2 days. Then 30 parts by volume of water is added to the mixture. After washing with three 15 parts by weight volume-portions of diethyl ether, the aqueous layer is separated, and the remaining diethyl ether in the aqueous layer is removed under reduced pressure. Five parts by weight of activated charcoal is added to the aqueous layer and the mixture is stirred for 30 minutes. The activated charcoal is filtered and further 1 part by weight of activated charcoal is added to the filtrate. After 20 minutes agitation, the activated charcoal is taken out by filtration. The combined activated charcoal is washed with a little water, and eluted twice with respective 300 and 200 parts by volume-portions of 50% (volume) ethanol containing 2% (volume) of concentrated aqueous ammonia. The eluate is concentrated to 40 parts by volume, then is passed through a column packed with 20 parts by volume of a strongly basic anion exchange resin in bead form (chloric type) (polystyrene trimethylbenzyl ammonium type resin sold under the name of Dowex-1 from Dow Chemical Company, Mich. USA). Then, the column is washed with 750 parts by volume of an acid aqueous saline solution containing 0.01 normal hydrochloric acid and 0.02 normal sodium chloride and then eluted with 600 parts by volume of an acid aqueous saline solution composed of 0.01 normal hydrochloric acid and 0.2 normal sodium chloride. After neutralizing with a diluted sodium hydroxide solution, the eluate is treated with activated charcoal to adsorb ATP as its sodium salt. The separated activated charcoal is washed with water and eluted with 60% (volume) ethanol containing 2% (volume) of concentrated aqueous ammonia. The eluate is concentrated to 0.5 part by volume, then 5 parts by volume of ethanol is added. The precipitate thus deposited is centrifuged and dried at low temperature to obtain 0.155 part by weight of tetra-sodium salt of ATP containing 4 mols of water of crystallization as a colorless crystalline powder. The yield is 47% relative to the theoretical.

References

Merck Index 146
I.N.p. 983
Tanaka, K.and Honjo, M.; US Patent 3,079,379; February 26, 1963; Assigned to Takeda Pharmaceutical Industries, Ltd.

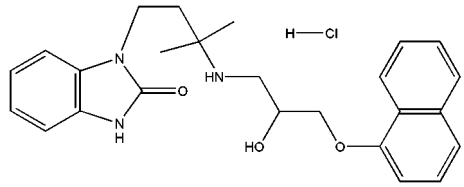
ADIMOLOL HYDROCHLORIDE

Therapeutic Function: Alpa- and Beta-adrenergic blocker

Chemical Name: ()-1-(3-((2-Hydroxy-3-(1-naphthyloxy)propyl)amino)-3-methylbutyl)-2-benzimidazolinone hydrochloride

Common Name: Adimolol hydrochloride; Imidolol hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 75708-29-1; 78459-19-5 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Adimolol hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

1-(3-Amino-3,3-dimethyl-n-propyl)benzimidazolidinone-2
1-[Naphthyl-1-oxyl]propylene-(2,3)-epoxide

Manufacturing Process

A mixture consisting of 3 g of 1-(3-amino-3,3-dimethyl-n-propyl) benzimidazolidinone-2, 3.3 g of 1-[naphthyl-(1)-oxyl]propylene-(2,3)-epoxide and 12 ml of 98% ethanol were refluxed for three hours. Thereafter, the ethanol was distilled off, the residue was taken up in some methanol, and the solution was acidified with 1 N hydrochloric acid and then extracted with ethyl acetate. The ethyl acetate was distilled out of the extract solution, and ether and some water were added to the residue, whereupon a crystalline substance separated out. The product was recrystallized from ethanol, yielding 60% of theory of ()-1-(3-((2-hydroxy-3-(1-naphthyloxy)propyl)amino)-3-methylbutyl)-2-benzimidazolinone, which had a melting point of 161°C.

In practice it is usually used as hydrochloride.

References

Koppe H. et al.; US Patent No. 4,255,430; March 10, 1981; Assigned to Boehringer Ingelheim GmbH, Ingelheim am Rhein, Fed. Rep. of Germany

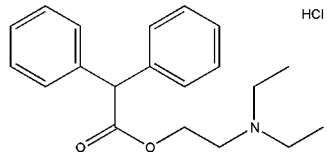
ADIPHENINE HYDROCHLORIDE

Therapeutic Function: Anticholinergic, Spasmolytic, Smooth muscle relaxant

Chemical Name: Benzeneacetic acid, α-phenyl-, 2-(diethylamino)ethyl ester, hydrochloride

Common Name: Adiphenine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 50-42-0; 64-95-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Adiphenine hydrochloride	Spectrum Chemicals and Laboratory Products, Inc.	-	-
Neuro-Trasentin	Aleve	-	-
Paxil	Frosst	-	-
Paxil	SKB	-	-
Paxil	GlaxoSmithKline	-	-
Trasentine	Ciba	-	-

Raw Materials

α,α-Diphenylacetic acid
Thionyl chloride
Diethylaminoethanol

Manufacturing Process

10.6 parts of α,α-diphenylacetic acid are treated with thionyl chloride and the diphenylacetylchloride thus produced is caused to react with 5.9 parts of diethylaminoethanol at 120°C. The α,α-diphenylacetic acid, 2-(diethylamino)ethanol ester hydrochloride thus produced is crystallized from ethyl acetate; it melts at 113-114°C.

References

Merck Index, Monograph number: 160, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Miescher K., Hoffmann K., US Patent No. 2,079,962; May 11, 1937; Assigned to Society of Chemical Industry, Basel, Switzerland

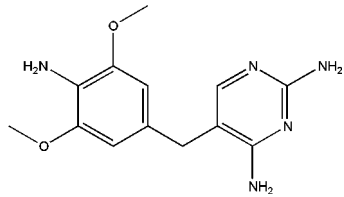
ADITEREN

Therapeutic Function: Diuretic

Chemical Name: 2,4-Diamino-5-(4-amino-3,5-dimethoxybenzyl)pyrimidine

Common Name: Aditeren

Structural Formula:



Chemical Abstracts Registry No.: 56066-19-4

Trade Name	Manufacturer	Country	Year Introduced
Aditeren	Onbio Inc.	-	-

Raw Materials

Aniline
Sodium nitrite
Aluminum oxide
Acetamide
Bromine
Dimethylsulfone
Sodium methylate
p-Anilinepropionitrtile
Guanidine carbonate
4-Toluenesulfonic acid
Bromosuccinimide
Palladium on carbon
Sodium hydride
Sodium borohydride
3-Hydroxy-5-keto-3-cyclohexenecarboxylic acid

Manufacturing Process

A solution of 6.9 g of sodium in 1 liter of absolute ethanol were treated with 54 g of guanidine carbonate and 31.0 g of 4-amino-α-(anilinemethylene)-3,5-dimethoxyhyrocinnamic acid nitrile and boiled under reflux for 20 hours. 500 ml of water were added and the alcohol was removed in vacuum. After standing at room temperature for 2 hours, the crystallized 2,4-diamino-5-(4-amino-3,5-dimethoxybenxyl)pyrimidine was filtered off under suction, washed with water and recrystallised from methanol; melting point 215°-216°C.

The starting material was prepared as follows:

13.8 g of sodium were dissolved in 900 ml of methanol. To this solution were added 46.8 g of 3-hydroxy-5-keto-3-cyclohexenecarboxylic acid. This mixture was stirred, held between -4° and -8°C by means of a cooling bath and treated during 30 minutes with a phenyl-diazonium chloride solution [prepared from 27.9 g of aniline, 450 ml of water, 72 ml of concentrated hydrochloric acid and 21.0 g of sodium nitrite in 90 ml of water]. The resulting mixture was stirred for a further 1 hour at -5°C to -10°C. The deposited, red reaction product was filtered off under vacuum and washed with ca 1000 ml of water. There was obtained 3-hydroxy-5-keto-4-phenyl-azo-3-cyclohexenecarboxylic acid of melting point 218°C.

60 g of 3-hydroxy-5-keto-4-phenyl-azo-3-cyclohexenecarboxylic acid, 200 ml of methanol, 1200 ml of benzene and 5 g of p-toluenesulphonic acid were boiled together under reflux on a water separator for 18 hours. After cooling, the solution was washed with 500 ml of a 5% sodium bicarbonate solution, then washed with water, dried and evaporated. The residue was dissolved in ethyl acetate and purified on an aluminum oxide column [500 g; activity stage I]. After evaporation of the ethyl acetate and recrystallisation of the residue from benzene/petroleum ether, there was obtained 3-hydroxIy-5-keto-4-phenyl-azo-3-cyclohexenecarboxylic acid methyl ester as a solid of melting point 144°C.

54.8 g of 3-hydroxy-5-keto-4-phenyl-axe-3-cyclohexenecarboxylic acid methyl ester, 12.0 g of acetamide and 2.0 g of bromosuccinimide were stirred in 600 ml of chloroform and treated dropwise with 32.0 g of bromine in 400 ml of chloroform [the reaction temperature being held below 35°C]. The separation of acetamide hydrobromide soon began. The mixture was stirred for a further 30 minutes at room temperature, the acetamide hydrobromide filtered off and the filtrate evaporated to dryness. The residue was taken up in a small amount of ethanol, filtered off under vacuum and washed with ethanol. There was obtained 3,5-dihydroxy-4-phenylazobenzoic acid methyl ester of melting point 216°-218°C.

A mixture of 27.2 g of 3,5-dihydroxy-4-phenylazobenzoic acid methyl ester, 150 ml of methanol and 64 g of dimethyl sulfate was treated during 45 minutes with a solution of 23 g of sodium hydroxide in 50 ml of water while stirring. Care was taken that the temperature did not exceed 55°C by means of a cooling bath. The mixture was stirred at room temperature for a further 1 hour, cooled with ice water, filtered off under vacuum and recrystallized from 400 ml of ethanol. Red crystals of 3,5-dimethoxy-4-phenylazobenzoic acid methyl ester were obtained; melting point 130°-132°C.

12 g of 3,5-dimethoxy-4-phenylazobenzoic acid methyl ester were dissolved in 400 ml of ethanol and, after the addition of 0.80 g of palladium on carbon, hydrogenated under atmospheric pressure and at room temperature. With slight warming, 2 moles of hydrogen were taken up during 1.5 hours. The catalyst was filtered off and the filtrate concentrated in vacuum. The resulting aniline was distilled off with steam. After cooling, the 4-amino-3,5-dimethoxybenzoic acid methyl ester which remained as an aqueous suspension, was filtered off under vacuum, dried and recrystallised from cyclohexane; melting point 115°-116°C.

A suspension of 214 g of dimethylsulphone and 78.2 g of sodium hydride (50% dispersion in oil) in 400 ml of absolute dimethyl sulfoxide was stirred at 50°C under nitrogen and with exclusion of moisture for 3 hours. The mixture was cooled to 30°C, whereupon 137 g of 4-amino-3,5-dimethoxybenzoic acid methyl ester were added, the temperature rising to 50°C. After stirring under nitrogen and at room temperature for ca 1 hour, the resulting mixture was left to stand for 3 hours and then dissolved in 2 liters of water under addition of ice. The solution was adjusted to pH 6-7 with glacial acetic acid. After stirring under ice-cooling for 1 hour, the crystallized 4'-amino-3',5'-dimethoxy-2-methylsulfonyl-acetophenone was filtered off under suction, washed with water, dried and recrystallised from ethyl acetate; MP: 166°-167°C.

A suspension of 123 g of 4'-ammo-3',5'-dimethoxy-2-methylsulphonyl-

acetophenone and 68 g of sodium borohydride in 1.5 liters of alcohol was stirred at room temperature for 20 hours. The suspension was diluted with 1.5 liters of water. The alcohol was evaporated in vacuum and the resulting 4-amino-3,5-dimethoxy-α-(methylsulfonylmethyl)benzyl alcohol was filtered off under suction, washed with water and dried; melting point 178°-179°C.

A mixture of 8.64 g of sodium methylate, 14.6 g of p-anilinepropionitrtile and 22.0 g of 4-amino-3,5-dimethoxy-α-(methylsulfonylmethyl)benzyl alcohol in 50 ml of absolute dimethyl sulfoxide was stirred at 50°C for 1 hour under nitrogen and with the exclusion of moisture. The solution was poured into 500 ml of ice-water and the resulting emulsion was extracted with two 500 ml portions of ethyl acetate. The ethyl acetate extracts were washed with two 250 ml portions of water, dried over magnesium sulfate and evaporated in vacuum. The residue was dissolved in 60 ml ethyl acetate. After standing at room temperature for 20 hours, the crystallized 4-amino-α-(anilinemethylene)-3,5-dimethoxyhydrocinnamic acid nitrile was filtered off under suction, washed with a small amount of ethyl acetate and dried; MP: 150°-151°C.

References

G.B. Patent No. 1,484,481; Sept. 11, 1974; F. Hoffmann-La Roche and CO., Aktiengesellschaft, Swiss Company, 124-184 Grenzacherstrasse Basle, Switzerland

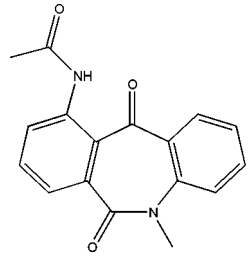
ADOSOPINE

Therapeutic Function: Urinary incontinence agent

Chemical Name: N-(6,11-Dihydro-5-methyl-6,11-dioxo-5H-dibenz[b,e] azepin-10-yl)acetamide

Common Name: Adosopine

Structural Formula:



Chemical Abstracts Registry No.: 88124-26-9

Trade Name	Manufacturer	Country	Year Introduced
Adosopine	Menarini Group	-	-

Raw Materials

Acetic anhydride	1-Aminoanthraquinone
Sodium methylate	Methyl iodide

Manufacturing Process

2 ml of acetic anhydride are added to 2.5 g of 10-amino-5,6-dihydro-11H-dibenzo[b,e]azepine-6,11-dione (prepared from 1-aminoanthraquinone in accordance with Caronna and Palazzo-Gaz. Chim. It. 83, 533, 1953) in 50 ml of dioxane. After maintaining for 2 h under reflux, the mixture is evaporated almost to dryness under reduced pressure, the residue is then poured into water, filtered and dried to give 2.0 g of crude product.

The 2.0 g of previously obtained crude product is suspended in 20 ml of N,N-dimethylformamide, and 710.0 mg of sodium methylate in 10 ml of methanol are added. After maintaining for 30 min at room temperature, 2.5 ml of methyl iodide are added, and mixture is allowed to stand for 24 h after which the mixture is poured into water, the product filtered off, dried and crystallized from ethanol, to give 5-methyl-10-acetamino-5,6-dihydro-11H-dibenzo[b,e] azepine-6,11-dione, melting point 199°-201°C.

References

Pestellini V. et al.; US Patent No. 4,551,451; Nov. 5, 1985; Assigned: A.Menarini S.a.S., Italy

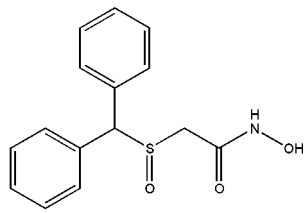
ADRAFINIL

Therapeutic Function: Psychostimulant

Chemical Name: Acetamide, 2-((diphenylmethyl)sulfinyl)-N-hydroxy-

Common Name: Adrafinil; Olmifon

Structural Formula:



Chemical Abstracts Registry No.: 63547-13-7

Trade Name	Manufacturer	Country	Year Introduced
Olmifon	Cephalon	-	-

Raw Materials

3-Chloroacetic acid	Sodium carbonate
Sulfuric acid	Hydroxylamine hydrochloride
Sodium methylate	Hydrogen chloride
Hydrogen peroxide	Thiourea
Chlorodiphenylmethane	Sodium hydroxide

Manufacturing Process

7.6 g (0.1 mol) of thiourea and 100 ml of dematerialized water are introduced into a 500 ml three-neck flask equipped with a magnetic stirrer, a dropping funnel and a condenser; the mixture is heated to 50°C and 20.25 g (18 ml; 0.1 mol) of chlorodiphenylmethane are then added all at once. The solution is left refluxing until it has become limpid, and is then cooled to 20°C, and 200 ml of 2.5 N NaOH are added dropwise. So the sodium benzhydrylthiolate is obtained.

A solution of sodium 3-chloroacetate is added to the solution of sodium benzhydrylthiolate at about 60°C. Thereafter the temperature is raised to the boil, the mixture is left under reflux for about 0.5 h and is then cooled, filtered over charcoal and acidified with concentrated HCl, and 3-(benzhydrylthio)acetic acid are thus precipitated.

To the solution of 3-(benzhydrylthio)acetic acid in 1,2-dichloroethane, methanol and concentrated H_2SO_4 have been added. The whole is heated to the reflux temperature for about 5 h, cooled, and decanted, the aqueous phase is discarded and the organic phase is washed with a saturated sodium bicarbonate solution and then with water until the wash waters have a neutral pH. After drying over $MgSO_4$ and evaporating the solvent, the 3-(benzhydrylthio)acetic acid methyl ester is obtained.

The 3-(benzhydrylthio)acetic acid methyl ester dissolved in methanol, is added to a solution of hydroxylamine base [prepared by neutralising 0.15 mol (10.4 g) of hydroxylamine hydrochloride with 0.15 mol of sodium methylate]. The whole is left at ordinary temperature (15°-25°C) for 48 h, the sodium chloride is filtered off, the methanol is evaporated, the residue is taken up with aqueous alkali, the solution is filtered over charcoal, the filtrate is acidified with concentrated HCl, and the 3-(benzhydrylthio)acethylhydroxamic acid (recrystallised from benzene) is thus obtained.

The 3-(benzhydrylthio)acethylhydroxamic acid, dissolved in anhydrous CH_3COOH, is reacted with H_2O_2. The mixture is left at 40°-45°C for about 1.5 h, the acetic acid is evaporated and the residue is taken up in 50 ml of ethyl acetate; the 2-[(diphenylmethyl)sulfinyl]-N-hydroxyacetamide (CRL 40028) crystallises (recrystallised from isopropanol).

References

Lafon L.; US Patent No. 4,066,686; Jan. 3, 1978; Assigned: Laboratoire L. Lafon, Maisons Alfort, France

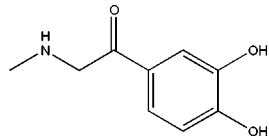
ADRENALONE

Therapeutic Function: Hemostatic, Sympathomimetic, Vasoconstrictor

Chemical Name: Ethanone, 1-(3,4-dihydroxyphenyl)-2-(methylamino)-

Common Name: Adrenalone; Adrenone

Structural Formula:



Chemical Abstracts Registry No.: 99-45-6

Trade Name	Manufacturer	Country	Year Introduced
Adrenalone	Yick-Vic Chemicals and Pharmaceuticals (HK) Ltd.	-	-

Raw Materials

ω-Chloro-3,4-dihydroxyacetophenone
Methylamine

Manufacturing Process

To a suspension of 1 part ω-chloro-3,4-dihydroxyacetophenone (prerared from chloroacetyl chloride and benzcatechole, see J. Russ. Phys. Chem. Ges., 25, 154) was added dropwise 1 part 60% solution of methylamine. Immediately was formed a residue of the salt of methylamine and ω-chloro-3,4-dihydroxyacetophenone. The dissolution of the salt was carried out by heating of the mixture. Then the salt was converted in crude 3,4-dihydroxy-α-methylaminoacetophenone. The product was dissolved in dilute hydrochloric acid. To this solution was added dropwise aqueous ammonium solution to prepare light yellow crystal of 3,4-dihydroxy-α-methylaminoacetophenone. The base and the hydrochloride of 3,4-dihydroxy-α-methylaminoacetophenone decomposed at temperature near 230°C and 240°C respectively.

