V

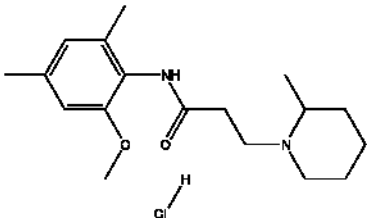
VADOCAINE HYDROCHLORIDE

Therapeutic Function: Antitussive, Local anesthetic

Chemical Name: N-(2-Methoxy-4,6-dimethylphenyl)-2-methyl-1-piperidinepropanamide monohydrochloride

Common Name: Vadocaine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 72005-58-4 (Base); 72032-54-3

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

Raw Materials

4,6-Dimethyl-o-anisidine
3-Chloropropionyl chloride
3-Methyl piperidine
Hydrogen chloride

Manufacturing Process

3-Chloro-4',6'-dimethyl-o-propananisidide was prepared by using 92.8 g (0.615 mol) 4,6-dimethyl-o-anisidine and 86 g (0.68 mol) of 3-chloropropionyl chloride, melting point 123-125°C. A mixture containing 40 g (0.165 mol) of 3-chloro-4',6'-dimethyl-o-propananisidide, 54.3 g of 3-methyl piperidine, and 330 ml of anhydrous benzene was heated for 72 hours at 65°C. 47.7 g

(84.5%) of N-(2-methoxy-4,6-dimethylphenyl)-2-methyl-1-piperidinepropanamide hydrochloride was obtained by deposition of product in anhydrous acetone saturated with hydrogen chloride; melting point 192-193°C (crystallization from a mixture isopropanol-acetone).

References

Juhani O. Kalla, Ekki J. Honkanen, Joachim E. Alberty, Jaakko J. Hukki; US Patent No. 4,353,914; Oct. 12, 1982; Assigned to Orion-yhtyma Oy, Finland

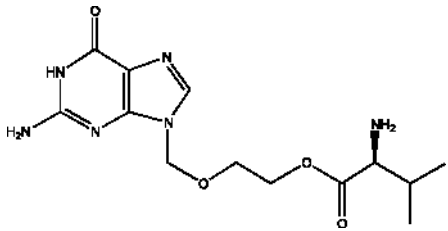
VALACYCLOVIR

Therapeutic Function: Antiviral

Chemical Name: L-Valine, 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl) methoxy)ethyl ester

Common Name: Aciclovir valinate; Valaciclovir; Valacyclovir

Structural Formula:



Chemical Abstracts Registry No.: 124832-26-4

Trade Name	Manufacturer	Country	Year Introduced
Valcivir	Cipla Limited	-	-
Valtrex	GlaxoWellcome	-	-
Rapivir	GlaxoSmithKline	-	-

Raw Materials

6H-Purin-6-one, 1,9-dihydro-2-amino-9-((2-hydroxyethoxy)methyl) (acyclovir)
Butyloxycarbonyl valine
Trifluoroacetic acid

Manufacturing Process

By dicyclohexylcarbodiimide catalyzed esterification of acyclovir (6H-purin-6-one, 1,9-dihydro-2-amino-9-((2-hydroxyethoxy)methyl)-) with the

butyloxycarbonyl valine. Treatment of ester obtained with trifluoroacetic acid leads to scission of the BOC group to provide L-valine ester with 9-((2-hydroxyethoxy)methyl)guanine (valacyclovir).

References

Merck Index, Monograph number: 10039, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.
Beauchamp L.M., Krenitsky T.A.; Drug Future, 1983, 18, 619

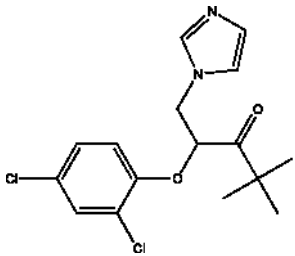
VALCONAZOLE

Therapeutic Function: Antifungal

Chemical Name: 2-(2,4-Dichlorophenoxy)-1-(1H-imidazol-1-yl)-4,4-dimethyl-3-pentanone

Common Name: Valconazole

Structural Formula:



Chemical Abstracts Registry No.: 56097-80-4

Trade Name	Manufacturer	Country	Year Introduced
Valconazole	JINGTIAN PORTLINK CO., LTD.	-	-

Raw Materials

Imidazole	Trimethylammonium chloride
Triethylamine	4-(2,4-Dichloro-phenoxy)-2,2-dimethylbutan-3-one
Methyl iodide	Paraformaldehyde