References

Merck Index, Monograph number: 170, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
DE Patent No. 152,814; 1903.08.15; Assigned to Farbwerke vorm. Meister and Bruening in Hoechst a. M.

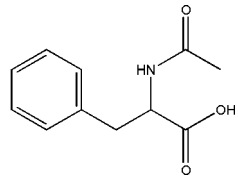
AFALANINE

Therapeutic Function: Antidepressant

Chemical Name: DL-Phenylalanine, N-acetyl-

Common Name: Afalanine

Structural Formula:



Chemical Abstracts Registry No.: 2901-75-9

Trade Name	Manufacturer	Country	Year Introduced
Afalanine	Sankyo	-	-

Raw Materials

Phenylalanine
Sodium hydroxide
Acetylbromide

Manufacturing Process

The phenylalanine was dispersed in water. A 1 N aqueous solution of sodium hydroxide was slowly added to this dispersion, and the pH of the solution reached a value of 7-8.

Then acetylbromide was dissolved in this solution, to give a N-acetylphenylalanine.

References

Shiogari T. et al.; EU Patent No. 0,178,911; April 23, 1986; Assigned: Sankyo company limited. N 1-6, 3-chome Nihonbashi Honcho Chuo-ku Tokyo (JP)

AFLOQUALONE

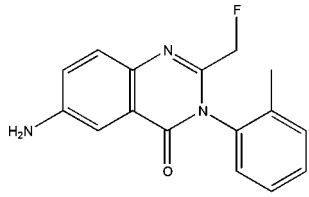
Therapeutic Function: Muscle relaxant

Chemical Name: 6-Amino-2-(fluoromethyl)-3-(o-tolyl)-4(3H)-quinazolinone

Common Name: -

Chemical Abstracts Registry No.: 56287-74-2; 56287-75-3 (Hydrochloride salt)

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Arofuto	TANABE SEIYAKU	Japan	1983

Raw Materials

Fluoroacetyl chloride
Acetic anhydride
N-(2-Amino-5-nitrobenzyl)-o-toluidine
Hydrogen

Manufacturing Process

14.4 g (0.053 mol) of N-(2-amino-5-nitrobenzoyl)-o-toluidine and 6.3 g (0.08 mol) of pyridine are dissolved in 300 ml of tetrahydrofuran. 12.2 g (0.126 mol) of fluoroacetyl chloride are added to the solution for 10 minutes under ice-cooling. The solution is stirred at the same temperature for 30 minutes and then at room temperature for 2.5 hours. The reaction solution is allowed to stand at room temperature overnight. The crystalline precipitate is collected by filtration, washed with water and then dried. 16.4 g of N-(2-fluoroacetamido-5-nitrobenzoyl)-o-toluidine are obtained. Yield: 93.7%; MP 238-239°C.

16.5 g (0.05 mol) of N-(2-fluoroacetamido-5-nitrobenzoyl)-o-toluidine and 25.5 g (0.25 mol) of acetic acid anhydride are dissolved in 250 ml of glacial acetic acid. The solution is refluxed for 2 hours under heating. Then, the reaction solution is evaporated to remove solvent. The residue thus obtained is poured into ice-water, and the aqueous mixture is adjusted to pH 9 with potassium carbonate. The crystalline precipitate is collected by filtration. 15.5 g of 2-fluoromethyl-3-(o-tolyl)-6-nitro-4(3H)-quinazolinone are obtained. Yield: 98.7%; MP 155-158°C (recrystallized from ethanol).

A mixture of 2.0 g (0.064 mol) of 2-fluoromethyl-3-(o-tolyl)-6-nitro-4(3H)-quinazolinone, 0.2 g of 5% palladium-carbon and 100 ml of acetic acid is shaken for 30 minutes in hydrogen gas. The initial pressure of hydrogen gas is adjusted to 46 lb and the mixture is heated with an infrared lamp during the reaction. After 30 minutes of this reaction, the pressure of hydrogen gas decreases to 6 lb. After the mixture is cooled, the mixture is filtered to remove the catalyst. The filtrate is evaporated to remove acetic acid, and the residue is dissolved in chloroform. The chloroform solution is washed with 5% aqueous sodium hydroxide and water, successively. Then, the solution is dried and evaporated to remove solvent. The oily residue thus obtained is dissolved in 2 ml of chloroform, and the chloroform solution is passed through a column of 200 g of silica gel. The silica gel column is eluted with ethyl acetate-benzene (1:1). Then, the eluate is evaporated to remove solvent. The crude crystal obtained is washed with isopropyl ether and recrystallized from

isopropanol. 0.95 g of 2-fluoromethyl-3-(o-tolyl)-6-amino-4(3H)-quinazolinone is obtained. Yield: 52.5%; MP 195-196°C.

References

DFU 7 (8) 539 (1982)
DOT 19 (1) 581 (1983)
Inoue, L., Oine, T., Yamado, Y., Tani, J., Ishida, R. and Ochiai, T.; US Patent 3,966,731; June 29, 1976; Assigned to Tanabe Seiyaku Co., Ltd.

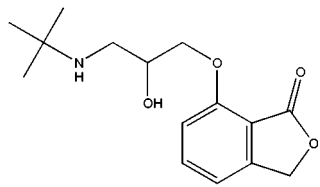
AFUROLOL

Therapeutic Function: Beta-adrenergic blocker

Chemical Name: 7-[3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-1(3H)-isobenzofuranone

Common Name: Afurolol

Structural Formula:



Chemical Abstracts Registry No.: 65776-67-2

Trade Name	Manufacturer	Country	Year Introduced
Afurolol	ZYF Pharm Chemical	-	-

Raw Materials

7-Hydroxyphthalide
1-Chloro-2,3-epoxypropane
t-Butylamine

Manufacturing Process

A mixture of 18.0 g (0.12 mole) 7-hydroxyphthalide, 180.0 g of 1-chloro-2,3-epoxypropane (2 moles) and 0.5 ml of piperidine is heated at 100°C for about 5 h and then the unreacted 1-chloro-2,3-epoxypropane is distilled off in vacuum to yield 12.0 g (48%) of 7-(2,3-epoxypropoxy)phthalide, melting point 88°-90°C, (crystallized successively from methanol and ethyl acetate).

The 7-(2,3-epoxypropoxy)phthalide is dissolved in methanol and t-butylamine are added to the solution at about 20°C. The solution is allowed to stand

overnight and, the mixture is evaporated in vacuum and the residue is dried to give 7-(2-hydroxy-3-t-butylamino-propoxy)phthalide.

References

Bellasio E.; US Patent No. 3,935,236; Jan. 27, 1976; Assigned: Gruppo Lepetit, S.p.A., Milan, Italy

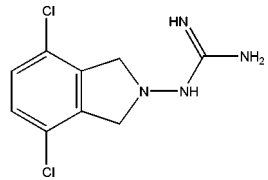
AGANODINE

Therapeutic Function: Antihypertensive

Chemical Name: Guanidine, (4,7-dichloro-2-isoindolinyl)-

Common Name: Aganodine

Structural Formula:



Chemical Abstracts Registry No.: 86696-87-9

Trade Name	Manufacturer	Country	Year Introduced
Aganodine	ZYF Pharm Chemical	-	-

Raw Materials

3,6-Dichlorophthalic anhydride
Lithium aluminum hydride
Cyanamide
Carbazic acid, tert-butyl ester
Hydrochloric acid
Sodium bicarbonate

Manufacturing Process

The solution of 3,6-dichlorophthalic anhydride in 300 ml of N,N-dimethylformamide are heated to the boiling point over 15 min with t-butylcarbazate. Subsequent to evaporation of the solvent, N-(t-butyloxycarbonylamino)-3,6-dichlorophthalimide is obtained from ethanol.

The solution of N-(t-butyloxycarbonylamino)-3,6-dichlorophthalimide in 400 ml of absolute tetrahydrofuran are slowly dripped into a suspension of aluminum lithium hydride in absolute tetrahydrofuran. The mixture is heated to the boiling point. Conventional processing yields N-(t-butyloxycarbonylamino)-4,7-dichloroisoindoline.

N-(t-Butyloxycarbonylamino)-4,7-dichloroisoindoline are introduced into concentrated hydrochloric acid and stirred at room temperature. The hydrochloride of 2-amino-4,7-dichloroisoindoline precipitates in the form of crystals is obtained, melting point 230°-232°C.

2-Amino-4,7-dichloroisoindoline hydrochloride and cyanamide are heated over 2 h to the boiling point in n-amyl alcohol. The solvent is evaporated off and the residue recrystallized from isopropyl alcohol and ethyl ether, yielding the (4,7-dichloroisoindolin-2-yl)guanidine in the form of hydrochloride, melting point 235°-237°C.

To obtained the base (4,7-dichloroisoindolin-2-yl)guanidine the salt (4,7-dichloroisoindolin-2-yl)guanidine hydrochloride is treated with sodium bicarbonicum.

References

Cohnen E, Armah B.; US Patent No. 4,526,897; July 2, 1985; Assigned: Beiersdorf Aktiengesellschaft, Hamburg, Fed.Rep. of Germany

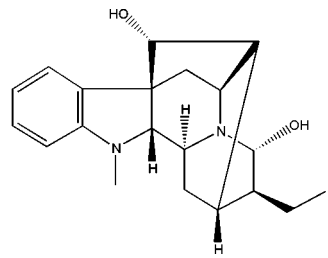
AJMALINE

Therapeutic Function: Antiarrhythmic

Chemical Name: Ajmalan-17,21-diol, (17R,21α)-

Common Name: Ajmaline; Rauwolfine

Structural Formula:



Chemical Abstracts Registry No.: 4360-12-7

Trade Name	Manufacturer	Country	Year Introduced
Ajmaline	Solvay Pharma	-	-
Aritmina	Farmacie Petrone	-	-
Aritmina	Solvay	-	-
Neo-Aritmina	Giulini Pharma	-	-
Gilurytmal	Solvay	-	-
Gilurytmal	Solvay Arzneimittel	-	-

Trade Name	Manufacturer	Country	Year Introduced
Gilurytmal	Solvay Pharmaceuticals (Spolka z o.o.)	-	-
Gilurytmal	Solvay Pharmaceuticals	-	-
Gilurytmal	Solvay Pharma, Klosterneuburg	-	-
Neo-Gilurytmal	Solvay Pharmaceuticals	-	-
Rauwolfine	Extrasynthese	-	-
Ritmos	Inverni	-	-
Serenol	Laboratoires Plantes et Medecines	-	-
Tachmalin	Arzneimittelwerk Dresden	-	-

Raw Materials

Rauwolfia canescens L. roots
Acetic acid
Ammonia

Manufacturing Process

Ajmaline isolated from *Rauwolfia sp. roots: Rauwolfia serpentine Benth., Rauwolfia vomitoria Afr., Rauwolfia canescens L.*

Threshed roots of *Rauwolfia canescens L.* extracted with 5% solution of acetic acid at room temperature for 24 h. Then extract was decanted to flask. This extract was alkalified with ammonia (alkaloid salts were converted to alkaloid bases). The obtained thus method solution was extracted with chloroform 3 or more times. Then chloroform extract was chromatographed on column through Al_2O_3 sorbent. After chromatography ajmalin was obtained, which had melting point at 205°C (recyrstallization from methanol).

References

Belikov A.S.; Alkaloids of Rauwolfia canescens L.//Chemistry of natural compounds 1969, 3. P.64

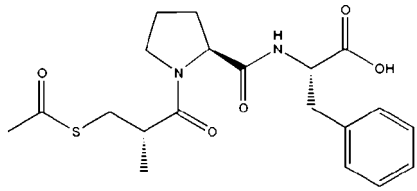
ALACEPRIL

Therapeutic Function: Antihypertensive

Chemical Name: L-Phenylalanine, N-(1-(3-(acetylthio)-2-methyl-1-oxopropyl)-L-prolyl)-, (S)-

Common Name: Alacepril; Cetapril

Structural Formula:



Chemical Abstracts Registry No.: 74258-86-9

Trade Name	Manufacturer	Country	Year Introduced
Alacepril	Sumika Fine Chemicals Co., Ltd.	-	-
Alacepril	ZYF Pharm Chemical	-	-
Cetapril	Dainippon Pharmaceutical Co., Ltd.	-	-

Raw Materials

N-Methylmorpholine
1-(D-3-Acetylthio-2-methylpropanoyl)-L-proline
Phenyl chloroformate
L-Phenylalanine t-butyl ester hydrochloride
Sodium bicarbonate
Hydrochloric acid
Anisole
Trifluoroacetic acid

Manufacturing Process

N-Methylmorpholine (1.03 g) was added to a solution of 1-(D-3-acetylthio-2-methylpropanoyl)-L-proline (2.65 g) in dry tetrahydrofuran (50 ml). The resulting solution was stirred and cooled at -20° to -15°C. Phenyl chloroformate (1.61 g) was added, and after 5 min, a solution of L-phenylalanine t-butyl ester hydrochloride (2.4 g) and N-methylmorpholine (1.03 g) in dry tetrahydrofuran (30 ml) was added. The mixture was stirred at -20° to -15°C for 1 h and then at room temperature overnight.

After removal of insoluble materials by filtration, the filtrate was concentrated under reduced pressure and the residue was dissolved in chloroform.

The chloroform solution was washed successively with 1 N sodium hydroxide, water, 10% citric acid, and water, dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with chloroform-methanol (99:1) to give 4.2 g the 1-(D-3-acetylthio-2-methylpropanoyl)-L-prolyl-L-phenylalanine tert-butyl ester.

1-(D-3-Acetylthio-2-methylpropanoyl)-L-prolyl-L-phenylalanine tert-butyl ester

(2.5 g) was dissolved in a mixture of anisole (18 ml) and trifluoroacetic acid (37 ml). The solution was allowed to stand at room temperature for 1 h and then concentrated to dryness under reduced pressure. The residue was crystallized from diethyl ether. The 1-(D-3-acetylthio-2-methylpropanoyl)-L-prolyl-L-phenylalanine was obtained (1.8 g), melting point 155°-156°C (recrystallization from ethanol/n-hexane).

References

Sawayama T. et al.; US Patent No. 4,248,883; Feb. 3, 1981; Assigned: Dianippon Pharmaceutical Co., Ltd., Osaka, Japan

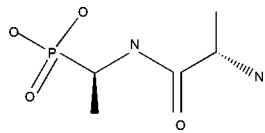
ALAFOSFALIN

Therapeutic Function: Antibacterial

Chemical Name: Phosphonic acid, ((1R)-1-(((2S)-2-amino-1-oxopropyl) amino)ethyl)-

Common Name: Alafosfalin; Alaphosfalin

Structural Formula:



Chemical Abstracts Registry No.: 60668-24-8

Trade Name	Manufacturer	Country	Year Introduced
Alafosfalin	Roche Product Limited	-	-

Raw Materials

N-Hydroxysuccinimide ester of N-benzyloxycarbonyl-L-alanine
(1R,S)-1-Aminoethylphosphonic acid
Benzylamine
Palladium on carbon
1R-(L-Alanylamino)ethanephosphonous acid
Mercuric chloride
Propylene oxide

Manufacturing Process

14.1 g (0.168 mol) of solid sodium bicarbonate were added to a solution of 7 g (0.056 mol) of (1R,S)-1-aminoethylphosphonic acid in 280 ml of water and 140 ml of ethanol while stirring at 0°C. While stirring this mixture at 0°C, a solution of 17.9 g (0.056 mol) of the N-hydroxysuccinimide ester of N-

benzyloxycarbonyl-L-alanine in 140 ml of warm ethanol was added dropwise over ca 15 minutes. The latter solution was washed in with 70 ml of ethanol. The heterogeneous mixture was stirred for 1 hour at 0°C and then for a further 16 hours at room temperature, the mixture becoming homogeneous. The mixture was evaporated and re-evaporated with 200 ml of water to give a gum, which was dissolved in 500 ml of water. The solution was extracted firstly with 500 ml of chloroform and then with 250 ml portions of chloroform, acidified to pH 2 with ca 80 ml of 2 N hydrochloric acid and again extracted with 500 ml of chloroform followed by two 250 ml portions of chloroform. The aqueous layer was concentrated and passed down a column of cation exchange resin (B.D.H., Zerolit 225, SRC 13, RSO_3H; 750 g; freshly regenerated in the acid cycle). The column was eluted with water and there were collected six 250 ml fractions. The first four fractions were combined, evaporated and re-evaporated with water to remove hydrogen chloride. There was obtained a final residue of (1R,S)-1-[(N-benzyloxycarbonyl-L-alanyl)-amino]ethylphosphonic acid which was separated as follows:

The latter residue was dissolved in 400 ml of water and titrated with 1 M benzylamine to pH 4.5. The resulting solution was concentrated and crystallized from water to give 5.3 g of the benzylamine salt of (1S)-1-[(N-benzyloxycarbonyl-L-alanyl)amino]ethylphosphonic acid of melting point 210-215°C. Concentration of the mother liquors followed by further recrystallization from water gave the benzylamine salt of (1R)-1-[(N-benzyloxycarbonyl-L-alanyl)amino]ethylphosphonic acid in a first crop of 0.59 g [melting point 226-228°C (decomposition); $[\alpha]_D^{20}$ = -32.3° (c = 1% in acetic acid)] and a second crop of 0.825 g] melting point 225-227°C (decomposition); $[\alpha]_D^{20}$ = -33.0° (c = 1% in acetic acid)]. Recrystallization of the first crop from water gave 0.333 g of pure benzylamine salt of the R-stereoisomer; melting point 226-228°C (decomposition); $[\alpha]_D^{20}$ = -33.1° (c=1% in acetic acid).

1.1 g (2.5 mmol) of the benzylamine salt of (1R)-1-[(N-benzyloxycarbonyl-L-alanyl)amino]-ethylphosphonic acid were dissolved in 4 ml of 2 N ammonium hydroxide, passed down a column of cation exchange resin (B.D.H., Zerolit 225, SRC 13, RSO_3H; 120 g; freshly regenerated in the acid cycle) and eluted with water. There were collected 200 ml of acid eluate, which was concentrated to 100 ml. To this were added 100 ml of methanol, 0.3 g of 5% palladium-on-charcoal catalyst and 3 drops of glacial acetic acid. The mixture was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off and the solvent evaporated. The residual gum was re-evaporated with three 50 ml portions of n-propanol to give 0.6 g of a gummy solid of melting point ca 275-280°C (decomposition). After further recrystallization from water and ethanol, there was obtained 0.2 g of (1R)-1-(L-alanylamino)-ethylphosphonic acid of melting point 295-296°C (decomposition); $[\alpha]_D^{20}$ = -44.0° (c=1% in water).

The different ways of synthesis of alafosfalin were described:

1). 1R-1-(L-alanylamino)-ethanephosphonous acid (0.034 M), mercuric chloride (0.068 M) and water (175 ml) were mixed and heated to reflux for 1 hour The white insoluble mercuric chloride which formed was removed by filtration and the aqueous filtrate was evaporated to dryness. The oily residue was dissolved in ethanol (20 ml) and propylene oxide was added until

precipitation was complete. Filtration gave 1R-1-(L-alanylamino)-ethylphosphonic acid, which was recrystallised from ethanol/water. MP: 293-295°C, $[\alpha]_D^{20}$ =-49.3° (1%, H_2O). Yield was 100% of theory.