Manufacturing Process

1). 0.9 moles 4-(2,4-dichlorophenoxy)-2,2-dimethylbutan-3-one, 1 mole trimethyl ammonium chloride and 1 mole paraformaldehyde were in 300 ml dry ethanol dissolved. 2 ml conc. hydrochloric acid was added and the mixture was heated to reflux for 2 hours. After adding of 1 extra mole of paraformaldehyde the mixture was heated to reflux for 2 hours and stood for

night at room temperature. Then it was poured into 1.2 L water and extracted with 1.5 L ether. The water layer was basified with solution of ammonia to pH 8 and extracted with 1 L ether. The ether phase was separeted and dried over sodium sulphate and the solvent was removed in vacuum to give [2-(2,4-dichlorophenoxy)-4,4-dimethyl-3-oxopentyl]trimethylammonium chloride.

2). 0.1 mol of above ammonium chloride was dissolved in 200 ml of dry tetrahydrofuran and 0.2 moles triethylamine was added by stirring at room temperature. A precipitate of triethylammonium chloride was filtered off and filtrate was distilled to dryness. The residue was immediately dissolved in 300 ml dry acetonitrile and 0.15 moles of methyl iodide were added dropwise at room temperature and by stirring. The mixture was stood at room temperature for 1 hour. Then it boiled for 30 minutes. After that, the solvents were evaporated and the residue was heated to boiling in the mixture of ethyl acetate/methyl ethyl ketone (1:1). On cooling the precipitate of [2-(2,4-dichlorophenoxy)-4,4-dimethyl-3-oxopentyl]trimethylammonium iodide was filtered off and washed with ether.

3). To a solution of 0.0464 moles [2-(2,4-dichlorophenoxy)-4,4-dimethyl-3-oxopentyl]trimethylammonium iodide in 250 ml dry acetonitrile 0.15 moles of imidazole was added and heated to reflux for 24 hours. The solvent was removed in vacuum. The residue was dissolved in 500 ml methylene chloride and washed with water. The organic phase was separated and dried over sodium sulphate. Methylene chloride was distilled off to give 2-(2,4-dichlorophenoxy)-1-(1H-imidazol-1-yl)-4,4-dimethyl-3-pentanone melted at 85-87°C. Hydrochloride melted at 118°C.

References

Kramer W. et al.; D.E. Patent No. 2,348,663; March 23, 1973; Bayer AG

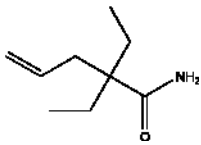
VALDETAMIDE

Therapeutic Function: Hypnotic

Chemical Name: 4-Pentenamide, 2,2-diethyl

Common Name: Valdetamide

Structural Formula:



Chemical Abstracts Registry No.: 512-48-1

Trade Name	Manufacturer	Country	Year Introduced
Insomnia	ICN		-
Valdetamide	Shanghai Lansheng Corporation	-	-

Raw Materials

Diethylacetonitrile
Potassium
Allyl bromide

Manufacturing Process

1 kg of diethylacetonitrile dissolved in 3 litres of dry ether is gradually mixed in a reflex apparatus, while stirring and heating, with 400 g of potassium. Thereupon evolution of hydrogen sets in and the potassium passes slowly into solution. After three hours any small amount of potassium, which may have remained unattacked is separated, and the solution is mixed with 1200 g of allyl bromide. The ether begins to boil and potassium bromide separates. The mass is heated for another hour, filtered, and the filtrate, after having distilled off the ether, is distilled in a vacuum. Thus diethylallylacetonitrile, distilling over at 78°C/9mm is obtained. By subsequent saponification with alcoholic potash the diethylallylacetamide is obtained. MP: 74°C.

References

I.G. Farbenindustrie Aktien Geselsheft; G.B. Patent No. 253,950; Sept. 22 1927; Assigned to Farbwerke, vorm. Meister Lucius and Bruning, a German company, of Hoechst a/Main, Germany

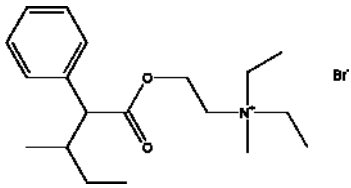
VALETHAMATE BROMIDE

Therapeutic Function: Anticholinergic

Chemical Name: N,N-Diethyl-N-methyl-2-[(3-methyl-1-oxo-2-phenylpentyl)oxy]ethanaminium bromide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 90-22-2

Trade Name	Manufacturer	Country	Year Introduced
Murel	Ayerst	US	1958
Barespan	Hishiyama	Japan	-
Baretaval	Shin Fuso	Japan	-
Beruhgen	Nissin	Japan	-
Elist	Sana-Torii	Japan	-
Epidosin	Kali-Chemie	W. Germany	-
Funapan	Funai	Japan	-
Kaichyl	Samoa	Japan	-
Letamate	Mohan	Japan	-
Narest	Isei	Japan	-
Pastan	Maruro	Japan	-
Release V	Mochida	Japan	-
Resitan	Grelan	Japan	-
Shikitan	Shiki	Japan	-
Shinmetane	Towa	Japan	-
Study	Toyo	Japan	-
Ulban-Q	Toho	Japan	-
Valate	Morishita	Japan	-
Valemate	Taiho	Japan	-
Valemeton	Sanko	Japan	-
Valethalin	Hokuriku	Japan	-
Valethamin	Sawai	Japan	-

Raw Materials

2-Butyl bromide
Methyl bromide
Sodium amide
Sulfuric acid
Benzyl cyanide
2-Diethylaminoethanol

Manufacturing Process

Benzyl cyanide is first reacted with 2-butylbromide in the presence of sodium amide to give 2-phenyl-3-methylvaleronitrile which is hydrolyzed by sulfuric acid to give 3-methyl-2-phenylpentanoic acid. 24 g of 2-phenyl-3-methylpentanoic acid are heated for one hour at 175° to 185°C with 30 g of 2-diethylaminoethanol and 0.5 g of sodium methylate. The excess diethylaminoethanol is removed in vacuo, the residue is dissolved in 300 cc of 2 N-acetic acid, the acid solution is shaken with ether and made alkaline with concentrated potassium carbonate solution and ice. The ether solution is washed with water, dried with sodium sulfate and evaporated. The residue is distilled under high vacuum, yielding 20 to 21 g of the basic ester (60% of the theoretical) is obtained, the ester boiling at 98° to 100°C at a pressure of 0.03 mm. The hydrochloride of the ester melts at 112°to 113°C and the methobromide at 100° to 101°C.

References

Merck Index 9711
Kleeman and Engel p. 939
I.N. p. 999

Martin, H. and Habicht, E.; U.S. Patent 2,987,517; June 6, 1961; assigned to Cilag Chemie Ltd., Switzerland.

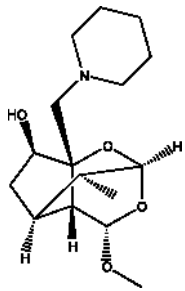
VALPERINOL

Therapeutic Function: Sedative, Antiepileptic, Antiparkinsonian

Chemical Name: (2R*,4R*,4aS*,5R*,7S*,7aR*,8R*)-Hexahydro-4-methoxy-8-methyl-7a-(piperidinomethyl)-2,5-methanocyclopenta-m-dioxin-7-ol

Common Name: Valperinol

Structural Formula:



Chemical Abstracts Registry No.: 64860-67-9

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

Raw Materials

Piperidine
Nickel Raney
Diethylamine
3-Iodomethyl-4β-acetoxy-8-methoxy-10-methylene-2,9-dioxatricyclo[4,3,1,$0^{(3,7)}$]decane

Manufacturing Process

Valperinol was prepared in 2 steps:

1). Preparation of 3-piperidinomethyl-4β-hydroxy-8-methoxy-10-methylene-2,9-dioxatricyclo[4,3,1,$0^{3,7}$]decane: 500 ml of piperidine is added to 250 g of sodium hydrogen carbonate and 190 g of 3-iodomethyl-4β-acetoxy-8-methoxy-10-methylene-2,9-dioxatricyclo[4,3, 1,$0^{3,7}$]decane. The mixture is heated to 150°C in an oil bath during 4 hours under thorough stirring and reflux condenser cooling and then is cooled to room temperature. After adding 7.5 liter of ether, 1 liter of water is added for dissolving the mixture, then 200

ml of a 40% sodium hydroxide solution is added and the mixture is shaken. After separation of the etherical phase the aqueous phase is extracted 3 times more with 500 ml of ether each. The united ether extracts are dried over sodium sulfate and clarified with active carbon and filtered by suction, then washed with ether. The filtrate is then evaporated in a rotation evaporator first at 50°C under reduced pressure, which is produced by means of a water jet pump and subsequently at 100°C under vacuum, which is produced by means of an oil pump. Thereby 180 g of oily 3-piperidinomethyl-4β-hydroxy-8-methoxy-10-methylene-2,9-dioxatricyclo[4,3,1,$0^{3,7}$]decane are obtained. These are used without further purifying for the preparation of 3-piperidinomethyl-4β-hydroxy-8-methoxy-10-methyl-2,9-dioxatricyclo[4,3,1,$0^{3,7}$]decane.