2). Papain (50 mg; 2.2 U/mg) was added to the solution of 0.5 mmol Z-L-Ala, 1.15 mmol racemic diisopropyl ester of 1-aminoethylphosphonic acid and 50 ml 2-mercaptoethanol in the mixture of 2.3 ml acetonitrile and 0.2 ml water The suspension was shaken for about 2 days until all the Z-ala was consumed (TLC-control). The enzyme was filtered off and washed with 10% $KHSO_4$, water, saturated $NaHCO_3$, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting phosphonopeptide was dissolved in 2 ml of 40% HBr in glacial acetic acid and left overnight. Anhydrous ether (10 ml) was added and the mixture was stirred for 10 min and upper phase decanted. The residue was evaporated, the remaining gum was dissolved in 2 ml of methanol and treated with excess of propylene oxide. The precipitated material was filtered off and crystallized from water water-ethanol to give pure alafosfalin, yield 60%, MP: 273-276°C (decomposition); $[\alpha]_D^{20}$ =-45° (0.2% in water). Only L-aminophosthonate is involved in the peptide bond formation because of papain presence.

References

Atherton F.R. et al.; US Patent No. 4,016,146; April 5, 1977; Assigned to Hoffmann-La Roche Inc., Nutely, N.Y.
Baylis E.; US Patent No. 4,331,591; May 25, 1982; Assigned to Ciba-Geigy Corporation, Ardsley, N.Y.
Solodenko V., Kukar V.; Tetrahedron Letters, v. 30, No. 49, pp 6917-6918, 1989

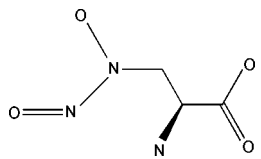
ALANOSINE

Therapeutic Function: Antineoplastic

Chemical Name: 3-(Hydroxynitrosoamino)-L-alanine

Common Name: Alanosine

Structural Formula:



Chemical Abstracts Registry No.: 5854-93-3

Trade Name	Manufacturer	Country	Year Introduced
Alanosine	Triangle Pharmaceuticals	-	-

Raw Materials

Streptomyces alanosinicus n. sp. ATCC 15710
Peptone-agar-glucose-yeast extract medium
Glucose
Dried whale meat (Pascor)
6% of Darco G-60 charcoal
Sodium methoxide

Manufacturing Process

Alanosine is an antibiotic isolated from the fermentation broth of Streptomyces alanosinicus n. sp.

Oat meal agar slants seeded with Streptomyces alanosinicus n. sp. ATCC 15710 were incubated at 20°C for 7 to 10 days and then used to inoculate 100 ml of a peptone-agar-glucose-yeast extract medium contained in 500 ml Erlenmeyer flask. The composition of this fermination medium is:

Meat extract	5.0 g./liter
Peptone	5.0 g./liter
Yeast extract	5.0 g./liter
Enzymatic casein hydrolysate	3.0 g./liter
Cerelose	2.0 g./liter
NaCl	1.5 g./liter

The medium is adjusted to pH 7.2 prior to sterilization for 20 minutes at 121°C and 15 Ibs steam pressure. The germination flasks are incubated at 28°C for 48 hours on rotary shaker having a 2 inch throw and making 240 rpm. A 3% transfer is made from the germination flask to 500 ml Erlenmeyer fermentation flaks containing 100 ml of medium TVF/5 having the following composition:

Glucose	50.0 g/L
Dried whale meat (Pascor)	10.0 g/L
$CaCO_4$	5.0 g/L
$(NH_4)_2SO_4$	1.0 g/L
$MgSO_4 \cdot 7H_2O$	1.0 g/L
$CuSO_4$ sol. 0.5%	1 ml
$FeSO_4$ sol. 0.1%	1 ml
$ZnSO_4$ sol. 0.2%	1 ml
$MnSO_4$ sol. 0.8%	1 ml

The medium is adjusted to pH 7.0 prior to sterilization for 20 minutes at 121°C. The fermentation flasks are incubated and agitated under similar conditions as the germination flasks. After 72 hours the mycelium was separated by centrifugation and the untreated broth assayed by the streak dilution method. 30 liters of broth are centrifuged and 6% of Darco G-60 charcoal is added to the clear solution, which is stirred for 30 minutes; then the charcoal is filtered off to give an almost colorless solution which is concentrated in vacuum at 45-50°C to 1.5 liters. The concentrated solution is poured under stirring into 5 liters of methanol, the formed precipitate is

filtered, washed with much acetone and dried in vacuum. Yield 230 g of crude product assaying about 10%.

Purification:

The above crude product is suspended in 400 ml of water and to the suspension, cooled to 4°C and kept stirred, sulfuric acid is added to pH 2.0-2.5; the undissolved residue is filtered off, the solution is further diluted with 400 ml of water and 1.6 liters of methanol are added to precipitate the antibiotic. The mixture is kept at 4°C for some hours to complete precipitation, then it is filtered, washed with acetone and dried in vacuum over P_2O_5. Yield 62 g of a product assaying 27%. The dried product is suspended in anhydrous methanol and the mixture is kept stirred; perchloric acid (75%) is added at about 4°C to reach a pH of 3.0, the undissolved portion is filtered off and the antibiotic is precipitated by adjusting the pH 5.5 with sodium methoxide. The suspension is allowed to decant for some hours at 4°C, then it is filtered and the precipitate is washed with diethyl ether. Yield 30 g (titer 43%). An amount of 3.2 g of the obtained antibiotic is dissolved in 60 ml of H_2O and the pH is adjusted to 8; the undissolved portion is filtered off and by the addition of glacial acetic acid, the pH is adjusted to 4-4.5. On cooling at 4°C, 1.2 g of antibiotic in crystalline form (assaying 75%) are obtained. An amount of 2.9 g of said crystalline antibiotic is dissolved in 900 ml of water heating the solution to 70-80°C, then it is filtered, concentrated to 200 ml and allowed to stand 8-10 hours at 4°C; then it is filtered and washed with cold water. Yield 1.45 g (97%). By further concentrating the solution to 100 ml a further amount of antibiotic is obtained: 1 g (80%). Alanosine melts at 190°C, $[\alpha]_D^{25}$= -37.8° (c=0.5, water).

Antibiotic was also prepared by syntheses from anhydrous hydroxylamine and methyl-2-acetamido-3-chloropropionate followed by reaction with $NaNO_2$ in dilute acetic acid. The prepared racemic product was separated on individual isomers.

References

Thiemann J. et al.; US Patent No. 3,676,490; July 11, 1972; Assigned to Lepetit S.P.A., Milan, Italy

Lancini G.C.A, Diena and E. Lassari; Tetrahedron Letters No. 16, pp. 1769-1772, 1966

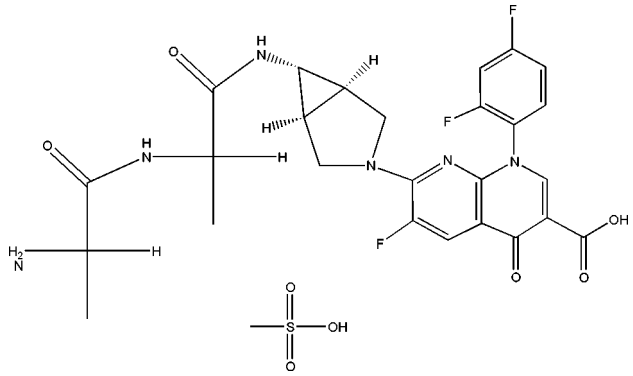
ALATROFLOXACIN MESYLATE

Therapeutic Function: Antibacterial

Chemical Name: L-Alaninamide, L-alanyl-N-(3-(6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl)-3-azabicyclo[3.1.0]hex-6-yl)-, (1α,5α,6α)-, monomethanesulfonate

Common Name: Alatrofloxacin mesilate

Structural Formula:



Chemical Abstracts Registry No.: 146961-77-5; 146961-76-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alatrofloxacin mesylate	Pfizer	-	-
Alatrofloxacin mesylate	Fairview Pharm	-	-
Alatrofloxacin mesilate	Cipla	-	-
Trovan Preservative Free	Pfizer	-	-
Trovan iv	Pfizer	-	-
Turvel iv	Roerig Farmaceutici Italiana S.p.A.	-	-
Turvel iv	Pfizer	-	-

Raw Materials

Diphenylphosphinous azide
Dihydropyrrole
Ethyldiazoacetate
Palladium
Alanylalanine
1-(2,4-Difluoro-phenyl)-6,7-difluoro-4-oxo-1,4-dihydro[1,8] naphthylridine-3-carboxylic acid ethyl ester

Manufacturing Process

The dipolar cycloaddition of ethyldiazoacetate to the protected dihydropyrrole (with carbobenzyloxy (CBZ) protecting group) gives the fused pyrrazolidine-(CBZ-3-ethylperoxy-1,3a,4,5,6,6a-hexahydro-pyrrolo{3,4-c}pyrazole). Pyrolysis results in loss of nitrogen and formation of the cyclopyrrolidine ring. The ester is then saponified to the corresponding carboxylic acid (CBZ-6-aza-bicyclo[3.1.0]hexene-3-carboxylic acid).This acid undergoes a version of the

Curtius rearrangement when treated with diphenylphosphinous azide to afford transient isocyanate. That reactive function adds tert-butanol from the reaction medium to afford the product as its butoxycarbonyl (BOC) derivative. CBZ-protecting group is removed by catalytic hydrogenation on Pd to afford the BOC-protected secondary amine - BOC-6-aza-bicyclo[3.1.0]hex-3-ylamine. In a standard quinolone reaction, this amine is then used to displace the more reactive fluorine at 7-position in the quinolone - 1-(2,4 difluoro-phenyl)-6,7-difluoro-4-oxo-1,4-dihydro[1,8]naphthylridine-3-carboxylic acid ethyl ester. Treatment of the displacement product with hydrogen chloride cleaves the BOC protecting group to afford the antibiotic trovafloxacin. The peptide-like alanylalanylamide derivative, alatrofloxacin can in principle be prepared by reaction of the ester precursor of trovafloxacin with alanylalanine followed by saponification and treatment by methane sulphonic acid (mesylate).

References

Lednicer D., The organic Chemistry of Drug Synthesis, vol. 5, Wiley, NY, p.123 (1985)
Brighty K.E.; US Patent No. 5,164,402; Nov. 17, 1992, Assigned to Pfizer Inc., New York, N.Y.
Lednicer D., The organic Chemistry of Drug Synthesis, vol.6, Wiley, NY, p.154 (1999)

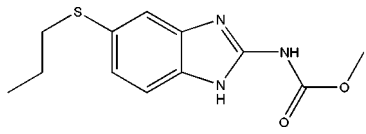
ALBENDAZOLE

Therapeutic Function: Anthelmintic

Chemical Name: [5-(Propylthio)-1H-benzimidazol-2-yl]carbamic acid methyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 54965-21-8

Trade Name	Manufacturer	Country	Year Introduced
Zentel	SK and F	France	1981

Raw Materials

3-Chloro-6-nitroacetanilide
Hydrogen
Methyl chloroformate
Propyl Mercaptan
Cyanamide

Manufacturing Process

A mixture of 6.65 g of 3-chloro-6-nitroacetanilide, 3.2 ml of propylmercaptan, 5.6 g of 50% sodium hydroxide and 100 ml of water is heated at reflux overnight. The cooled mixture is filtered to give the desired 2-nitro-5-propylthioaniline, MP 69.5-71.5°C after recrystallization from ethanol then hexane-ether. NMR ($CDCl_3$) 40%.

The aniline (2.5 g) is hydrogenated with 1.9 ml of concentrated hydrochloric acid, 100 ml ethanol and 5% palladium-on-charcoal to give 4-propylthio-o-phenylene-diamine hydrochloride.

A mixture of 2.5 ml of 50% sodium hydroxide in 5 ml of water is added to a mixture of 1.9 g of cyanamide, 2.2 g of methylchloroformate, 3.5 ml of water and 3 ml of acetone over 45 minutes below 10°C, pH raised to 6.5. A molar equivalent solution of the diamine in 100 ml of ethanol is added. The mixture is heated until the easily volatile solvents are expelled, to about 85°C, then maintained at this temperature with some water added for one-half hour. The product, methyl 5-propylthio-2-benzimidazolecarbamate, is separated, washed to give a colorless crystalline solid, MP 208-210°C.

References

Merck Index 197
DFU 2 (2) 81 (1977)
OCDS Vol.2 p. 353 (1980)
DOT 15 (3) 89 (1979)
I.N. p. 50
Gyurik, R.J. and Theodorides, V.J.; US Patent 3,915,986; October 28, 1975; Assigned to Smith Kline Corp.

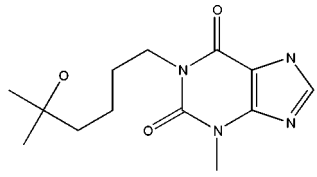
ALBIFYLLINE

Therapeutic Function: Vasodilator

Chemical Name: 3,7-Dihydro-1-(5-hydroxy-5-methylhexyl)-3-methyl-1H-purine-2,6-dione

Common Name: Albifylline

Structural Formula:



Chemical Abstracts Registry No.: 107767-55-5

Trade Name	Manufacturer	Country	Year Introduced
HWA-138	Hoechst-Roussel	-	-

Raw Materials

1-Chloro-5-hexanone
3-Methylxanthine
Palladium on carbon
Methyl magnesium chloride
Benzyl bromide

Manufacturing Process

1-(5-Hydroxy-5-methylhexyl)-3-methylxanthine may be prepared next way:

1). 1-Chloro-5-hydroxy-5-methylhexane:

A solution of 67.3 g (0.5 mol) of 1-chloro-5-hexanone in 50 ml of anhydrous ether is added dropwise to 44.9 g (0.6 mol) of methyl magnesium chloride in the form of a 20% strength solution in tetrahydrofuran and 200 ml of dry ether at 0° to 5°C, while stirring. The mixture is then subsequently stirred initially at room temperature for one hour and then while boiling under reflux for a further hour, the tertiary alkanolate formed is decomposed by addition of 50% strength aqueous ammonium chloride solution, the ether phase is separated off and the aqueous phase is extracted by shaking with ether. The combined ethereal extracts are washed in succession with aqueous sodium bisulfite solution and sodium bicarbonate solution as well as a little water, dried over sodium sulfate, filtered and concentrated in vacuo and the liquid residue is subjected to fractional distillation under reduced pressure. Yield: 64.1 g (85.1% of theory), boiling point (20 mbar) 95-97°C, refractive index n_D^{25} =1.4489.

2). 7-Benzyl-3-methylxanthine:

20 g (0.5 mol) of sodium hydroxide dissolved in 200 ml of water are added to a suspension of 83 g (0.5 mol) of 3-methylxanthine in 500 ml of methanol, the mixture is stirred at 70°C for one hour, 85.5 g (0.5 mol) of benzyl bromide are then added dropwise at the same temperature and the reaction mixture is kept between 70°C and 80°C for 5 hours. It is then cooled and filtered cold with suction, the product on the suction filter is washed with water and dissolved in 1000 ml of 1 N sodium hydroxide solution under the influence of heat, the solution is filtered and the pH is brought slowly to 9.5 with 4 N hydrochloric acid, while stirring. The crystals are filtered off from the still warm solution, washed with water until free from chloride and dried in vacuum. Yield: 81.7 g (63.8% of theory), melting point: 262-264°C.

3). 7-Benzyl-1-(5-hydroxy-5-methylhexyl)-3-methylxanthine:

A mixture of 20.5 g (0.08 mol) of 7-benzyl-3-methylxanthine, 12.4 g (0.09 mol) of potassium carbonate and 13.61 g (0.09 mol) of above 1-chloro-5-hydroxy-5-methylhexane in 300 ml of dimethylformamide is heated at 110° to 120°C for 8 hours, while stirring, and is then filtered hot and the filtrate is evaporated under reduced pressure. The residue is taken up in chloroform, the mixture is washed first with 1 N sodium hydroxide solution and then with

water until neutral and dried, the solvent is distilled off in vacuum and the solid residue is recrystallized from ethyl acetate, with the addition of petroleum ether Yield: 23.8 g (80.3% of theory), melting point: 109-111°C.

4). 1-(5-Hydroxy-5-methylhexyl)-3-methylxanthine:

14.8 g (0.04 mol) of the above mentioned 7-benzylxanthine are hydrogenated in 200 ml of glacial acetic acid over 1.5 g of palladium (5%) on active charcoal at 60°C under 3.5 bar in the course of 24 hours, while shaking. After cooling, the mixture is blanketed with nitrogen, the catalyst is filtered off, the filtrate is concentrated under reduced pressure and the solid residue is recrystallized from ethyl acetate. Yield of albifylline: 9.6 g (85.6% of theory), MP: 192-193°C.

References

Gebert U. et al.; US Patent No. 4,833,146; May 23, 1989; Assigned to Hoechst Aktiengeselschaft, Frankfurt am Main, Fed. Rep. of Germany

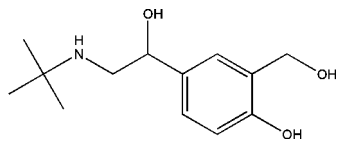
ALBUTEROL

Therapeutic Function: Bronchodilator

Chemical Name: α^1-[[(1,1-Dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol

Common Name: Salbutamol, α'-tert-Butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol

Structural Formula:



Chemical Abstracts Registry No.: 18559-94-9; 51022-70-9 (Sulfate)

Trade Name	Manufacturer	Country	Year Introduced
Ventolin	Allen and Hanburys	UK	1969
Sultanol	Glaxo	W. Germany	1971
Ventoline	Glaxo	France	1971
Ventolin	Glaxo	Italy	1973
Ventolin	Sankyo	Japan	1973
Ventolin	Glaxo	Switz.	1981
Ventolin	Glaxo	US	1981
Broncollenas	Llenas	Spain	-
Buto-Asma	Aldo Union	Spain	-
Proventil	Schering	US	-

Trade Name	Manufacturer	Country	Year Introduced
Rotacaps	Schering	-	-
Salbumol	Medica	Finland	-
Salbutol	Iltas	Turkey	-
Salbuvent	Leiras	Finland	-
Salbuvent	Nyegaard	Norway	-

Raw Materials

5-(N-Benzyl-N-tert-butylglycyl)salicylic acid methyl ester hydrochloride
Lithium aluminum hydride
Hydrogen

Manufacturing Process

(a) α^1-Benzyl-tert-butylaminomethyl-4-hydroxym-xylene-α^1,α^3-diol: 3.0 g of 5-(N-benzyl-N-tert-butylglycyl)-salicylic acid methyl ester hydrochloride in 40 ml of water was basified with sodium bicarbonate solution and extracted into ether. The ethereal solution was dried over $MgSO_4$ and evaporated and the basic residue in 20 ml of dry tetrahydrofuran was added with stirring to 1.0 g of lithium aluminum hydride in 100 ml of dry tetrahydrofuran, over a period of 5 minutes. The light gelatinous precipitate that formed was stirred and refluxed for 8 hours after which time 7 ml of water was carefully added and the solvents were removed under reduced pressure.

The residue was acidified with dilute hydrochloric acid and brought to pH 8 with sodium hydroxide and sodium bicarbonate. The mixture was filtered and the filtrate and orange solid were separately extracted with chloroform. The combined, dried, chloroform solutions were evaporated to give 22 g of the crude basic triol as an orange solid, when triturated with ether. A portion of the material was recrystallized from ether/light petroleum (BP 40-60°C) to give a white solid, MP 109-111°C.

In an alternative process, sodium borohydride was used as the reducing agent, as follows:

36 g of 2-(benzyl-tert-butylamino)-4'-hydroxy-3'-hydroxymethyl acetophenone, hydrochloride was shaken with 100 ml of 10% sodium carbonate solution and 100 ml of ethyl acetate. The ethyl acetate layer was separated, washed with water, dried over anhydrous sodium sulfate and evaporated in vacuum.

The residual gum was dissolved in 360 ml of ethanol and cooled to 15°C in an ice/water bath, 8 g of sodium borohydride was then added in portions over 30 minutes while maintaining the temperature at 15-20°C. After a further 30 minutes at 20°C the solution was stirred at room temperature for 2 hours. The solution was again cooled in ice and 250 ml of 2 N sulfuric acid were slowly added, then the solution was evaporated in vacuum until the ethanol had been removed. The clear aqueous solution was then treated with 250 ml of 10% sodium carbonate solution and the oil which precipitated was extracted into ethyl acetate. The ethyl acetate layer was washed with sodium carbonate solution, then with water, and was dried over anhydrous sodium

sulfate and evaporated in vacuum, to a small volume. Petroleum ether (BP 40-60°C) was added, and after standing overnight a white solid was obtained. This was filtered off to give 23 g of the product, MP 110-114°C.

(b) α^1-tert-Butylaminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol: 0.8 g of α^1-benzyl-tert-butyl-aminomethyl-4-hydroxy-m-xylene-α^1,α^3-diol in 20 ml of ethanol and 2 ml of water was shaken with hydrogen in presence of 0.50 g of pre-reduced 10% palladium on charcoal catalyst. When uptake of hydrogen was complete, the solution was filtered and evaporated under reduced pressure to give 0,4 g of the base as a colorless oil which yielded a white solid, MP 144-145°C when triturated with ether/cyclohexane. Recrystallization from ethyl acetate-cyclohexane gave a white solid, MP 147-149°C.

References

Merck Index 206
DFU 4 (9) 629 (1979)
Kleeman and Engel p. 813
PDR 40 pp. 916, 1649
OCDS Vol. 2 p. 43 (1980)
DOT 16 (8) 269 (1980)
I.N. p. 860
REM p. 881
Lunts, L.H.C. and Toon, P.; US Patent 3,644,353; February 22, 1972; Assigned to Allen and Hanburys Ltd.

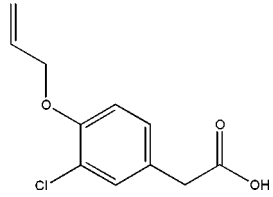
ALCLOFENAC

Therapeutic Function: Antiinflammatory

Chemical Name: 3-Chloro-4-(2-propenyloxy)benzene-acetic acid

Common Name: (4-(Allyloxy)-3-chlorophenyl]acetic acid

Structural Formula:



Chemical Abstracts Registry No.: 22131-79-9

Trade Name	Manufacturer	Country	Year Introduced
Mervan	Cooper	Switz.	-
Prinalgin	Berk	UK	1971
Neoston	Beiersdorf	W. Germany	1972

Trade Name	Manufacturer	Country	Year Introduced
Allopydin	Chugai	Japan	1976
Zumaril	Abbott	Italy	1976
Epinal	Kyorin	Japan	1976
Darkeyfenac	Cuatrecasas-Darkey	Spain	-
Desinflam	Sintyal	Argentina	-
Medifenac	Medici	Italy	-
Mervan, Mirvan	Continental Pharma	Belgium	-
Vanadian	Federico Bonet	Spain	-
ZumariI	Sidus	Italy	-
Rentenac	Tosi	Italy	-

Raw Materials

3-Chloro-4-allyloxyphenyl acetonitrile
Potassium hydroxide

Manufacturing Process

103.7 grams of 3-chloro-4-allyloxyphenylacetonitrile in 500 cc of ethanol, 100 grams of potassium hydroxide and 100 cc of water are refluxed for 4 hours. Maximum of alcohol is evaporated, the residue is diluted with water and ice, and acidified with 20% HCl. The solid is filtered and washed with petroleum ether. 91.5 grams of acid are obtained (Yield: 81%) which is recrystallized from aqueous methanol; MP 92-93°C.

References

Merck Index 209
Kleeman and Engel p. 19
OCDS Vol. 2 p. 68 (1980)
DOT 8 No. 9, 329 (1972)
I.N. p. 50
British Patent 1,174,535; December 17, 1969; Assigned to Madan AG, Switzerland

ALCLOMETASONE DIPROPIONATE

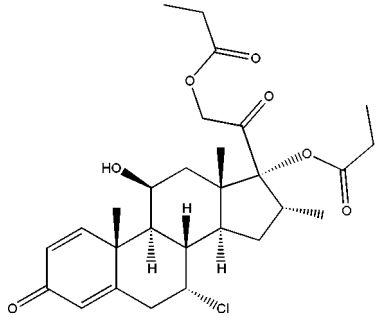
Therapeutic Function: Antiinflammatory, Antiallergic

Chemical Name: Pregna-1,4-diene-3,20-dione, 7-chloro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (7α,11β,16α)-

Common Name: Alclometasone dipropionate; Perderm; Modrasone

Chemical Abstracts Registry No.: 66734-13-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Alclovate	GlaxoSmithKline	-	-
Afloderm	Belupo	-	-
Miloderme	Schering-Plough	-	-

Raw Materials

16α-Methyl-1,4,6-pregnatriene-11β,17α,21-triol-3,20-dione 17,21-dipropionate
Hydrogen chloride
Sodium borohydride

Manufacturing Process

A). Add 16α-methyl-1,4,6-pregnatriene-11β,17α,21-triol-3,20-dione 17,21-dipropionate (2.0 g) to dioxane (24 ml) which has been saturated with dry hydrogen chloride gas. Stir at room temperature for 16 hours, pour into ice water (600 ml), separate the resultant precipitate by filtration, wash the precipitate with water and dry in air. Separate the components in the foregoing precipitate on silica gel via thin layer chromatography utilizing as developing solvent ether:hexane (2:1), and elute with ethyl acetate the band containing 7α-chloro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17,21-dipropionate as shown by ultraviolet light. Evaporate the combined ethyl acetate eluates and triturate the resultant residue with acetone:ether, then filter and dry the triturated precipitate to obtain 7α-chloro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17,21-dipropionate.

Alternatively, the 7α-chloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17,21-dipropionate is prepared according to following procedures B and C.

B). Saturate dry tetrahydrofuran (137 ml) at 0°C with dry hydrogen chloride gas. Add 16α-methyl-1,4,6-pregnatriene-17α,21-diol-3,11,20-trione 17,21-dipropionate (6.85 g) and stir the reaction mixture at 0°C for 1 hour. Pour into ice water (1 liter) and stir for ½ hour. Separate the resultant precipitate by filtration, wash with water, and air dry to give 7v-chloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17,21-dipropionate. Purify from methanol:acetone containing a trace of propylene oxide; $[\alpha]_D^{26}$ +76.2°

(dimethylformamide).

C). To a solution of 7v-chloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17,21-dipropionate (3.2 g) in tetrahydrofuran (24 ml) and methanol (8 ml) at 0°C under an atmosphere of nitrogen add sodium borohydride (0.697 g) and stir the reaction mixture for 15 min at 0°C. Pour into ice water (1.8 liters) and 250 ml of 1 N hydrochloric acid. Separate the resultant precipitate by filtration and air dry to give 7α-chloro-16α-methyl-11β,17α,21-triol-3,20-dione 17,21-dipropionate. Purify by crystallizing twice from acetone:methanol:isopropyl ether; m.p. 212°-216°C; $[\alpha]_D^{26}$ +42.6° (dimethylformamide). λ_{max} 242 nm (methanol, ε 15,600).

By saponification of 7α-chloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione 17,21-dipropionate is prepared (7α,11β,16α)-7-chloro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione.

References

Green M., Shue Ho-Jane; US Patent No. 4,124,707; Nov. 7, 1978; Schering Corporation (Kenilworth, NJ)

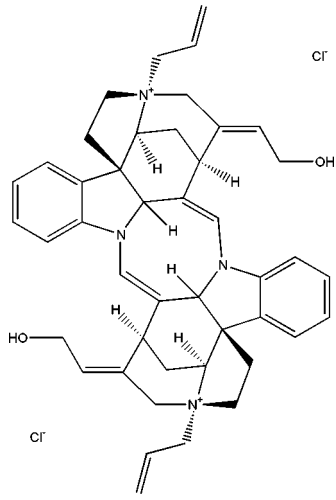
ALCURONIUM CHLORIDE

Therapeutic Function: Muscle relaxant

Chemical Name: N,N'-Diallylnortoxiferinium dichloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 15180-03-7

Trade Name	Manufacturer	Country	Year Introduced
Alloferin	Roche	UK	1966
Alloferin	Roche	W. Germany	1968
Alloferine	Roche	France	1968
Dialferin	Nippon Roche	Japan	1969
Toxiferin	Roche	-	-

Raw Materials

Diallyl Nortoxiferine Diiodide
Chloride Ion Exchange Resin

Manufacturing Process

31 g of diallylnortoxiferine diiodide are suspended in 1 liter of water and shaken with 1,100 ml of Amberlite IRA-400 [chloride ion form, described Merck Index, 7th edition, Merck and Co., Inc., Rahway, New Jersey (1960), page 1584], for 2 hours. The diiodide thereby goes into solution. The ion exchanger is filtered off and then washed in 3 portions with a total of 1 liter of water. The combined filtrates are then allowed to run through a column of 300 ml of Amberlite IRA-400 (chloride ion form), rinsed with 300 ml of water and the eluate evaporated to dryness in a vacuum while excluding air. The residue gives on recrystallization from methanol/ethanol crystalline pure colorless diallylnortoxiferine dichloride in a yield of 18.6 g. The compound contains 5 mols of water of crystallization after equilibration in air.

References

Merck Index 215
Kleeman and Engel p. 19
I.N. p.51
Boller, A., Els, H. and Furst, A.; US Patent 3,080,373; March 5, 1963; Assigned to Hoffman La Roche, Inc.

ALDOSTERONE

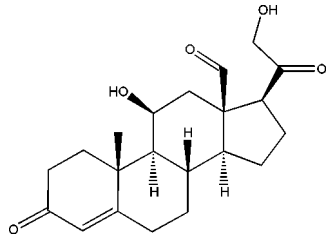
Therapeutic Function: Mineralocorticoid

Chemical Name: Pregn-4-en-18-al, 11,21-dihydroxy-3,20-dioxo-, (11β)-

Common Name: Aldosterone; Elektrocortin; Oxocorticosterone; Reichstein's substance X

Chemical Abstracts Registry No.: 52-39-1

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Aldosterone	Sigma Chemical Company	-	-
Aldosterone	Andard-Mount Company Limited	-	-
Aldocorten	Ciba	-	-

Raw Materials

3α,11β-Dihydroxy-D-homo-18-noretiocholan-17α-one

Sodium hydride	Potassium hydroxide
Acrylonitrile	4-Toluenesulfonic acid monohydrate
Acetic acid	Sodium borohydride
Ozone	Sodium metaperiodate
Sodium arsenite	Sodium bicarbonate
Potassium iodide	Piperidine
Pyridine	Acetic anhydride
Zinc	Diazomethane
Lithium	Bromobenzene
Thyonyl chloride	Palladium
Chromic oxide	Dinitrophenylhydrazine
Furfural	Hydrogen chloride

Manufacturing Process

In 1.0 L of methanol (purified by distillation from potassium hydroxide) was dissolved 27.02 g of 3α,11β-dihydroxy-D-homo-18-noretiocholan-17α-one (melting point 169°-173°C Patent No. 2,847,457; May 26, 1955). The solution was cooled to 5°C, and 54 ml of freshly distilled furfural was added. The air in the flask was replaced by nitrogen, 400 ml of 15% aqueous potassium hydroxide was added and the flask was sealed tightly. The solution was allowed to stand at room temperature overnight. The precipitate was collected on a filter, washed generously with water, and was dried to constant weight in vacuo, yielding 28.45 g of 3α,11β-dihydroxy-D-homo-18-noretiocholan-17-furfurylidene-17α-one as colorless lustrous plates, melting point 193°-194°C (after repeated recrystallization from methanol and acetone-petroleum ether).

A solution of 48 mg of sodium hydride in 6 ml of anhydrous methanol was cooled to 5°C, and to it was added slowly 1.20 ml of acrylonitrile (b.p. 75°-78°C). The solution was allowed to stand at room temperature for an 1 h and then cooled again to 5°C. The 3α,11β-dihydroxy-D-homo-18-noretiocholan-17-

furfurylidene-17α-one was added and the solution was stirred at room temperature for 2 h and then heated at reflux for 2 h. After a total of 8 h of heating at reflux the mixture was cooled to 5°C, and acetic acid was added until the solution was acidic. It was then diluted with water and extracted with ethyl acetate. The extract was washed with aqueous sodium bicarbonate and water, dried over magnesium sulfate, and distilled to dryness under reduced pressure. The product was crystallized from a small volume of acetone, and the crystals were washed with hot petroleum ether and then ether. This gave 750 mg of 3α,11β-dihydroxy-13α-(2-cyanoethyl)-D-homo-18-noretiocholan-17-furfurylidene-17α-one as colorless plates, melting point 193°-194°C (after repeated recrystallization from methanol).

A solution of 1.02 g of 3α,11β-dihydroxy-13α-(2-cyanoethyl)-D-homo-18-noretiocholan-17-furfurylidene-17α-one in 60 ml of methanol and 5 ml of pyridine was cooled to -70°C, and a stream of oxygen containing ozone was passed through until the solution turned a faint blue color (25 min). The solution was quickly put under reduced pressure to remove any dissolved ozone, and after 3 min a solution of 1.0 g of sodium borohydride in 10 ml of water was added slowly, allowing the solution to warm to 0°C. Within two min after the borohydride was added (an acidified portion of the solution gave no starch-iodide test, indicating absence of ozonide). An additional 3.0 g of borohdride was added in 1 g portions at 1 h intervals, and the solution was allowed to stand for a total of 35 h. Acetic acid was added slowly and stirring until the solution yield pH 5. The methanol was distilled, under reduced pressure, the last portions being co-distilled with ethyl acetate and water. The aqueous solution was then extracted three times with ethyl acetate. The extracts were washed in turn with 5% aqueous hydrochloric acid (cold), water, aqueous sodium bicarbonate, and water. The combined ethyl acetate solutions were dried over sodium sulfate and concentrated to dryness under reduced pressure. The crude product (71%) of 3α,11β,17,17a-tetrahydroxy-13α-(2-cyanoethyl)-D-homo-18-noretiocholan was obtained as colorless rods, melting point 137°-140°C (several recrystallization from aqueous methanol).

To a solution of 280 mg of 3α,11β,17,17a-tetrahydroxy-13α-(2-cyanoethyl)-D-homo-18-noretiocholan in 17 ml of methanol at room temperature contained in a 25 ml volumetric flask there was added 162 mg of sodium metaperiodate in 8 ml of water. A small amount of water was added to bring the volume to 25 ml. After 15 min an aliquot was withdrawn and added to a measured amount of sodium arsenite solution containing sodium bicarbonate and potassium iodide. After 10 min, the solution was titrated with standard iodine solution. The solution was diluted with water and extracted twice with ethyl acetate, each extract being washed in turn with sodium combined, dried over magnesium sulfate and concentrated to dryness under reduced pressure, yielding 265 mg of a colorless, amorphous product of 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene.

A solution of 240 mg of 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene dissolved in 30 ml of anhydrous methanol containing 20 mg of p-toluenesulfonic acid monohydrate was allowed to stand at room temperature for 36 h. Aqueous sodium bicarbonate was added and the methanol was evaporated under reduced pressure. An ether extraction of the aqueous layer afforded 260 mg of a benzene soluble oil, which was chromatographed on 12 g of florisil. The 4b-

methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether was eluted between 20% benzene in ether and ether.

A solution of 560 mg of the 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether in 10 ml of pyridine and 5 ml of acetic anhydride was heated at 100°C for 10 min. The solution was cooled and poured on iced aqueous sodium bicarbonate. The mixture was extracted with ether, the extract being washed with water, dried over magnesium sulfate and concentrated to dryness at aspirator pressure. The pyridine was removed at 2 mm with as little heating as possible. From a small volume of methanol, the colorless oil remaining gave a heavy precipitate of crystals which was washed with petroleum ether (b.p. 32°-35°C). The pure 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate was obtained as colorless prisms, melting point 126°-127°C, by several recrystallizations from methanol.

The 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate (360 mg) was stirred in 3 ml of ether. Upon the addition of 9 ml of 70% aqueous acetic acid the crystals dissolved immediately. The solution was allowed to stand at room temperature for 16 h and was then extracted with ether. The extract was washed thoroughly with water and aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated to dryness under reduced pressure, yielding 337 mg of oil. On trituration with ether there was obtained 305 mg of crystals of 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol methyl ether 7α-acetate as platelets, melting point 85°-105°C after recrystallizations from benzene-petroleum ether.

After standing at room temperature for 10 min, a solution of 710 mg of the 4b-methyl-1β-(2-formylethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol methyl ether 7α-acetate in 5 ml of piperidine and 10 ml of benzene was heated at brisk reflux in a nitrogen atmosphere. After 3 h the solvents were removed under reduced pressure, leaving 820 mg of 4b-methyl-1β-[3-(1-piperidyl)-2-propenyl]-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol methyl ether 7α-acetate as colorless oil.

Through a solution of 810 mg of crude 4b-methyl-1β-[3-(1-piperidyl)-2-propenyl]-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 2β,4v-lactol methyl ether 7α-acetate in 60 ml of methylene chloride and 1.5 ml of pyridine at -70°C was passed a stream of oxygen containing ozone until the solution turned blue (17 min). 3 g of zinc dust and 6 ml of glacial acetic acid were added immediately. The stirred solution was allowed to warm to 0°C and to remain at that temperature for 30 min. The solution was filtered and washed with aqueous sodium bicarbonate. The organic solvent was dried over magnesium sulfate and was distilled below room temperature, affording 750 mg of a benzene soluble, pale yellow oil. The product was chromatographed and eluted 310 mg (45%) of 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol methyl ether 7α-acetate.

A solution of 310 mg of the chromatographed noncrystalline 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol methyl ether 7α-acetate in 60 ml of anhydrous methanol containing 40 mg of p-toluenesulfonic acid monohydrate was allowed to stand at room temperature for 9 h. Aqueous sodium bicarbonate was added, and methanol was evaporated under reduced pressure. The remaining mixture was extracted with ether and extract was dried over magnesium sulfate and concentrated to dryness in vacuo, affording 325 mg of oil. This was chromatographed on 12 g of florisil. Ether eluted 285 mg of oil which crystallized from petroleum ether, giving 230 mg of 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate as irregular prisms, melting point 149°-152°C.

A solution of 220 mg of the 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(2-cyanoethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate in 5 ml of methanol and 10 ml of 10% aqueous potassium hydroxide was heated at reflux 17 h. The methanol was distilled off and the remainder was extracted with chloroform. The aqueous solution was cooled to 5°C and was acidified to pH 4 with cold 3 N hydrochloric acid. The solution was rapidly extracted twice with cold ethyl acetate, each extract being washed in turn 3 times with water. To the combined extracts (300 ml) was added 10 ml of methanol followed by solution excess diazomethane in 50 ml of ether. After 10 min the diazomethane was blown off, and the solvent was evaporated under reduced pressure, affording 235 mg of an oil. Chromatography of this material on 6 g of florisil and elution gave 220 mg of 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(2-methylcarboxyethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether.

Excess phenyllithium (prepared from 0.210 g of lithium wire and 2.4 g of bromobenzene following the directions given by J.C.W. Evans and C.F.H. Allen, Org. Syntheses, vol. 2, p. 22 (1943)) in 20 ml of ether was added to 215 mg of the 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(2-methylcarboxyethyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether in 20 ml of anhydrous ether under an atmosphere of nitrogen. After the solution was stirred at room temperature for 2 h, the excess reagent was decomposed by the drop wise addition of ethanol. Water was added, and the mixture was extracted with ether. The extract was washed with water, dried over magnesium sulfate and concentrated to dryness under reduced pressure, yielding 310 mg of an oil which was chromatographed ed on 6 g of florisil; ether eluted 267 mg of an oil which giving 252 mg of 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(3,3,3-hydroxydiphenylpropyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether as needles, melting point 116°-119°C (from ether).