2). Preparation of 3-piperidinomethyl-4β-hydroxy-8-methoxy-10-methyl-2,9-dioxatricyclo[4 ,3,1,$0^{3,7}$]decane: A hydrogenation apparatus is flushed with nitrogen for 10 minutes and then flushed with hydrogen for 10 minutes and then is filled with nitrogen. 100 g of moist Raney nickel are washed into the hydrogenation flask by means of methanol and are prehydrogenated under low excess pressure and stirring for about 2 minutes at room temperature. After introducing the solution of 180 g of the substance 3-piperidinomethyl-4β-hydroxy-8-methoxy-10-methylene-2,9-dioxatricyclo[4,3,1,$0^{3,7}$]decane in 250 ml of methanol into the hydrogenation flask, there is further washed in a mixing solution of sodium hydroxide, which is prepared by dissolving 20 g of sodium hydroxide in a small amount of water, cooling this solution to room temperature and diluting it with methanol to the five fold amount. The mixture is hydrogenated under a low excess of pressure at room temperature for about 30 minutes. After the hydrogen uptake has stopped, the mixture is filtered over theorite through a suction filter which is then washed with methanol (the catalyst must not become dry; danger of fire). 30 ml of acetic acid are added to the filtrate, the solution is evaporated at 60oC., then cooled to room temperature and the residue taken up in ether and worked into a paste with 250 ml of silica gel (particle size 0.2-0.5 mm). After evaporation of the solvent at 50°C, the residue is taken up in a n-hexane and subsequently is evaporated at 60°C. The residue is filtered over a column of 500 g of silica gel (particle size 0.2-0.5 mm) using first 1 liter of n-hexane and then n-hexane containing 1.5% diethylamine as an eluating solvent. After evaporation of the filtrate at 60°C, 150 g of oily 3-piperidinomethyl-4β-hydroxy-8-methoxy-10-methyl-2,9-dioxatricyclo[4,3,1,$0^{3,7}$]decane (valperinol) are obtained. Empirical formula: $C_{16}H_{27}NO_4$. Molecular weight: 297.399.

References

Thies P.W. et al.; US Patent No. 4,242,341; December 30, 1980; Assigned to Kali-Chemie Pharma GmbH, Hanover, Fed. Rep. of Germany

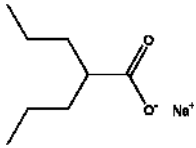
VALPROATE SODIUM

Therapeutic Function: Anticonvulsant, Antiepileptic

Chemical Name: Valeric acid, 2-propyl-, sodium salt

Common Name: Natrii valproas; Sodium valproate; Valproate sodium

Structural Formula:



Chemical Abstracts Registry No.: 1069-66-5

Trade Name	Manufacturer	Country	Year Introduced
Anticon	Generics-UK	UK	-
Apilepsin	Krka	Slovenia	-
Depacon	Abbott Laboratories	-	-
Depakene	Abbott Laboratories	-	-
Depakine	Sanofi-Winthrop Industrie	France	-
Encorate	Sun Pharma	-	-
Epilim	Sanofi-Synthelabo	-	-
Esfar	Midy-Munich	-	-
Pragmaten	Armstrong	-	-
Valproate de sodium	Sanofi Chimie	France	-
Valproate sodium	Danisco Ingredients	Denmark	-
Valproate sodium	Katwijk Chemie bv	Netherlands	-

Raw Materials

Ethyl cyanoacetate
n-Propyl bromide
Sodium
n-Propanol

Manufacturing Process

(a) Di-n-propyl cyanacetic acid

First of all, a sodium n-propylate solution was prepared from 7.42 g (0.322 mol) of sodium and 180 ml of anhydrous n-propanol, by heating with gentle reflux until complete dissolution of the sodium.

Into a 500 ml spherical flask, equipped with a dropping funnel, a mechanical stirrer, a thermometer and a condenser, above which was disposed a calcium chloride trap, were introduced 16.95 g (0.141 mol) of ethyl cyanacetate and 40.69 g (0.33 mol) of n-propyl bromide. This mixture was heated to 45°C and then there was added thereto, slowly and while stirring, the previously prepared solution of sodium n-propylate, keeping the temperature of the reaction medium at 50°-55°C by gentle external cooling.

With the completion of the operation of introduction, the mixture was brought to reflux temperature in 30 minutes and kept at this temperature for 3 hours. The n-propanol was then distilled and the distillation stopped when the temperature of the residual mass had reached 115°C.