A solution of 250 mg of the 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(3,3,3-hydroxydiphenylpropyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether, in 10 ml of pyridine and 5 ml of acetic anhydride was heated at 100°C for 10 min. The solution was cooled and poured onto iced aqueous sodium bicarbonate. The mixture was extracted with ether, dried over magnesium sulfate and concentrated to dryness under reduced pressure, affording 255 mg (95.2%) of the colorless 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(3,3,3-hydroxydiphenylpropyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether

7α-acetate.

To a solution of 250 mg of the 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(3,3,3-hydroxydiphenylpropyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate in 10 ml of benzene and 1.0 ml of pyridine at 0°C was added 0.5 ml of thyonyl chloride. After standing at 0°C for 15 min, the solution was poured onto iced sodium bicarbonate, and resulting mixture was extracted with ether. The extract was dried over magnesium sulfate, and the ether was removed under reduced pressure. Pyridine (20 ml) was added and solution was heated at 100°C for 20 min. The solution was then concentrated to dryness under reduced pressure and the residue was dissolved in a small volume of benzene. The benzene solution was poured on 6 g of florisil; elution with ether provided 230 mg of colorless 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(3,3-diphenyl-2-propenyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate.

Through a solution of 225 mg of the 4b-methyl-1β-(2-formylmethyl)-2β-formyl-2-(3,3-diphenyl-2-propenyl)-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate in 30 ml of methylene dichloride and 0.15 ml of pyridine at -70°C was passed a stream of oxygen containing ozone. When the solution turned a faint blue color, 3 g of zinc dust and 6 ml of glacial acetic were added immediately. The solution was stirred at 0°C until it gave a negative starch iodide test (10 min); the mixture was filtered, washing the zinc with additional methylene dichloride. The organic solution was washed with aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated to dryness in vacuo, giving 230 mg of oil. This was chromatographed on 5 g of florisil; elution with ether gave 110 mg of 4b-methyl-1β,2α-bis-(2-formylmethyl)-2β-formyl-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate.

In 1 ml of ether was dissolved 20 mg of the crude 4b-methyl-1β,2α-bis-(2-formylmethyl)-2β-formyl-4β,7α-dihydroxyperhydrophenanthrene 1β-methyl acetal 2β,4β-lactol methyl ether 7α-acetate. To this was added 3 ml of 70% aqueous acetic acid, and the homogeneous solution was allowed to stand at room temperature to 10 h. The material was extracted with ether, and extract was washed with aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated to dryness under reduced pressure, yielding 15 mg of 4b-methyl-1β,2α-bis-(2-formylmethyl)-2β-formyl-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol 7α-acetate.

A benzene solution (5 ml) of 15 mg of the 4b-methyl-1β,2α-bis-(2-formylmethyl)-2β-formyl-4β,7α-dihydroxyperhydrophenanthrene 2β,4β-lactol 7α-acetate containing 3.4 mg of piperidine and 6.2 mg of acetic acid was heated at 60°C in slow stream of nitrogen with an azeotropic separator. After 1 h, half the solution was withdrawn, diluted with benzene, and washed with diluted aqueous hydrochloric acid and with aqueous sodium bicarbonate. The benzene extract dried over magnesium sulfate and concentrated to dryness under reduced pressure, giving 3α-acetoxy-17-formyl-16-etiocholen-11β-ol-18-one 11β,18-lactol as colorless oil.

The 3α-acetoxy-17-formyl-16-etiocholen-11β-ol-18-one 11β,18-lactol can be converted to aldosterone by conventional methods as follows.

The unsaturated 3α-acetoxy-17-formyl-16-etiocholen-11β-ol-18-one 11β,18-lactol is hydrogenated in the presence of palladium catalyst to saturate the 16,17-double bond, and then saturated aldehyde are oxidized by treatment with chromic oxide in pyridine to give 3α-acetoxy-11β-ol-18-one-pregnane 11β,18-lactone 17-carboxylic acid.

Then as a result of reaction of 3α-acetoxy-11β-ol-18-one-pregnane 11β,18-lactone 17-carboxylic acid and HCl the 3α-acetoxy-11β-ol-18-one-pregnane 11β,18-lactone 17-carboxylic acid chloride was obtained. The 3α-acetoxy-11β-ol-18-one-pregnane 11β,18-lactone 17-carboxylic acid chloride was treated with diazomethane to give 3α-acetoxy-11β-ol-18-one-pregnane 11β,18-lactone 17-diazoketone.

The saponification of acetoxy group and reacting of 3α-acetoxy-11β-ol-18-one-pregnane 11β,18-lactone 17-diazoketone with acetic acid were carried out to afford acetic acid 3α,11β-dihydroxy-18,20-dione-pregnane 11β,18-lactone 17-oxoethyl ether.

The 3-keto-δ^4 system is introduced by conventional methods, that is, by oxidation of the 3-hydroxy group to a 3-keto group with chromic oxide. Bromination at the 4-position, and finally dehydrobromination with dinitrophenylhydrazine or with lithium chloride in dimethylformamide were carried out to give acetic acid 11β-hydroxy-3,18,20-trione-pregn-4-ene 11β,18-lactone 17-oxoethyl ether.

2 Methods of producing of aldosterone:

1. Further, acetic acid 11β-hydroxy-3,18,20-trione-pregn-4-ene 11β,18-lactone 17-oxoethyl ether has been converted to 11β,21-dihydroxy-3,18,20-trione-pregn-4-ene by methods of reduction of the lactone group and deacetylation of 17-oxoethyl group, described by Schmidlin, Anner, Biller and Wettstein (Experimentia, XI, 365 (1955).

2. Further, acetic acid 11β-hydroxy-3,18,20-trione-pregn-4-ene 11β,18-lactone 17-oxoethyl ether has been converted to 11β-hydroxy-18-one-pregn-4-ene 11β,18-lactone-3,20-bis-ethylenketal 17-oxoethyl ether, which was reduced with lithium-aluminum hydride to 3,20-bis-ethylenketal aldosterone. Then by hydrolisation of 3,20-bis-ethylenketal aldosterone with $HClO_4$ aldosterone can be obtained.

References

Johnson W.S., Johns W.F.; US Patent No. 3,049,539; August 14, 1962; Assigned: Wisconsin Alumini Research Foundation, Madison,Wis., a corporation of Wisconsin

Chaletsky A.M.; Pharmaceutical Chemistry, 'Medicina', L., 1966. 761p.

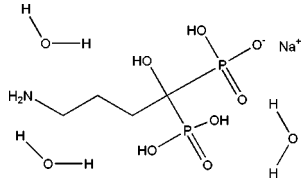
ALENDRONATE SODIUM TRIHYDRATE

Therapeutic Function: Antiosteoporotic

Chemical Name: (4-Amino-1-hydroxybutylidene)diphosphonic acid monosodium salt trihydrate

Common Name: Alendronate sodium

Structural Formula:



Chemical Abstracts Registry No.: 129318-43-0; 66376-36-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Adronat	Neopharmed	Italy	-
Adronat	Tecnifar	Portugal	-
Alendronate sodium	BARR	-	-
Arendal	Syncro	Argentina	-
Alendros	Abiogen	Italy	-
Brek	TRB	Argentina	-
Dronal	Sigma Tau	Italy	-
Elandur	Sidus	Argentina	-
Endronax	Sintofarma	Brazil	-
Fosalan	Merck Pharmaceutical Corporation	-	-
Fosamax	Merck Sharp and Dohme	Netherlands	-
Holadren	Laboratorio Chile S.A.	-	-
Lafedam	Elvetium	Argentina	-
Marvil	Elisium	Argentina	-
Onclast	Teijin Pharma Ltd.	Japan	-
Osteoral	Ache	-	-
Phostarac	Rontag	Argentina	-
Regenesis	Elea	Argentina	-
Teiroc	Teijin Pharma Ltd.	Japan	-

Raw Materials

Phosphorous acid
Phosphorus trichloride
4-Aminobutyric acid

Manufacturing Process

4-Amino-1-hydroxybutylidene-1,1-diphosphonic acid (ABDT).

Orthosphophorous acid (102.7 g; 1.25 moles) is introduced into a 2 liter-flask with condenser, stirrer and dropping funnel, placed on a thermostatized bath; the air is then removed with a nitrogen stream which is continued during all the reaction. The acid is melted by heating the bath to 95°C. When melting is complete, 4-aminobutyric acid (103.3; 1 mole) is added under stirring which is continued till obtaining a doughy fluid. Phosphorous trihalide (176 ml; 2 moles) is added dropwise causing the mixture to boil and evolution of gaseous hydrochloric acid which is damped by means of a suitable trap. The addition rate is adjusted so as to keep a constant reflux for about 60 minutes. When the addition is nearly over, the mixture swells, slowly hardening. Stirring is continued as long as possible, whereafter the mixture is heated for further 3 hours. Without cooling, but removing the bath, water (300 ml) is added, first slowly and then quickly. Heating and stirring are started again. Decolorizing charcoal is added and the mixture is boiled for about 5 minutes, then hot-filtered on paper and the filtrate is refluxed for 6 hours. After cooling is slowly poured in stirred methanol (1500 ml) causing thereby the separation of a white solid which collected and dried (161 g; 64.6%). The structure of ABDT is confirmed by IR spectrum, proton magnetic and nuclear magnetic resonance spectrum and elemental analysis.

The sodium salt of this acid may be prepared by adding of equivalent of sodium hydroxide.

References

G. Staibano; US Patent No. 4,705,651; Nov. 10, 1987; Assigned to Instituto Gentili S.p.A., Pisa, Italy

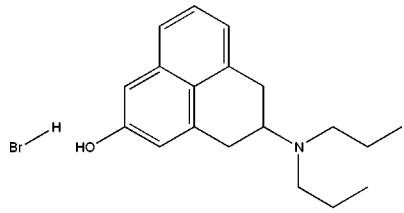
ALENTAMOL

Therapeutic Function: Antipsychotic, Dopamine agonist

Chemical Name: 1H-Phenalen-5-ol, 2-(dipropylamino)-2,3-dihydro-, hydrobromide, (+/-)

Common Name: Alentamol

Structural Formula:



Chemical Abstracts Registry No.: 121514-27-0

Trade Name	Manufacturer	Country	Year Introduced
U 68553B	Upjohn Company	-	-

Raw Materials

Triethylamine	5-Methoxy-2,2-dicarboxy-2,3-dihydro-1H-phenalene
Hydrogen chloride	Diphenyl phosphoryl azide
Trifluoroacetic acid	t-Butyl carbamate
Sodium hydroxide	Hydrogen bromide
n-Propyl bromide	Potassium carbonate

Manufacturing Process

The solid 5-methoxy-2,2-dicarboxy-2,3-dihydro-1H-phenalene, was decarboxylated (one carboxyl group removed) by heating in an oil bath at 190°-210°C for 50 min. The resulting liquid was cooled, and the solid was ground to a fine powder to obtain 37.1 g (98% yield) of the subtitled 2-carboxyl-5-methoxy-2,3-dihydro-1H-phenalene, melting point 194°-196°C.

A mixture of the 5-methoxy-2,3-dihydro-1H-phenalen-2-yl-carboxylic acid, (37.1 g; 0.153 mole), 42.1 g (0.153 mole) of diphenyl phosphoryl azide, 17.0 g (0.168 mole) of triethylamine and 1950 ml of dry tert-butyl alcohol was refluxed for 21 h. The initially formed solution became a suspension. The solvent was evaporated in vacuo and the residue was taken up in a chloroform/water mixture. The resulting suspension was filtered. The filtrate was separated, the aqueous phase was extracted with chloroform, and the combined organic liquid phases was washed with 5% w/v sodium hydroxide aqueous solution (3x100 ml), with water and with saturated sodium chloride salt solution and then dried over magnesium sulfate and evaporated.The resulting residual yellow solid, 35.9 g, was extracted with boiling SKELLYSOLVE B brand of hexanes (5x200 ml), the resulting solution was concentrated to about 300 ml, clarified with diethyl ether and allowed to crystallize at 0°C to obtain 28.6 g of the 5-methoxy-2-(tert-butoxycarbonylamino)-2,3-dihydro-1H-phenalene, melting point 113°-115°C.

Trifluoroacetic acid, 85 ml, was added to 30.5 g (0.0958 mole) of the 5-methoxy-2-(tert-butoxycarbonylamino)-2,3-dihydro-1H-phenalene. The resulting solution was stirred for 20 min. Ice was then added, and the resulting mixture was made pH basic with 20% w/w sodium hydroxide in water solution and stirred for 1 h at room temperature. The mixture was extracted well with chloroform, the chloroform extract was separated and washed with water, with saturated sodium chloride solution; dried with magnesium sulfate, and evaporated to give 18.8 g (92% yield) of the 2-amino-5-methoxy-2,3-dihydro-1H-phenalene as a brown oil.

This 2-amino-5-methoxy-2,3-dihydro-1H-phenalene was converted to its hydrochloride salt in methanol with 1.5 N hydrogen chloride in diethyl ether solution to give 18.11 g of the 2-amino-5-methoxy-2,3-dihydro-1H-phenalene hydrochloride as colorless needle crystals, melting point 252°C (dec.).

A mixture of 2-amino-5-methoxy-2,3-dihydro-1H-phenalene, 2.6 g (0.0122 mole), released from its hydrochloride, 6.46 g (0.0525 mole) of n-propyl

bromide, 7.25 g (0.0525 mole) of potassium carbonate and 50 ml of acetonitrile was refluxed for 20 h. Another 3.3 g of n-propyl bromide, 3.6 g of potassium carbonate and 25 ml of acetonitrile were added to the reaction mixture. The mixture was refluxed for 26 h. GC analysis of a sample of the reaction mixture indicated complete reaction. The mixture was evaporated, and the residue was taken up in a diethyl ether/water mixture. The organic liquid layer was washed with saturated sodium chloride (salt) solution and dried with magnesium sulfate, and evaporated. The residue was dissolved in petroleum ether (boiling point 30°-60°C), and filtered from some insoluble brown material, and the filtrate was evaporated to leave the 2-(di-n-propylamino)-5-methoxy-2,3-dihydro-1H-phenalene.

The 2-(di-n-propylamino)-5-methoxy-2,3-dihydro-1H-phenalene was dissolved in diethyl ether, treated with ethereal hydrogen chloride which resulted in the formation of the crude gummy solid hydrogen chloride salt. 2.67 g (66% yield) of the 2-(di-n-propylamino)-5-methoxy-2,3-dihydro-1H-phenalene hydrochloride, melting point 196°-197°C (crystallized from a methanol/diethyl ether).

A mixture of 2-(di-n-propylamino)-5-methoxy-2,3-dihydro-1H-phenalene, (1.65 g; 5.55 mmol), released from the hydrochloride salt, and 20 ml of 48% aqueous hydrogen bromide solution was heated for 15 min in an oil bath at 125°-130°C. The reaction mixture was evaporated, the residue was dissolved in a minimum amount of methanol, diethyl ether was added until the mixture became cloudy, and the mixture was filtered through a filter aid (CELITE) to remove some oily impurity. The filtrate was diluted with diethyl ether and seeded. There was obtained 1.28 g (63% yield) of the 2-(di-n-propylamino)-2,3-dihydro-lH-phenalen-5-ol hydrobromide, melting point 233°-234°C (dec.).

References

Szmuszkovicz J. et al.; Patent Coop. Treaty (WIPO), 1987, 87/04153; July 16, 1987; Assigned: The UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US)

ALEXIDINE

Therapeutic Function: Antiseptic

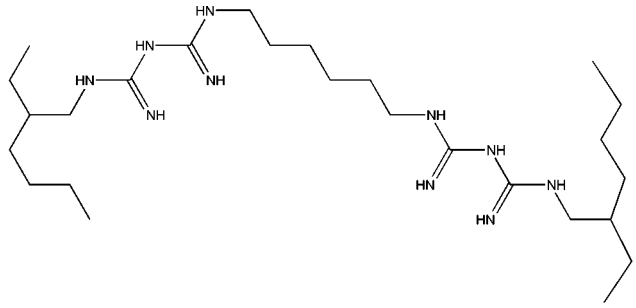
Chemical Name: 2,4,11,13-Tetraazatetradecanediimidamide, N,N''-bis(2-ethylhexyl)-3,12-diimino-

Common Name: Alexidine

Chemical Abstracts Registry No.: 22573-93-9

Trade Name	Manufacturer	Country	Year Introduced
Alexidine	Science Lab.	-	-
Alexidine	Chemos GmbH	-	-

Structural Formula:



Raw Materials

1,1'-Hexamethylene-bis(3-cyanoguanidine)
Ethylhexylamine hydrochloride

Manufacturing Process

A mixture of 16 g (0.09 mole) 1,1'-hexamethylene-bis(3-cyanoguanidine) and 20 d (0.12 mole) 2-ethylhexylamine hydrochloride is heated at 150-155°C for 3 hours. The mixture is cooled and the product is dissolved in 75 ml of hot water. The solution is treated with activated charcoal. 1,1'-Hexamethylene-bis-(5-(ethylhexyl)biguanide) is recrystalluized from methanol-ether, melting point 220.6-223.4°C.

References

Fr. Patent No. 1,463,818; Apr. 8, 1965; Assigned to Sterling Drug Inc.
Residant in USA

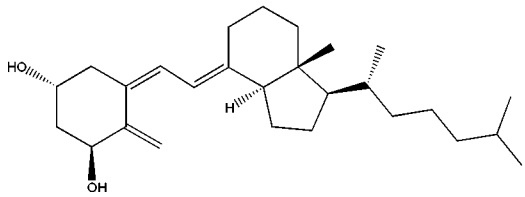
ALFACALCIDOL

Therapeutic Function: Calcium regulator, Vitamin

Chemical Name: 9,10-Secocholesta-5,7,10(19)-triene-1,3-diol

Common Name: 1α-Hydroxycholecalciferol; 1α-Hydroxyvitamin D_3

Structural Formula:



Chemical Abstracts Registry No.: 41294-56-8

Trade Name	Manufacturer	Country	Year Introduced
One-Alpha	Leo	UK	1978
Eins-Alpha	Thomae	W. Germany	1980
Alfarol	Chugai	Japan	1981
One-Alpha	Teljin	Japan	1981
Delakmin	Roussel	France	-
Etalpha	Leo	Denmark	-
Un-Alfa	Leo	-	-

Raw Materials

Cholesta-1,5,7-trien-3β-ol
4-Phenyl-1,2,4-triazoline-3,5-dione
m-Chloroperbenzoic acid
Lithium aluminum hydride

Manufacturing Process

1. Preparation of 1,4-cyclized adduct of cholesta-1,5,7-trien-β-ol and 4-phenyl-1,2,4-triazoline-3,5-dione: a solution of 400 mg of cholesta-1,5-7-trien-3β-ol in 30 ml of tetrahydrofuran is cooled with ice, and 190 mg of 4-phenyl-1,2,4-triazoline-3,5-dione is added little by little to the solution under agitation. The mixture is agitated at room temperature for 1 hour and the solvent is distilled under reduced pressure. The residue is purified by chromatography using a column packed with silica gel. Fractions eluted with ether-hexane (7:3 v/v) are collected and recrystallization from ether gives 550 mg of a 1,4-cyclized adduct of cholesta-1,5,7-trien-3β-ol and 4-phenyl-1,2,4-triazoline-3,5-dione having a melting point of 178°C to 182°C.

2. Preparation of 1,4-cyclized adduct of cholesta-5,7-dien-3β-ol-1α-epoxide and 4-phenyl-1,2,4-triazoline-3,5-dione: 1.25 g of the 1,4-cyclized adduct of cholesta-1,5,7-trien-3β-ol and 4-phenyl-1,2,4-triazoline-3,5-dione is dissolved in 50 ml of chloroform, and 560 mg of m-chloroperbenzoic acid is added to the solution. The mixture is agitated for 20 hours at room temperature, and 200 mg of m-chloroperbenzoic acid is further added and the mixture is agitated again for 20 hours. The reaction mixture liquid is diluted with chloroform, washed with a 10% aqueous solution of potassium carbonate and dried with magnesium sulfate. Then, the solvent is distilled under reduced pressure. The residue is purified by silica gel chromatography, and first effluent fractions eluted with ether are collected, and recrystallization from methanol gives 680 g of a crystal melting at 172°C to 173°C. The second ether effluent fractions are collected, and recrystallization from methanol gives 400 mg of a 1,4-cyclized adduct of cholesta-5,7-dien-3β-ol-1α,2α-epoxide and 4-phenyl-1,2,4-triazoline-3,5-dione having a melting point of 152°C to 154°C.

3. Preparation of cholesta-5,7-diene-1α,3β-diol: a solution of 500 mg of the 1,4-cyclized adduct of cholesta-5,7-dien-3β-ol-1α,2α-epoxide and 4-phenyl-1,2,4-triazoline-3,5-dione in 40 ml of tetrahydrofuran is added dropwise under agitation to a solution of 600 mg of lithium aluminum hydride in 30 ml of THF. Then, the reaction mixture liquid is gently refluxed and boiled for 1 hour and cooled, and a saturated aqueous solution of sodium sulfate is added to the reaction mixture to decompose excessive lithium aluminum hydride. The organic solvent layer is separated and dried, and the solvent is distilled. The

residue is purified by chromatography using a column packed with silica gel. Fractions eluted with ether-hexane (7:3 v/v) are collected, and recrystallization from the methanol gives 400 mg of cholesta-5,7-diene-1α,3β-diol.

4. Preparation of 1α,3β-dihydroxyprovitamin D_3: a solution of 25 mg of cholesta-5,7-diene-1α,3β-diol in 650 ml of ether is subjected to radiation of ultraviolet rays for 14 minutes in an argon gas atmosphere by passing it through a Vycor filter using a 200-W high pressure mercury lamp (Model 654A-36 manufactured by Hanobia). The solvent is distilled at room temperature under reduced pressure. This operation is repeated twice, and 50 mg of the so obtained crude product is fractionated by chromatography using a column packed with 20 g of Sephadex LH-20. The first effluent fractions eluted with chloroform-hexane (65:35 v/v) give 13.5 mg of oily 1α,3β-dihydroxyprovitamin D_3. The composition exhibits a maximum ultraviolet absorption at 260 nm in an ether solution.

5. Preparation of 1α-hydroxycholecalciferol: a solution of 13.5 mg of 1α,3β-dihydroxyprovitamin D_3 in 200 mi of ether is allowed to stand still in the dark at room temperature in an argon gas atmosphere for 2 weeks. During this period, the position of the maximum ultraviolet absorption is shifted from 260 nm to 264 nm, and the absorption intensity becomes 1.6 times as high as the original intensity. The solvent is distilled at room temperature under reduced pressure, and the residue is purified by chromatography using a column packed with 10 g of Sephadex LH-20. The fractions eluted with chloroform-hexane (65:35 v/v) give 6.5 mg of oily 1α-hydroxycholecalciferol.

References

Merck Index 4730
Kleeman and Engel p. 21
DOT 6 (3) 104 (1970); 14 (10) 441 (1978)
I.N. p. 52
Ishikawa, M., Kaneko, C., Suda, T., Yamada, S., Eguchi, Y., Sugimoto, A. and Sasaki, S.; US Patent 3,929,770; December 30, 1975; Assigned to Wisconsin Alumni Research Foundation

ALFADOLONE

Therapeutic Function: Anesthetic

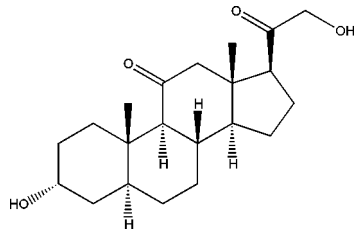
Chemical Name: 5α-Pregnane-11,20-dione, 3α,21-dihydroxy-

Common Name: Alfadolone; Alphadolone

Chemical Abstracts Registry No.: 14107-37-0

Trade Name	Manufacturer	Country	Year Introduced
Alphadolone	RiboTargets Ltd.	-	-

Structural Formula:



Raw Materials

Acetic acid	3β-Acetoxy-5α-pregn-16-ene-11,20-dione
Potassium hydroxide	4-Toluenesulfonyl chloride
Potassium acetate	Palladium on carbon
Hydrogen	Boron trifluoride etherate
Lead tetraacetate	Sodium bicarbonate

Manufacturing Process

A solution of 3β-acetoxy-5α-pregn-16-ene-11,20-dione (Chamberlin et al., J.Amer. Chem Soc., 1951, 73, 2396) (25.7 g) in dioxan (Analar, 500 ml) was treated with potassium hydroxide (10 g) and water 250 ml and the mixture allowed to stand at room temperature for 1 h. After a further 1 h at 40°C the mixture was diluted with water and the product filtered off. The crude material was dissolved in chloroform and filtered through a column of grade III neutral alumina (100 g). The material obtained was crystallized from acetone-petroleum to give pure 3β-hydroxy-5α-pregn-16-ene-11,20-dione (17.65 g, 77.5%) as small plates, melting point 217.5°C.

A solution of 3β-hydroxy-5α-pregn-16-ene-11,20-dione (39.6 g) in dry pyridine (165 ml) was treated with toluene-p-sulfonyl chloride (43.9 g) to give the toluene sulfonate (56.7 g), melting point 147-151°C. A portion (10.7 g) of this material was crystallized from ethyl acetate-petroleum to give the pure 3β-toluene-p-sulfonyloxy-5α-pregn-16-ene-11,20-dione (9.2 g) as plates, melting point 154°-155°C.

2 Methods of producing of 3α-hydroxy-5α-pregn-16-ene-11,20-dione from 3β-toluene-p-sulfonyloxy-5α-pregn-16-ene-11,20-dione:

1. A solution of 3β-toluene-p-sulfonyloxy-5α-pregn-16-ene-11,20-dione (19.1 g) in N,N-dimethylformamide (160 ml) and water (16.0 ml) was treated with potassium acetate (29.2 g) and the mixture heated at 115°C for 2.5 h. The solvents were removed in vacuo and residue partitioned between chloroform and water. The chloroform extract was washed with water, dried and evaporated. The residue was taken up in methanol (500 ml) and solution flushed with nitrogen. Potassium hydroxide (17 g) in water (70 ml) was added and the solution refluxed for 1 h. Glacial acetic acid was added to bring the pH to about 6 and most of the methanol evaporated in vacuo. Dilution with water gave a gummy precipitate which was extracted into chloroform to give the crude product. This material was extracted with ether and the residue boiled with benzene. The insoluble material was crystallized from chloroform-petroleum to give 3α-hydroxy-5α-pregn-16-ene-11,20-dione (3.28 g) as large

prisms, melting point 243°-244°C.

2. A mixture of the 3β-toluene-p-sulfonyloxy-5α-pregn-16-ene-11,20-dione (60 g; 0.124 mole) in N,N-dimethylformamide (350 ml) and potassium acetate (92 g, 0.94 mole) in water (935 ml) was stirred at 115°C for 4 h. The brown solution was cooled and most of the N,N-dimethylformamide removed by evaporation at 50°C and 4 mm to give a brown solid mass. Another run with to sylate (58 g, 0.12 mole), potassium acetate (90 g, 0.91 mole), N,N-dimethylformamide (350 ml) and water (35 ml) was carried out as described above. The combined aqueous fractions were extracted with chloroform (3 x 100 ml) and dried over magnesium sulfate. The chloroform was removed in vacuo and residual N,N-dimethylformamide was evaporated at 50°C and 4 mm to give the crude 3α-acetate-5α-pregn-16-ene-11,20-dione (92 g) as a brown solid.

A solution of 3α-acetate-5α-pregn-16-ene-11,20-dione (92 g) in dioxin (1000 ml) was mixed with a solution of potassium hydroxide (45 g, 0.8 mole) in water (500 ml) to give a two-phase system. A homogeneous solution was obtained by the addition of dioxin (440 ml) and water (625 ml). Nitrogen was bubbled through the solution which was heated at 50°C for 2 h. The port colored solution was treated with glacial acetic acid (40 ml) to bring the pH about 7 and two thirds of the solvent was removed by distillation in vacuo (water pump). Water (3 L) was added to the resultant mixture (which had already begun to crystallize) and the precipitated solid was filtered off, washed with water and dried over phosphorus pentoxide to give the crude 3α-hydroxy-5α-pregn-16-ene-11,20-dione (73.9 g).

Producing of 3α,21-dihydroxy-5α-pregnane-11,20-dione from 3α-hydroxy-5α-pregn-16-ene-11,20-dione:

A solution of 3α-hydroxy-5α-pregn-16-ene-11,20-dione (200 mg) in freshly distilled tetrahydrofuran (8 ml) with 5% palladium on carbon (100 mg) was hydrogenated till hydrogen uptake ceased. The mixture was filtered through a pad of kieselguhr and the tetrahydrofuran removed in vacuo to give 3α-hydroxy-5α-pregnane-11,20-dione (196 mg), melting point 171°-172°C.

Boron trifluoride etherate (37.9 ml) was added to a stirred solution of 3α-hydroxy-5α-pregnane-11,20-dione (6.64 g, 20 mmol) and lead tetraacetate (10.1 g, 22 mmol) in dry benzene (280 ml) and methanol (15.1 ml) at room temperature. After 2 h the mixture was poured into water (2 L) and extracted with ether (1 L). The combined ether extracts were washed successively with sodium bicarbonate solution and water, dried over magnesium sulfate, and concentrated in vacuo to give a white crystalline mass. Four recrystallizations from acetone-petroleum (b.p. 40°-60°C) gave 21-acetoxy-3α-hydroxy-5α-pregnane-11,20-dione as fine needles (4.22 g, 54%), melting point 172°-173°C.

The 3α,21-dihydroxy-5α-pregnane-11,20-dione is conveniently prepared by the deacylation of 21-acetoxy-3α-hydroxy-5α-pregnane-11,20-dione under basic conditions, for example, in the presence of potassium or sodium hydrogen carbonate, conveniently in the presence of a solvent e.g. methanol, ethanol or tetrahydrofuran, reesterifying the resultant product.

References

Davis B. et al.; US Patent No. 3,781,435; December 25, 1973

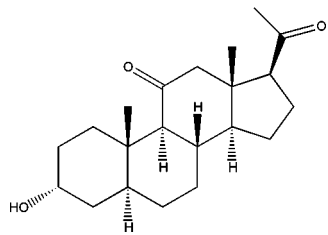
ALFAXALONE

Therapeutic Function: Anesthetic component

Chemical Name: 3-Hydroxypregnane-11,20-dione

Common Name: Alphaxolone

Structural Formula:



Chemical Abstracts Registry No.: 23930-19-0

Trade Name	Manufacturer	Country	Year Introduced
Althesin	Glaxo	UK	1972
Alfadion	Nippon Glaxo	Japan	1978
Alfathesin	Glaxo	France	-
Aurantex	Glaxo	W. Germany	-

Raw Materials

3α-Hydroxy-5α-pregn-16-ene-11,20-dione
Hydrogen

Manufacturing Process

A solution of 3α-hydroxy-5α-pregn-16-ene-11,20-dione (200 mg) in freshly distilled tetrahydrofuran (8 ml) with 5% palladium on carbon (100 ml) was hydrogenated until hydrogen uptake ceased. The mixture was filtered through a pad of kieselguhr and the tetrahydrofuran removed in vacuum to give 196 mg, MP 171°C to 172°C.

References

Merck Index 225
Kleeman and Engel p. 23
DOT 8 (11) 407 (1972)

I.N. p. 53
Davis, B., Pearce, D.R. and Phillips, G.H., British Patent 1,317,184; May 16, 1973; Assigned to Glaxo Laboratories, Ltd.
Davis, B. and Phillips, G.H.; US Patent 3,714,352; January 30, 1973; Assigned to Glaxo Laboratories, Ltd.

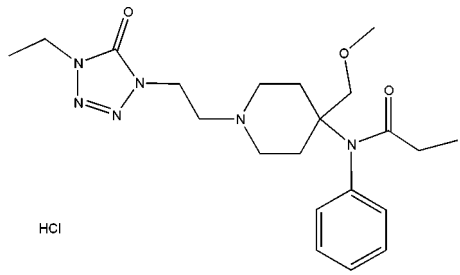
ALFENTANIL HYDROCHLORIDE

Therapeutic Function: Narcotic analgesic

Chemical Name: N-[1-[2-(4-Ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxy-methyl)-4-piperidinyl]-N-phenylpropaneamide hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 69049-06-5

Trade Name	Manufacturer	Country	Year Introduced
Rapifen	Janssen	Belgium	1983
Rapifen	Janssen	Netherlands	1983
Rapifen	Janssen	W. Germany	1983
Rapifen	Janssen	UK	1983
Rapifen	Janssen	Switz.	1983

Raw Materials

1-Ethyl-1,4-dihydro-5H-tetrazol-5-one
1-Bromo-2-chloroethane
N-[4-(Methoxymethyl)-4-piperidinyl]-N-phenylpropanamide

Manufacturing Process

A mixture of 22 parts of 1-ethyl-1,4-dihydro-5H-tetrazol-5-one, 45 parts of 1-bromo-2-chloroethane, 26 parts of sodium carbonate, 0.3 part of potassium iodide and 240 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is cooled, water is added and the layers are separated. The aqueous phase is extracted three times with

dichloromethane. The combined organic phases are dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using trichloromethane as eluent. The pure fractions are collected and the eluent is evaporated, yielding 28.4 parts (80%) of 1-(2-chloroethyl)-4-ethyl-1,4-dihydro-5H-tetrazol-5-one as a residue.

A mixture of 1.8 parts of 1-(2-chloroethyl)-4-ethyl-1,4-dihydro-5H-tetrazol-5-one, 3.45 parts of N-[4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide, 5 parts of sodium carbonate, 0.2 part of potassium iodide and 240 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silicagel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and crystallized from 2-propanone, yielding 1.5 parts (33.3%) of N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl]-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide monohydrochloride monohydrate; melting point 140.8°C.

References

DFU 6 (6)335 (1981)
OCDS Vol. 3 p. 118 (1984)
DOT 19 (12) 683 (1983)
I.N. p. 53
Janssens, F.; US Patent 4,167,574; September 11, 1979; Assigned to Janssen Pharmaceutica NV.

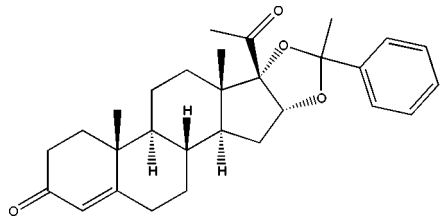
ALGESTONE ACETOPHENIDE

Therapeutic Function: Progestin, Contraceptive

Chemical Name: 16,17-[(1-Phenylethylidene)bis(oxy)]pregn-4-ene-3,20-dione

Common Name: 16α,17α-Dihydroxyprogesterone acetophenide; Alphasone acetophenide

Structural Formula:



Chemical Abstracts Registry No.: 24356-94-3

Trade Name	Manufacturer	Country	Year Introduced
Neolutin Depo	Medici	Italy	1982
Neolutin Depositum	Orma	Italy	-
Droxone	Squibb	US	-
Decadroxone	Squibb	-	-
Decadroxate	Sauibb	-	-

Raw Materials

16α,17α-Dihydroxyprogesterone
Acetophenone

Manufacturing Process

To a suspension of 500 mg of 16α,17α-dihydroxyprogesterone in 25 ml of freshly redistilled acetophenone is added 0.125 ml of 72% perchloric acid and the mixture is agitated at room temperature for one hour. The clear solution is washed with dilute sodium bicarbonate to remove excess acid and the acetophenone layer, after addition of chloroform is separated from the aqueous phase. The organic layer is dried over sodium sulfate and after removal of the chloroform and acetophenone in high vacuum the residue is crystallized from 95% alcohol. The pure acetophenone derivative has a melting point of about 142°C to 144°C.

References

Merck Index 227
Kleeman and Engel p. 24
OCDS Vol. 2 p. 171 (1980)
DOT 19 (2) 110 (1983)
I.N. p. 54
Fried, J.; US Patent 2,941,997; June 21, 1960; Assigned to Olin Mathieson Chemical Corp.
Fried, J. and Diassi, P.A.; US Patent 3,008,958; November 14, 1961; Assigned to Olin Mathieson Chemical Corp.

ALIBENDOL

Therapeutic Function: Choleretic, Spasmolytic

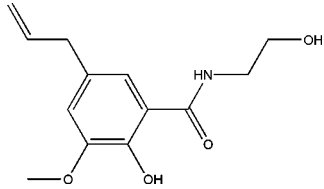
Chemical Name: 2-Hydroxy-N-(2-hydroxyethyl)-3-methoxy-5-(2-propenyl) benzamide

Common Name: -

Chemical Abstracts Registry No.: 26750-81-2

Trade Name	Manufacturer	Country	Year Introduced
Cebera	Bouchara	France	1981

Structural Formula:



Raw Materials

2-Hydroxy-3-methoxy-5-allylbenzoic acid
Ethanol
Ethanolamine

Manufacturing Process

36 g of ethyl ester of 2-hydroxy-3-methoxy-5-allyl-benzoic acid [obtained by the process described by Pearl, et al., J. Amer. Chem. Soc., Vol. 71, 1067-1068 (1949)] and 61 g of ethanolamine were admixed and left to stand for 1 hour at ambient temperature after which it was heated for 1 hour at 120°C. The mixture was extracted with chloroform and the organic phases were washed with half diluted hydrochloric acid, then with water, and the chloroform evaporated off. The residue, after recrystallization from benzene, was a 78% yield of 2-hydroxy-3-methoxy-5-allyl-N-(β-hydroxyethyl)-benzamide having a melting point of 95°C. The product appeared in the form of colorless crystals which were insoluble in water and soluble in dilute sodium hydroxide.

References

Merck Index 230
DOT 18 (10) 525 (1982)
Clemence, F. and Le Martret, O.; US Patent 3,668,238; June 6, 1972; Assigned to Roussel Uclaf.

ALIFEDRINE HYDROCHLORIDE

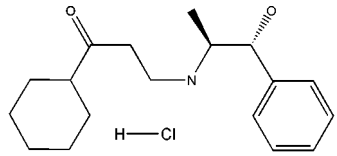
Therapeutic Function: Sympathomimetic; Cardiotonic

Chemical Name: 1-Propanone, 1-cyclohexyl-3-((2-hydroxy-1-methyl-2-phenylethyl)amino)-, (R-(R*,S*))-, hydrochloride

Common Name: Alifedrine

Chemical Abstracts Registry No.: 72913-80-5

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Alifedrine hydrochloride	Chemiewerk Homberg	-	-

Raw Materials

1-Acetyl-1-cyclohexene
1-Norephedrine
Palladium on carbon
Aluminum chloride
Dimethylamine hydrochloride
Cyclohexanecarboxylic acid chloride
Cyclohexyl-β-chloroethyl ketone

Manufacturing Process

There are some means to produce aliflurane:

1). 2.2 g (0.01 mol) of (2-dimethylaminoethyl)cyclohexylketone hydrochloride (produced by Mannich reaction from 1-acetyl-1-cyclohexene with formaldehyde and dimethylamine hydrochloride and subsequent hydrogenation with Pd/C as catalyst) and 1.5 g (0.01 mol) of 1-norephedrine were dissolved in 20 ml of warm isopropanol. The product crystallizing out in the cooling was filtered off with suction and recrystallized from ethanol. Yield of desired 1-propanone, 1-cyclohexyl-3-((2-hydroxy-1-methyl-2-phenylethyl)amino)-, (R-(R*,S*) hydrochloride 24%, M.P: 219-221°C.