The crude ester obtained in this way was then treated with a solution of 7.5 g of flaked sodium hydroxide in 67.5 ml of water. The mixture was introduced into a 250 ml spherical flask, equipped with a condenser, and then the reaction medium was slowly brought to 60°-70°C. This temperature was maintained for 3 hours, whereafter the mixture was cooled to about 50°C and the ethanol which had formed and the residue of n-propanol were eliminated under a pressure of 70 mm Hg. The solution thus obtained was cooled to 20°C and acidified, while stirring, by addition of 26.25 g of 36% hydrochloric acid. During this operation, the temperature of the reaction medium was kept below 40°C by cooling. Stirring was continued for 30 minutes, whereafter the mixture was left standing for 30 minutes. The oily layer of di-n-propyl cyanacetic acid was decanted and the aqueous phase extracted with 35 ml of toluene. The extract in toluene was then added to the decanted di-n-propyl cyanacetic acid, whereafter the solution in toluene was washed, in a separation funnel, with a solution of 1.5 g of sodium chloride in 14 ml of water. The toluenic phase was decanted and the toluene distilled under atmospheric pressure.

Using this procedure, 25 g of crude di-n-propyl cyanacetic acid were obtained.

(b) Di-n-propyl acetonitrile

Into a 100 ml spherical flask fitted with a thermometer and a condenser were introduced 25 g of crude di-n-propyl cyanacetic acid obtained by the method previously described, and the mixture was heated on an oil bath.

Decarboxylation commenced at a temperature in the region of 140°C. The mixture was refluxed at about 160°C and at 190°C for 2 hours. This temperature was maintained until the release of gas was completed, this taking 2 hours. The di-n-propyl acetonitrile thus formed was then slowly distilled and the fraction passing over between 165°C and 175°C was collected. A second distillation was then carried out. Using this procedure, 14.7 g of di-n-propyl acetonitrile were collected. Boiling point: 170°C. Yield: 83%, relatively to the ethyl cyanacetate used. Di-n-propyl acetonitrile may be saponifyed with equal molecular quantity of NaOH to give the desired valproic acid (valproate). After that it may be converted into the sodium salt with help of equivalent NaOH to give the valproate sodium.

References

Eugene H. et al.; US Patent No. 3,325,361; June, 13 1967; Assigned to Chemerton Corporation, Chicago Ill., a corporation of Delaware

Chignac et al.; US Patent No. 4,155,929; May 22, 1979; Assigned to Labaz, Paris, France

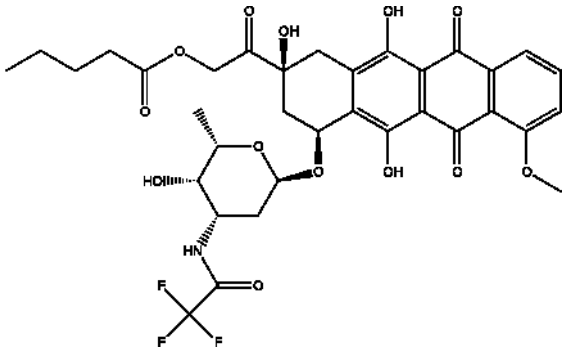
VALRUBICIN

Therapeutic Function: Antineoplastic

Chemical Name: Adriamycin, trifluoroacetyl-, 14-valerate

Common Name: Valrubicin

Structural Formula:



Chemical Abstracts Registry No.: 56124-62-0

Trade Name	Manufacturer	Country	Year Introduced
Valstar	Anthra Pharmaceuticals, Inc.	-	-
Valtaxin	Anthra Pharmaceuticals, Inc.	-	-
Valtrexin	Paladin Labs	-	-

Raw Materials

Pyridine	14-Iodo-N-trifluoroacetyldaunomycin hydrochloride
Sodium valerate	Trifluoroacetic anhydride
Adriamycin	Valeryl chloride

Manufacturing Process

N-Trifluoroacetyladriamycin-14-valerate

The first way. A mixture of 1.65 g of 14-iodo-N-trifluoroacetyldaunomycin, prepared and purified according to the procedure of Arcamone et al., U.S. Pat. No. 3,803,124, and 1.37 g of sodium valerate in 165 ml of anhydrous acetone was heated at reflux for 2 hours. The reaction mixture was cooled to room temperature and filtered, and the filter cake was washed with anhydrous acetone until the washings were no longer colored. The combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was treated with a 1:1 mixture of water and chloroform (total volume 200 ml), and the aqueous layer was separated and discarded. The chloroform extract was washed twice with cold water, once with aqueous pH 7 buffer, and finally with saturated aqueous sodium chloride. The chloroform solution was

dried over sodium sulfate and the chloroform solvent was removed by evaporation under reduced pressure. The residue was dissolved in a small volume of chloroform and the product was precipitated by the addition of petroleum ether (b.p. 38°-49°C). Three additional precipitations from chloroform and petroleum ether afforded 1.36 g of N-trifluoroacetyladriamycin-14-valerate, m.p. 135°-136°C, in analytical purity and homogeneous by thin layer chromatography (silica gel G; chloroform:methanol:water, 120:20:1 by volume) and high pressure liquid chromatography.

The second way. A suspension of 750 mg of 14-bromodaunomycin hydrochloride, prepared as described in Arcamone et al. U.S. Pat. 3,803,124, and 2.48 g of powdered sodium valerate in 520 ml of anhydrous acetone was heated at reflux for 2 hours. The reaction mixture was cooled to room temperature and filtered. The filter cake was washed with anhydrous acetone until the washings were free of color. The combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was dissolved in 150 ml of 0.1 N HCl and the aqueous acid solution was extracted with three 50 ml portions of chloroform to remove aglycone by-products. The aqueous layer, after the addition of 3 ml of methanol, was extracted with four 25 ml portions of 1-butanol. The butanol extracts were combined and evaporated under reduced pressure at 35°C until no further distillate appeared. Filtration of the suspension at this point afforded, after thorough washing with ethyl acetate and drying, 347.7 mg of adriamycin-14-valerate hydrochloride, m.p. 176°-177°C. A second crop of 62.2 mg of product was obtained from further concentration of the filtrate at a somewhat higher temperature. Both crops of material were of high purity by thin layer chromatographic analysis (silica gel G plates; solvent system: chloroform:methanol:water, 100:20:1 by volume).

A suspension of 300 mg of adriamycin-14-valerate hydrochloride in 20 ml of ethyl acetate was treated with 0.45 ml of trifluoroacetic anhydride in small portions over a few minutes until all solids had dissolved. The solution was mixed immediately with equal portions of water and chloroform (total volume 100 ml). The chloroform layer was separated and washed once with water and twice with pH 7 aqueous buffer. The chloroform solution was dried over sodium sulfate and then was evaporated to dryness under reduced pressure. The residue was dissolved in 25 ml of methanol, and the resulting solution was heated at reflux for 5 minutes, then cooled and evaporated to dryness. The residue was redissolved in 4 ml of chloroform, and the crude product was precipitated by the addition of 20 ml of petroleum ether (b.p. 38°-49°C). The crude material was purified by chromatography on a silicic acid column. Elution with chloroform containing 0.75% ethanol afforded 181 mg of N-trifluoroacetyladriamycin-14-valerate, identical chromatographically and by spectral comparison with samples of product prepared as described above.

The third way. A suspension of 193.4 mg of adriamycin free base in 20 ml of methylene chloride and 20 ml of dry dioxane was treated with 1.2 ml of trifluoroacetic anhydride with stirring at room temperature. The clear solution was diluted with chloroform and the organic layer was extracted with water. The chloroform solution was then washed with two 20 ml portions of aqueous pH 10 buffer, and then was dried over sodium sulfate. The dried chloroform solution was evaporated under reduced pressure. The residue was dissolved in 40 ml of methanol, and the methanol solution was heated at reflux for 5 minutes. The methanol solvent was then evaporated to dryness to give a

residue which weighed 189.3 mg. Of this residue 170 mg was purified by chromatography on a column of silicic acid. Elution with chloroform containing 20% ethyl acetate by volume afforded 90.8 mg of pure N-trifluoroacetyladriamycin.

A solution containing 5.0 mg of N-trifluoroacetyladriamycin dissolved in 0.5 ml of anhydrous pyridine was treated with 18 microliters of valeryl chloride, which was added in small portions over a two-day period. The reaction was monitored by thin layer chromatography and when the presence of N-trifluoroacetyladriamycin could no longer be observed, the reaction mixture was diluted with 10 ml of chloroform. The chloroform solution was extracted three times with pH 4 buffer and once with pH 7 buffer. The dried chloroform solution was then evaporated under reduced pressure, and the residue was purified by preparative thin layer chromatography on silica gel G with chloroform:methanol:water (120:20:1 by volume) as the solvent system. The major orange-colored band was removed and washed free of silica gel with a mixture of methanol and ethyl acetate. Upon evaporation of the methanol and ethyl acetate, 2.19 mg of N-trifluoroacetyladriamycin-14-valerate was obtained. This material was idential by spectral and chromatographic comparison with samples of N-trifluoroacetyladriamycin-14-valerate prepared by earlier described methods.

References

Israel et al.; US Patent No. 4,035,566; July 12, 1977; Assigned to Sidney Farber Cancer Institute, Inc., Boston, Mass.