2). 13.8 g (0.1 mol) of cyclohexylvinyl ketone (obtainable by the splitting off of HCl during the distillation of cyclohexyl-β-chloroethyl ketone) and 15.1 g (0.1 mol) of 1-norephedrine were dissolved in 50 ml of isopropanol. The desired compound crystallized out as the free base in the standing overnight. The hydrochloride was made with isopropanolic hydrochloric acid. M.P. of the hydrochloride: 219-221°C.

3). The oily cyclohexyl-β-chloroethyl ketone obtained from a solution of 200 g (1.36 mol) of cyclohexanecarboxylic acid chloride in 500 ml of dried 1,2-dichloroethane by portion-wise addition of 182 g (1.3 mol) of AlCl3 at -5°C, then leading ethylene through, subsequent hydrolysis with 500 ml of water at room temperature and concentration of the organic phase dried with Na2SO4 in a vacuum (analogous to U.S. Pat. No. 2,792,406) was added to a solution of 164 g (1.09 mol) of 1-norephedrine in 1000 ml of dioxane. The desired product crystallized out overnight, was filtered off with suction and recrystallized from ethanol/water 1:1 (by volume). Yield: 67% (based on the cyclohexane carboxylic acid chloride). M.P. of the hydrochloride: 219-221°C.

References

Engel J. et al.; US Patent No. 4,542,159; September 17, 1985; Assigned to Degussa Aktiengeselschaft, Frankfurt, Fed. Rep. of Germany

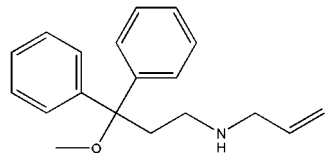
ALIMADOL

Therapeutic Function: Analgesic

Chemical Name: N-(3-Methoxy-3,3-diphenylpropyl)allylamine

Common Name: Alimadol

Structural Formula:



Chemical Abstracts Registry No.: 52742-40-2

Trade Name	Manufacturer	Country	Year Introduced
Alimadol	ZYF Pharm Chemical	-	-

Raw Materials

Trifluoroacetic anhydride
Allyl bromide
3,3-Diphenyl-3-methoxypropylamine
Hexamethyl phosphoric acid amide

Manufacturing Process

12 g 3,3-diphenyl-3-methoxypropylamine, 13.5 g trifluoroacetic acid anhydride, 6.0 g pyridine and 100 ml benzene was heated by stirring for 1 hour at 40°C. Then in was cooled to 0°C and poured in water. The organic layer was separated, washed with diluted HCl and water, and evaporated to dryness. The residue N-(3,3-diphenyl-3-methoxypropyl)trifluoroacetamide melted at 108°-110°C. Yield: 98%.

8 g above amide was in 80 ml hexamethyl phosphoric acid amide dissolved mixed with 1.7 g sodium hydride and stirred for 3 hours. Then 5.7 g allyl bromide was added dropwise and the mixture was stirred for 30 minutes. It was diluted with water and extracted with benzene. Benzene layer was separated, evaporated to dryness. The residue was mixed with 100 ml of 75% ethanol and 1 g sodium hydroxide and heated for 1 hour. Ethanol was distilled off and reaction product was extracted with ether. Yield of N-(3-methoxy-3,3-diphenylpropyl)allylamin (or 1,1-diphenyl-1-methoxy-3-allylaminopropane) was 6.5 g (97%). MP: 40°-50°C. Hydrochloride melted at 137°-138°C.

References

Hollinger R. et al.; DE Patent No. 2,339,528; Sept. 11, 1972; Lenia GmdH, Chem. u. pharm. Erzeugnisse-Indusriebedarf, 8000 Munchen

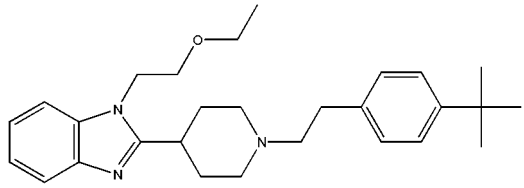
ALINASTINE

Therapeutic Function: Antihistaminic, Antiallergic

Chemical Name: Benzimidazole, 2-(1-(p-tert-butylphenethyl)-4-piperidyl)-1-(2-ethoxyethyl)-

Common Name: Alinastine

Structural Formula:



Chemical Abstracts Registry No.: 154541-72-7

Trade Name	Manufacturer	Country	Year Introduced
Alinastine	Fabrica Espanola de Productos Quimicos y Farmaceuticos	-	-

Raw Materials

Sodium hydride
2-(2-Ethoxyethyl)tosylate
2-[1-(2-(4-(1,1-Dimethylethyl)phenyl)ethyl)piperidin-4-yl]-1H-benzimidazole

Manufacturing Process

1.5 g of a sodium hydride suspension in oil are added to another suspension of 10.83 g of 2-[1-(2-(4-(1,1-dimethylethyl)phenyl)ethyl)piperidin-4-yl]-1H-benzimidazole in 150 ml of dimethylformamide and the mixture is stirred for 1 h at room temperature, then a solution of 2-(2-ethoxyethyl)tosylate in dimethylformamide are slowly added. The mixture is heated at 60°C for 16 h, poured onto water and extracted with ether. The extracts are washed with water, dried over anhydrous sodium sulfate and concentrated. The obtained oil is purified by column chromatography yielding 6.0 g of 1-(2-ethoxyethyl)-2-[1-(2-(4-(1,1-dimethylethyl)phenyl)ethyl)piperidine-4-yl]-1H-benzimidazole, melting point 138°-140°C.

References

Orjales-Venero A., Rubio-Royo V.; US Patent No. 5,322,850; June 21, 1994; Assigned: Fabrica Espanola de Productos Quimicos y Farmaceuticos, S.A., Leiva-Lamiaco, Spain

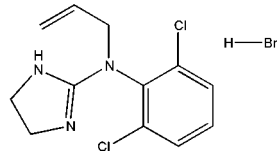
ALINIDINE HYDROBROMIDE

Therapeutic Function: Antiarrhythmic, Bradycardic, Analgesic

Chemical Name: N-(2,6-Dichlorophenyl)-4,5-dihydro-N-2-propenyl-1H-imidazol-2-amine monohydrobromide

Common Name: Alinidine hydrobromide

Structural Formula:



Chemical Abstracts Registry No.: 71306-36-0

Trade Name	Manufacturer	Country	Year Introduced
Alinidine hydrobromide	Boehringer Ingelheim Laboratories	-	-

Raw Materials

2-(2',6'-Dichlorophenylamino)-2-imidazoline
Allyl bromide

Manufacturing Process

2-(N-Allyl-N-(2,6-dichlorophenyl)amino)-2-imidazoline:

A mixture consisting of 2.0 g of 2-(2',6'-dichlorophenylamino)-2-imidazoline, 3 ml of allyl bromide, 1 ml of pyridine and 10 ml of absolute methanol was heated for about 15 hours at 100°C in a closed tube. Thereafter, the reaction mixture was evaporated to dryness in vacuum, the residue was dissolved in a small amount of dilute hydrochloric acid, the resulting solution was purified by extraction with ether, and the ether extracts were discarded. The acidic aqueous solution was made alkaline with 5 N sodium hydroxide where upon an oily substance separated out which crystallized through upon standing for some time on an ice bath. The crystalline product was collected by vacuum filtration, washed with distilled water and dried. 1.5 gm (83% of theory) of the compound having a melting point of 130-131°C was obtained.

References

Stahle H. et al.; US Patent No. 3,708,485; January 2, 1973; Assigned to Bohehringer Ingelheim am Rein, Germany

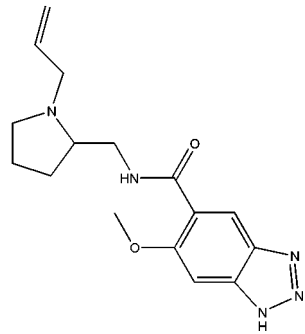
ALIZAPRIDE

Therapeutic Function: Neuroleptic, Antiemetic

Chemical Name: 6-Methoxy-N-[[1-(2-propenyl)-2-pyrrolidinyl]methyl]-H-benzotriazole-5-carboxamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 59338-93-1

Trade Name	Manufacturer	Country	Year Introduced
Plitican	Delagrange	France	1981
Vergentan	Delagrange	W. Germany	1981

Raw Materials

2-Methoxy-4,5-azimidobenzoic acid
1-Allyl-2-aminomethylpyrrolidine
Phosphoric anhydride

Manufacturing Process

38.6 g (0.2 mol) of 2-methoxy-4,5-azimidobenzoic acid were dissolved in anhydrous toluene and 56 g (0.4 mol) of 1-allyl-2-amino-methylpyrrolidine were added. The mixture was heated to 50°C and then 42 g (0.3 mol) of phosphoric anhydride were added. The mixture was warmed at reflux temperature for 3 hours and then cooled to 80°C. After adding water, the aqueous layer was alkalized. The crystals were filtered, washed with water and then dissolved in 450 ml of acetone. After crystallization, the product was

filtered, washed and dried.

40.4 g (yield 65%) of N-(1'-allyl-2'-pyrrolidylmethyl)-2-methoxy-4,5-azimidobenzamide having a melting point of 139°C were obtained.

References

Merck Index 231
DFU 6 (1) 11 (1981)
DOT 18 (4) 162 (1982)
I.N. p.55
Bulteau, G., Acher, J., Collignon, C. and Monier, J.C.; US Patent 4,039,672; August 2, 1977; Assigned to Societe D'Etudes Scientifiques et Industrielles de I'lle-de-France

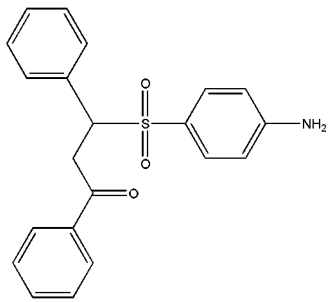
ALKOFANONE

Therapeutic Function: Antidiarrheal

Chemical Name: 3-[(4-Aminophenyl)sulfonyl]-1,3-diphenyl-1-propanone

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 7527-94-8

Trade Name	Manufacturer	Country	Year Introduced
Clafanone	Roche	US	1956

Raw Materials

Benzal acetophenone
p-Aminobenzene sulfinic acid

Manufacturing Process

38 g benzal-acetophenone and 25 g p-aminobenzene-sulfinic acid are refluxed

for 5 hours in 700 cc of 85% ethyl alcohol. Fine crystals soon begin to appear and fill the reaction vessel. While still hot, the mixture is suction-filtered. The reaction product is washed first with 750 cc warm absolute alcohol, then with 500 cc water, and finally again with 300 cc alcohol, and then dried in vacuum. Yield 32 g. MP 210-212°C with decomposition.

References

Merck Index 240
Goldberg, M.W.; US Patent 2,421,836; June 10, 1947; Assigned to Hoffmann-La Roche, Inc.

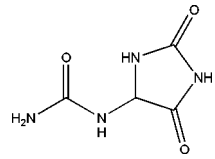
ALLANTOIN

Therapeutic Function: Vulnerary, Antiulcer (topical), Antipsoriatic

Chemical Name: Urea, (2,5-dioxo-4-imidazolidinyl)-

Common Name: Allantoin

Structural Formula:



Chemical Abstracts Registry No.: 97-59-6

Trade Name	Manufacturer	Country	Year Introduced
Allantoin	Arocor Holdings Inc.	-	-
Allantoin	Hunan Xinyu	-	-
Allantoin	Akema Fine Chemicals	-	-
Allantoin	Allan Chemical Corporation	-	-
Allantoin	Hangzhou Greenda Chemical Co., Ltd.	-	-
Allantoin	Kunshan Hua Xin Daily Chemicals Co., Ltd.	-	-
Allantoin	Omikron	-	-
Allantoin	Xiamen Linyo Technology Co., Ltd.	-	-
Cutemol	Summers Laboratories Inc.	-	-
Egopsoryl	Ego Pharmaceuticals	-	-
Egopsoryl	SMP Vet	-	-
Herker	Herker Industries	-	-
Soothex	Jamieson Laboratories Ltd.	-	-

Raw Materials

Urea	Glyoxal
Sulfuric acid	Cobalt(II) nitrate hexahydrate
Sodium nitrite	Hydrogen chloride
Ammonium sulfate	

Manufacturing Process

To a mixture of 13.14 kg 40% solution of glyoxal in water and a solution of 0.5 L of concentrated HCl in 3 L of water was added 1.8 g $Co(NO_3)_2 \cdot 6H_2O$. The mixture was heated at 50-60°C, to the solution was added 20 g of sodium nitrite and then at 40-60°C was added dropwise the mixture of 6 L of concentrated HNO3, 4.2 L of water and 30 g of sodium nitrite. The product obtained was mixed with 2.4 kg ammonium sulfate and filtrated. The filtrate was heated with 14.5 kg urea at 70°C for 10 hours. Allantoin was filtrated and recrystallized from the water; M.P. 233-235°C.

References

Merck Index, Monograph number: 255, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
DE Patent No. 1,939,924, 18 Feb., 1971
Christmann et al.; US Patent No. 2,802,011; Aug. 6, 1957; Assigned to Carbogen Corporation, New York
DE Patent No. 2,714,938; 11.05.1978

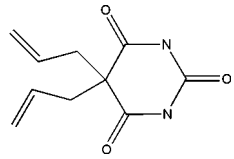
ALLOBARBITAL

Therapeutic Function: Sedative, Hypnotic

Chemical Name: Barbituric acid, 5,5-diallyl-

Common Name: Diallylbarbituric acid, Allobarbital, Diallymal

Structural Formula:



Chemical Abstracts Registry No.: 52-43-7

Trade Name	Manufacturer	Country	Year Introduced
Allobarbital	Fluorochem Ltd.	-	-
Dorm	Funke	-	-

Raw Materials

Allyl bromide
Barbituric acid
Sodium hydroxide

Manufacturing Process

To a mixture of 43 parts barbituric acid, 200 parts of water and 5 parts of cuprous sulfate in 10 parts of water is added 82 parts of allylbromide. Then at room temperature is added 27 parts of sodium hydroxide (10% aqueous solution). 5,5-Diallylbarbituric acid is isolated by filtration. After recrystallization from water 5,5-diallylbarbituric acid has melting polint 169-170°C.

References

Patent DE 268158; 30.June 1911; Assigned to Geselschaft fur Chemische Industrie in Basel
Patent DE 526854; 22. Feb. 1930; Assigned to F.Hoffmann-La Roche and Co. Act.-Ges. in Basel

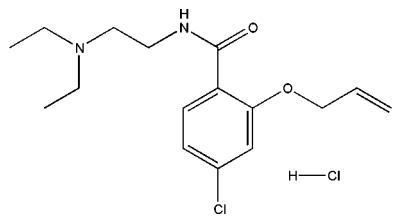
ALLOCLAMIDE HYDROCHLORIDE

Therapeutic Function: Antitussive

Chemical Name: Benzamide, 4-chloro-N-(2-(diethylamino)ethyl)-2-(2-propenyloxy)-, monohydrochloride

Common Name: Alloclamide hydrochloride; Depryn; Pectex

Structural Formula:



Chemical Abstracts Registry No.: 5107-01-7; 5486-77-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Alloclamide hydrochloride	ZYF Pharm Chemical	-	-

Raw Materials

2-Hydroxy-4-chlorobenzoic aci	Allyl bromide
β-Diethylaminoethylamine	Thionyl chloride

Manufacturing Process

(a) 200 g of 2-hydroxy-4-chlorobenzoic acid and 1 liter of methanol are brought to reflux. Dry hydrogen chloride gas is bubbled through the mixture during a time period of 8 hours. The excess of methanol is evaporated, the residue is poured into cold water, neutralized and extracted with ether. After evaporation of the solvent the product is distilled under vacuum. The boiling point of the compound at 15 mm Hg is 127°C, and the yield is 85% of the theoretical.

(b) The production of 2-allyloxy-4-chloromethyl benzoate:

4-Chloro-2-hydroxymethyl benzoate 186 g (1 mole), 152 g anhydrous potassium carbonate, 133 g redistilled allyl bromide in 350 ml acetone are heated of refluxing under agitation. At the end of 6 hours the reaction is completed. The reaction mixture is filtered for removal of the mineral salts. The acetone is evaporated. There is thus obtained an oily residue, which rapidly crystallizes. After recrystallization from methanol the obtained product is a white crystal solid, which melts at 56°C. The yield is 84%.

(c) The production of 2-allyl-oxy-4-chlorobenzoyl chloride:

The 2-allyloxy-4-chloromethyl benzoate obtained under (b) above is saponified under the usual conditions on for obtaining the corresponding acid, and the corresponding acid is obtained in a yield of 91%, the acid melting at 87°C.

The chloride of the acid is prepared by treating 1 mol of the acid with 1.5 moles of thionyl chloride (freshly rectified on linseed oil) in the presence of benzene. There is thus obtained a pale yellow viscous liquid, which can be further used without preliminary distillation.

(d) Preparation of the amide and of the hydrochloride:

115.5 g (0.5 mol) of the benzoyl chloride produced under (c) above is dissolved in 500 ml of anhydrous chloroform. There is added to this solution drop by drop while agitating and under cooling in an ice bath 116 g of β-diethylaminoethylamine. After the addition is completed the agitation is continued for 1 hour at ambient temperature. The reaction mass is then washed with water, the chloroform is evaporated, the residue is taken up the minimum of absolute alcohol, and there is then added a slight excess of absolute alcohol saturated with hydrogen chloride. The hydrochloride crystallizes by the addition of anhydrous ether. After recrystallization in absolute alcohol plus ether there is obtained white crystals, which are soluble in water and in alcohol. The 2-allyloxy-4-chloro-N-(β-diethylaminoethyl)benzamide hydrochloride melts at 125°-127°C.

References

Mauvernay R-Y.; US Patent No. 3,160,557; Dec. 8, 1964; Assigned to Centre European de Recherches Mauvernay, Chateau de Bardon, Riom, Puy-de-Dome, France

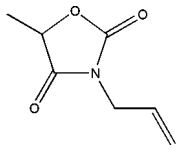
ALLOMETHADIONE

Therapeutic Function: Anticonvulsant, Antiepileptic

Chemical Name: 2,4-Oxazolidinedione, 5-methyl-3-(2-propenyl)-

Common Name: Allomethadione, Aloxidone

Structural Formula:



Chemical Abstracts Registry No.: 526-35-2

Trade Name	Manufacturer	Country	Year Introduced
Aloxidone	ZYF Pharm Chemical	-	-

Raw Materials

Allyl bromide
Urea
5-Methyloxazolidine-2,4-dione
Ethyl lactate

Manufacturing Process

A mixture of 11.4 parts of 5-methyloxazolidine-2,4-dione and 15 parts anhydrous potassium carbonate in 150 parts of dry acetone is stirred for 0.5 hour. 15 parts of allyl bromide are then added and the mixture boiled under reflux with stirring for 4 hours. After cooling and filtering, the solvent and any unchanged allyl bromide are removed by distillation. The residue is extracted with ether end the extract washed with saturated aqueous sodium bicarbonate until the subsequent water-washings are either neutral or just alkaline to litmus paper. The solvent is then distilled and the residue fractionated when 3-allyl-5-methyloxazolidine-2,4-dione is obtained in 65% yield as a colorless oil, BP: 88°-90°C/1.8 mm, n_d^{20} = 1.4710.