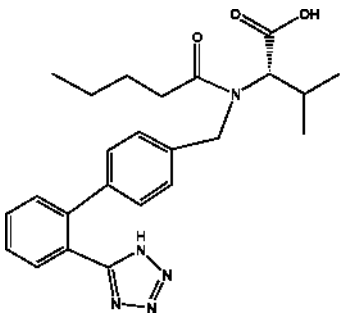
VALSARTAN

Therapeutic Function: Antihypertensive

Chemical Name: L-Valine, N-(1-oxopentyl)-N-((2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl)

Common Name: Valsartan

Structural Formula:



Chemical Abstracts Registry No.: 137862-53-4

Trade Name	Manufacturer	Country	Year Introduced
Diovan	Novartis Pharma	Switz.	-
Starval	Ranbaxy	-	-
Valzaar	Torrent	India	-

Raw Materials

Tributyltin azide
Triethylamine
n-Valeryl chloride
(L)-Valine methyl ester hydrochloride
2'-Cyanobiphenyl-4-carbaldehyde
Sodium cyanoborohydride

Manufacturing Process

0.5 g of 2'-cyanobiphenyl-4-carbaldehyde, 2.5 g of molecular sieve 5 A in tetrahydrofuran with stirring at room temperature for 36 hours; then the reaction mixture was cooled to 0°-5°C, 0.815 g of (L)-valine methyl ester hydrochloride and 180 mg of sodium cyanoborohydride dissolved in 4.8 ml of methanol are added. The mixture is stirred at room temperature for 24 hours and then concentrated in vacuo yields N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine methyl ester after flash chromatography.

1.15 g of N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine methyl ester, 0.625 ml of triethylamine in 9 ml of dichloromethane are treated 0.56 ml of n-valeryl chloride at 0°C and stirred at room temperature overnight and then evaporated to dryness. The residue is taken up in diethyl ether and the diethyl ether mixture is washed with sodium hydrogencarbonate solution and brine. Flash chromatography (180 g of silica gel; ethyl acetate/petroleum ether 1:1) yields N-valeryl-N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine methyl ester. (S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-amine. The product can be prepared starting from 1.40 g of N-valeryl-N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine methyl ester and 2.25 g of tributyltin azide with subsequent flash chromatography; melting interval 105°-115°C (from ethyl acetate).

References

Buhlmayer et al.; US Patent No. 5,399,578; March 21, 1995; Assigned Ciba-Giegy Corp. (Ardsley, N.Y.)

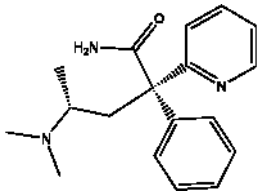
VAMICAMIDE

Therapeutic Function: Anticholinergic, Spasmolytic

Chemical Name: 2-Pyridineacetamide, α-(2-(dimethylamino)propyl)-α-phenyl

Common Name: Mepivamide; Vamicamide

Structural Formula:



Chemical Abstracts Registry No.: 132373-81-0

Trade Name	Manufacturer	Country	Year Introduced
Vamicamide	Fujisawa Pharmaceutical	-	-

Raw Materials

4-(N,N-Dimethylamino)-2-phenyl-2-(2-pyridyl)-valeronitrile
Sulfuric acid

Manufacturing Process

Conc. sulfuric acid (11 ml) was added to 4-(N,N-dimethylamino)-2-phenyl-2-(2-pyridyl)-valeronitrile (6.3 g) at 0°C. Then water (1 ml) was added thereto. After being heated at 90°C for 3 hours, the mixture was poured into ice-water, adjusted to pH 10 with 10% aqueous sodium hydroxide and extracted with ethyl acetate (3x50ml). The extracts were combined, and washed with water, dried over magnesium sulfate and evaporated under reduced pressure. The obtained crude crystal was recrystallized from diethyl ether to give 4-(N,N-dimethylamino)-2-phenyl-2-(2-pyridyl)-valeramide (1.89 g). MP: 132-134°C.

Recrystallization from 40% water ethanol gave MP: 156-157°C. The structure of the product was confirmed by UR, NMR (CDCl3) spectra and elemental analysis.