The dry sodium salt of 5-methyloxazolidine-2,4-dione, obtained from 4.6 parts of sodium, 100 parts of ethanol, 12 parts of urea and 23.6 parts of ethyl lactate, is suspended in 100 parts of dry benzene and 30.25 parts of allyl bromide are added. The mixture is boiled under reflux for 20 hours and the benzene decanted or filtered from any solid. The solution is washed with

saturated aqueous sodium bicarbonate until the subsequent water-washings are neutral or just alkaline to litmus paper. The dried benzene solution is then distilled to remove solvent and the residue fractionated, when 3-allyl-5-methylosazolidine-2,4-dione is obtained in 27% yield as a colorless oil, BP: 89°-90°C/1 mm, n_d^{20} = 1.4712.

The dry sodium salt of 5-methyloxazolidine-2,4-dione obtained as above is mixed with 100 parts of dry dioxane and 31.25 parts of allyl bromide are added. After boiling under reflex for 24 hours, decanting the solution and distilling off the dioxane under reduced pressure, the residue is dissolved in ether and the ethereal extract mashed with aqueous sodium bicarbonate as above. Fractionation of the residue after removing the olvent furnishes 3-allyl-5-methyloxazolidine-2,4-dione in 48.5% yield as a colorless oil; BP: 94°-95°C/11.75 mm; n_d^{20} = 1.4710.

References

Davis J.S.H. and Hook W.H.; GB Patent No. 632,423; June 28, 1948; British Schering Research Laboratories, Great Britain

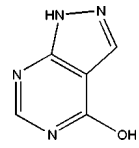
ALLOPURINOL

Therapeutic Function: Xanthine oxidase inhibitor, Gout therapy

Chemical Name: 1H-Pyrazolo[3,4-d]pyrimidin-4-ol

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 315-30-0

Trade Name	Manufacturer	Country	Year Introduced
Zyloprim	Burroughs-Wellcome	US	1966
Zyloric	Wellcome	Switz.	-
Zyloric	Burroughs-Wellcome	UK	1966
Zyloric	Wellcome	W. Germany	1967
Zyloric	Wellcome	Italy	1968
Zyloric	Wellcome	Japan	1969
Zyloric	Wellcome	France	1969
Lopurin	Boots	UK	1980
Adenock	Tanabe	Japan	-
Adenock	Shiraimatsu	Japan	-
Allopin	Yeni	Turkey	-

Trade Name	Manufacturer	Country	Year Introduced
Allomaron	Nattermann	W. Germany	-
Alloprim	Iltas	Turkey	-
Alloprin	ZCN	Canada	-
Allopur	Gea	Denmark	-
Allopur	Nyegaard	Norway	-
Allopurinol	Sigfried	W. Germany	-
Allopurinol	Efeka	W. Germany	-
Allopurinol	Woelm Pharma	W. Germany	-
Allopurinol	Lederle	Japan	-
Allopurinol	Kowa	Japan	-
Allopurinol	Showa	Japan	-
Allorin	Towa	Japan	-
Allozym	Sawai	Japan	-
Allural	Nativelle	Italy	-
Allural	Pan Quimica	Spain	-
Allurit	Schoum	Italy	-
Aloc	Toho Iyaku	Japan	-
Alositol	Tanabe	Japan	-
Anoprocin	Nippon Shoji	Japan	-
Antigot	Yurtoglu	Turkey	-
Anzief	Nippon Chemiphar	Japan	-
Aprinol	Daisan	Japan	-
Apurin	Gea	Denmark	-
Apurin	Madica	Finland	-
Apurol	Siegfried	Switz.	-
Bleminol	Desitin	W. Germany	-
Caplenal	Berk	UK	-
Capurate	Fawns and McAllan	Australia	-
Cellidrin	Henning	W. Germany	-
Cosuric	DDSA	UK	-
Dabroson	Hoyer	W. Germany	-
Embarin	Diabetylin	W. Germany	-
Epidropal	Fresenius	W. Germany	-
Flogorex	Lancet	Italy	-
Foligan	Henning	W. Germany	-
Geapur	Gea	Denmark	-
Gichtex	Gerot	Austria	-
Ketawrift	Ohta	Japan	-
Ketobun A	Isei	Japan	-
Lopurin	Generics Corp.	US	-
Lysuron	Boehringer Mannheim	W. Germany	-
Masaton	Zensei	Japan	-
Melianin	Kohjin	Japan	-
Mephanol	Mepha	Switz.	-
Milurit	EGYT	Hungary	-

Trade Name	Manufacturer	Country	Year Introduced
Monarch	SS Pharmaceutical	Japan	-
Nektronan	ICN Pharmaceuticals Inc.	W. Germany	-
Neufan	Teikoku	Japan	-
Neufan	Teisan	Japan	-
Novopurol	Novopharm	Canada	-
Progout	Protea	Australia	-
Puricos	Lennon	S. Africa	-
Purinol	Horner	Canada	-
Riball	Mitsui	Japan	-
Roucol	Rougier	Canada	-
Serviprinol	Servipharm	Switz.	-
Suspendol	Merckle	W. Germany	-
Takanarumin	Takata	Japan	-
Urbol	Heilit	W. Germany	-
Urbol	Gea	Denmark	-
Uredimin	Chassot	Switz.	-
Uricemil	Farnex	Italy	-
Uricemil	Fardeco	Italy	-
Uriconorm	Streuli	Switz.	-
Uridocid	Reig Jofre	Spain	-
Uriscel	Armour Med.	Italy	-
Urobenyl	Endopharm	W. Germany	-
Urolit	Magis	Italy	-
Urosin	Boehringer Mannheim	W. Germany	-
Urozyl-SR	Restan	S. Africa	-
Urtias	Sabona	W. Germany	-
Vedatan	Corvi	Italy	-
Xanturat	Gruenenthal	W. Germany	-
Zylol	Teva	Israel	-

Raw Materials

Cyanoacetamide
Morpholine
Triethylorthoformate
Hydrazine hydrate

Manufacturing Process

3-Morpholino-2-cyanoacrylamide: A stirred mixture of cyanoacetamide (63 g), triethylorthoformate (134 g), morpholine (82.5 g) and acetonitrile (37.5 ml) was heated under reflux for 4 hours. The initial reflux temperature was 117°C and the final reflux temperature was 82°C.

At the end of the reflux period the mixture was cooled to 30°C and the heavy

crystalline precipitate was collected and washed with 2 x 75 ml of ethanol. The product was dried in vacuum at 30°C. Wt = 111 g. Yield = 82%, MP 173-175°C.

3-Aminopyrazole-4-carbxamide hemisulfate: To water (253 ml) at 60°C was added 3-morpholino-2-cyanoacrylamide (63.4 g) and 85% technical hydrazine hydrate (22.7 g). The mixture was rapidly heated to 95°C and the temperature was maintained at >90°C for 20 minutes. The mixture was then cooled to 60°C and the pH carefully adjusted to 1.5 by the addition of a mixture of sulfuric acid (45.7 g) and ice. The acidified reaction was cooled to 5°C and the crystalline product collected and washed with cold water (2 x 100 ml) and acetone (2 x 50 ml). The product was dried in vacuum at 80°C. Wt =5.8 g. Yield =95%, MP 237-239°C.

4-Hydroxypyrazolo[3,4-d]pyrimidine: A suspension of 3-aminopyrazole-4-carboxamide hemisulfate (113 g) in formamide (325 g) was stirred and heated to 145°C. The reaction was held at 145°C for 5 hours. The reaction was then cooled to 30°C and the product collected and washed with formamide (2 x 50 ml), water (2 x 150 ml) and acetone (2 x 100 ml). Wt of crude product = 79 g. The crude product was recrystallized by dissolution in a solution made from sodium hydroxide (25 g) in water (1,200 ml) with treatment at 25°C with charcoal (8 g), followed by reprecipitation by the addition of concentrated hydrochloric acid to pH 5. The product was collected and washed with cold water (2 x 300 ml), acetone (2 x 200 ml) and dried in vacuum at 60°C. Wt = 70 g. Yield = 80%.

References

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Kleeman and Engel p. 27
PDR pp. 685,774,830,993,1606
OCDS Vol. 1 pp. 152, 269 (1977)
I.N. p. 57
REM p. 1111
Druey, J. and Schmidt, P.; US Patent 2,868,803; January 13, 1959; Assigned to Ciba Pharmaceutical Products Inc.
Hitchings, G.H. and Falco, E.A.; US Patent 3,474,098; October 21, 1969; Assigned to Burroughs Wellcome and Co.
Cresswell, R.M. and Mentha, J.W.; US Patent 4,146,713; March 27, 1979; Assigned to Burroughs Wellcome and Co.

ALLYLESTRENOL

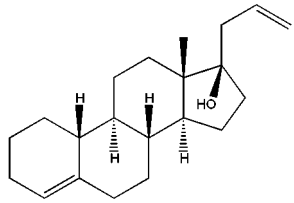
Therapeutic Function: Progestin; Antiandrogen

Chemical Name: 17α-Allylestr-4-en-17β-ol

Common Name: Alilestrenol; Allylestrenol; Allyloestrenol

Chemical Abstracts Registry No.: 432-60-0

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Alilestrenol	Terapia	-	-
Alilestrenol PA	AAA Principio Activo	-	-
Allyloestrenol	Belco Pharma	-	-
Allyloestrenol	Huei-Ho Industries	-	-
Anin	Ind-Swift Ltd.	-	-
Astanol	Rekvina Pharma	-	-
Gestanin	Organon	-	-
Gestanin	Donmed	-	-
Gestanon Tab.	Organon	-	-
Gestin	Walter Bushnell	-	-
Gestormone	Zorka	-	-
Gravidin	Alidac	-	-
Gynonys	Sankyo	-	-
Fetugard	Biddle Sawyer	-	-
Fulterm	Micro Nova	-	-
Maintane Tab.	Jagsonpal	-	-
Nidagest	Systopic	-	-
Orageston	Akzo	-	-
Pregular	Helios	-	-
Profar	Infar	-	-
Premaston	Kalbe	-	-
Profar	Infar	-	-
Turinal	Richter Co.	-	-
Turinal	Gedeon Richter	-	-
Turinal	Medimpex	-	-
Turinal	Mekim	-	-
Turinal Tab.	October Pharma Co.	-	-

Raw Materials

Methylamine
Chromium trioxide
Acetic acid
Allyl bromide
Lithium
Oestradiol-3-methylether
Magnesium

Manufacturing Process

To 145 ml of dry methylamine which is cooled to -20°C 1.5 g of lithium cut to

small pieces are added. To the solution which is blue in color after 10-20 min, a solution of 3.0 g of oestradiol-3-methylether in 145 ml of absolute ether is added drop wise. Subsequently the reaction mixture is stirred at -10°C for 40 h, after which 50 ml of absolute ethanol are added. Then the methylamine is distilled off at law pressure.

To the remaining solution 50 ml of ether and 50 ml of water are added. The water layer is separated and extracted with ether. The ethereal layer is washed with a 2 N hydrochloric acid solution, subsequently with a saturated sodium bicarbonate solution, and then with water. The ethereal solution is dried and evaporated to dryness. The resulting crude reaction product is dissolved in a mixture of benzene and petroleum ether (1:3) and chromatographed over aluminium oxide. The δ^4-17β-hydroxy-oestrene obtained after chromatographic purification has a melting point of 80°-90°C and 95°-100°C after repeated crystallization from petroleum ether.

A solution of 13.2 g of chromium trioxide in a mixture of 120 ml of water and 20 ml of acetic acid is added, with stirring, to a solution of 20 g of δ^4-17β-hydroxy-oestrene in 400 ml of benzene. Subsequently the reaction mixture is vigorously stirred at room temperature for 16 h, after which the benzene layer is separated.

The remaining aqueous layer is extracted a few times with benzene and the benzene extracts collected are then added to the separated benzene layer. The benzene extracts are successively washed with dilute sulfuric acid and water and then evaporated to dryness. The residue is crystallized from acetone, and the δ^4-17β-oxo-oestrene, melting point 114°-116°C is obtained.

To a mixture of 22.4 ml of absolute ether and 1.84 g of magnesium, a mixture of 2.72 ml of allyl bromide and 2.72 ml of absolute ether is added in nitrogen atmosphere. Subsequently a solution of 2 g of δ^4-17β-oxo-oestrene in 30 ml of absolute ether is added to this reaction mixture, after which the whole is stirred for 4 h. Then the reaction mixture is poured into acidified ice water. The aqueous mixture is extracted with ether; the ether layer is separated, washed with water, dried over sodium sulfate and evaporated to dryness. The residue is recrystallized from a mixture of ether and petroleum ether, giving δ^4-17β-hydroxy-17α-allyl-oestrene, melting point 79.5°-80°C.

References

GB Patent No. 841,411; April 2, 1958; Assigned: Organon Laboratories Limited, a British Company of Brettenham House, Lancaster Place, London

ALMAGATE

Therapeutic Function: Antacid

Chemical Name: Magnesium, (carbonato(2-))heptahydroxy(aluminum)tri-, dihydrate

Common Name: Almagate

Structural Formula: $AlMg_3(CO_3)(OH)_7$

Trade Name	Manufacturer	Country	Year Introduced
Almagate	AGARWAL PHARCHEM (I) PVT. LTD.	-	-

Chemical Abstracts Registry No.: 66827-12-1

Raw Materials

Aluminum hydroxide
Magnesium hydroxide
Triethylamine
Ammonium hydroxide
Water

Manufacturing Process

2 Methods of producing of basic aluminium magnesium carbonate:

1. A suspension of aluminum hydroxide (9.57 g, corresponding to 5.09 g of Al_2O_3 0.05 mol), magnesium hydroxide of 92.09% purity (18.87 g; 0.3 mol), concentrated ammonium hydroxide (4.89 ml; 0.33 mol) and water (500 ml) was boiled under reflux for 6 h while a stream of carbon dioxide was passed through the mixture. Then the reaction mixture was cooled, and the insoluble compound was filtered off, washed several times with water and dried in vacuum at a temperature of 60°C. Basic aluminum magnesium carbonate (31.1 g) was obtained.

2. A suspension of aluminium hydroxide (9.57 g, corresponding to 5.09 g of Al_2O_3 0.05 mol) magnesium hydroxide of 92.09% purity (18.87 g; 0.3 mol), triethylamine (33.4 g; 0.33 mol) and water (500 ml) was boiled under reflux for 8 h while a stream of carbon dioxide was passed through the mixture. After cooling, the insoluble compound was filtered off, washed several times with water and dried at 60°C under reduced pressure. Basic aluminum magnesium carbonate (30.8 g) was obtained.

References

Spickett R.G.W. et al.; US Patent No. 4,447,417; May 8, 1984; Assigned: Anphar S.A., Madrid, Spain

ALMASILATE

Therapeutic Function: Antacid

Chemical Name: Magnesium aluminosilicate (MgAl2Si2O8) hydrate

Common Name: Simagel; Almasilate

Structural Formula: $MgAl_2Si_2O_8 \cdot H_2O$

Trade Name	Manufacturer	Country	Year Introduced
Megalac Almasilat	Krewel Meuselbach	-	-
Simagel	Philopharm	-	-

Chemical Abstracts Registry No.: 71205-22-6

Raw Materials

Magnesium chloride
Aluminum sulfate
Caustic soda
Sodium silicate (Na_2O, 9%, SiO_2, 29%)

Manufacturing Process

203 g of crystalline magnesium chloride such as is used as a food additive, containing 46% $MgCl_2$, is dissolved in 600 ml of water, to which 96 g of caustic soda dissolved in 250 ml of water is added with stirring and a solution comprising 50 ml of water with 207 g of sodium silicate (Na_2O, 9%, SiO_2, 29%) is further added and is then vigorously stirred to produce basic sodium magnesium silicate (which is designated as Slurry A).

Secondly 593 g of aluminum sulfate containing 17.2% Al_2O_3, dissolved in 1,700 ml of water is gently added with stirring to 216 g of caustic soda dissolved in 600 ml of water, to which 50 ml of water added to 207 g of sodium silicate (Na_2O 9%, SiO_2, 29%) is slowly added and is then vigorously stirred to produce tetrabasic dialuminum silicate (which is designated as Slurry B). Slurry A and Slurry B are mixed up vigorously with stirring for 3 hours at room temperature. The thus obtained white gel-like precipitate is washed by decantation to remove free alkali, sodium sulfate, sodium chloride, etc. produced as reaction by-products. The residue is filtered and dried at 105°-110°C and 340 g of white powder of fine particle size is obtained as the final product. The molar ratio of MgO to Al_2O_3, to SiO_2, in this product is approximately 1: 1: 2.

203 g of crystalline magnesium chloride such as is used as a food additive, containing 46% $MgCl_2$, and 593 g of aluminum sulfate containing 17.2% Al_2O_3, are dissolved in 2,300 ml of water, to which a solution comprising 272 g of caustic soda with 800 ml of water, is slowly added with stirring. Thereafter, a solution comprising 414 g of sodium silicate (Na_2O, 9%, SiO_2, 29%) with 100 ml of water is added, the mixture is heated and is stirred for five hours, while keeping the temperature at 60°C. When the reaction mixture becomes neutral it is allowed to cool and to stand, the supernatant fluid is withdrawn and the white gel-like precipitate is washed by decantation to remove the impurities and dried at 105°-110°C and 350 g of white powder of fine particle size is obtained as the final product (almasilate).

References

Hidetaka Uoda et al.; GB Patent No. 1,153,513; Feb. 17, 1967; Fuji Kagaku Kogyo Kaushiki Kaisha, a Japanese Company, of 55 Yokohooji, Kamiichimachi, Naka-Niikawa-gun, Toyama-ken, Japan

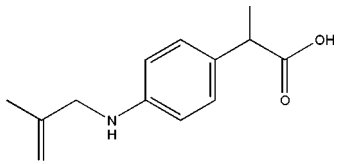
ALMINOPROFEN

Therapeutic Function: Analgesic, Antiinflammatory

Chemical Name: Benzeneacetic acid, α-methyl-4-((2-methyl-2-propenyl) amino)-

Common Name: Alminoprofen; Minalfene

Structural Formula:



Chemical Abstracts Registry No.: 39718-89-3

Trade Name	Manufacturer	Country	Year Introduced
Alminoprofen	ZYF Pharm Chemical	-	-
Minalfene	Bouchara-Recordati	-	-

Raw Materials

Methyl 2-(p-nitrophenyl)acrylate
Methallyl chloride
Palladium on charcoal
Pyridine

Manufacturing Process

Methyl 2-(p-aminophenyl)propionate:

Methyl 2-(p-nitrophenyl)acrylate (52 g) is hydrogenated in ethanol (500 ml) in the presence of 5% palladium-over-charcoal, while maintaining the temperature at +5°C. The theoretical amount of hydrogen is taken up within one hour. After separation of the catalyst and concentration to dryness, the resulting material gives methyl 2-(p-aminophenyl)proprionate which crystallizes: MP: = 40°-43°C.

Methyl 2-(p-methallylaminophenyl)propionate hydrochloride:

A mixture of methyl 2-(p-aminophenyl)propionate (44.75 g), methallyl chloride (34 g) and pyridine (30 ml) in isopropanol (400 ml) is boiled during 30 hours. The solvent is removed in vacuo and the residue is taken up into water and ether. After separation, the organic phase is washed repeatedly with water, after which it is dried and concentrated in vacuo. The resulting oil is fractionally distilled in vacuo (0.1 mm Hg; 5 g of oil essentially consisting of methyl 2-(p-aminophenyl)propionate are collected at 115°-120°C; 30 g of oil consisting of a mixture of mono- (80%) and disubstituted (20%) amines is collected at 128°-130°C. This oil is used to prepare the hydrochloride, which is recrystallized from ethyl acetate, to give white crystals (22.7 g) melting at