References

Ueda I. et al.; US Patent No. 4,564,621; January 14, 1986; Assigned to Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan

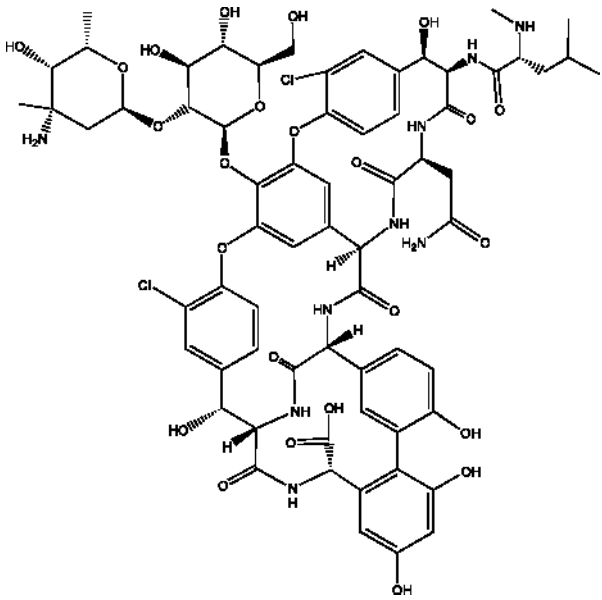
VANCOMYCIN

Therapeutic Function: Antibacterial

Chemical Name: Vancomycin

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1404-90-6

Trade Name	Manufacturer	Country	Year Introduced
Vancocin	Lilly	US	1958
Vancomycin	Shionogi	Japan	1981
Vancomycin	Lilly	W. Germany	1981

Raw Materials

Bacterium Streptomyces orientalis
Nutrient medium

Manufacturing Process

An agar slant is prepared containing the following ingredients: 20 grams starch, 1 gram asparagine, 3 grams beef extract, 20 grams agar, and 1 liter water. The slant is inoculated with spores of S. orientalis, Strain M43-05865, and is incubated for about 10 days at 30°C. The medium is then covered with sterile distilled water and scraped to loosen the spores. The resulting suspension of spores is preserved for further use in the process.

A liquid nutrient culture medium is prepared containing the following ingredients: 15 grams glucose, 15 grams soybean meal, 5 grams corn steep solids, 2 grams sodium chloride, 2 grams calcium carbonate, and 1 liter water. The medium is sterilized at 120°C for about 30 minutes in a suitable flask and cooled. 10 ml of a spore suspension prepared as set forth above are used to inoculate the medium. The inoculated medium is shaken for 48 hours at 26°C

on a reciprocating shaker having a 2-inch stroke, at 110 rpm.

The fermented culture medium which comprises a vegetative inoculum is used to inoculate a nutrient culture medium containing the following ingredients: 20 grams blackstrap molasses, 5 grams soybean peptone, 10 grams glucose, 20 grams sucrose, 2.5 grams calcium carbonate, and 1 liter water.

The medium is placed in a container having a suitable excess capacity in order to insure the presence of sufficient oxygen and is sterilized by heating at 120°C for about 30 minutes. When cool, the medium is inoculated with about 25 ml of a vegetative inoculum as described above, and the culture is then shaken for about 80 hours at 26°C. The pH of the medium at the beginning of fermentation ranges from about 6.5 to about 7.0 and the final pH is about 7.0 to about 8.0. A fermentation broth thus obtained contained about 180 μg of vancomycin per ml.

References

Merck Index 9731
PDR p. 1070
I.N. p. 1000
REM p. 1211
McCormick. M.H. and McGuire, J.M.; US Patent 3,067,099; December 4, 1962; assigned to Eli Lilly and Company

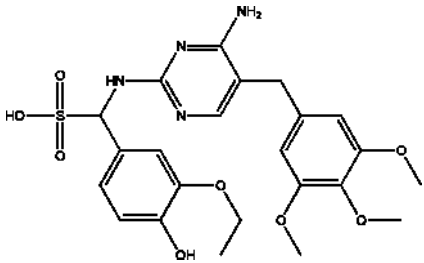
VANEPRIM

Therapeutic Function: Antibacterial

Chemical Name: (+/-)-α-[[4-Amino-5-[(3,4,5-trimethoxyphenyl)methyl]-2-pyrimidinyl]amino]-3-ethoxy-4-hydroxybenzenemethanesulfonic acid

Common Name: Vaneprim

Structural Formula:



Chemical Abstracts Registry No.: 81523-49-1

Trade Name	Manufacturer	Country	Year Introduced
Vaneprim	JINGTIAN PORTLINK CO., LTD.	-	-

Raw Materials

Trimethoprime
Vanillin
Sulfurous anhydride
Sodium hydroxide

Manufacturing Process

Successively, 145 g (0.5 mole) of trimethoprime and 83 g (0.5 mole) of vanillin was added to 500 ml of pyridine, and about 130 g of sulfurous anhydride was added in three hours. The temperature of the reaction mixture rose spontaneously between 40° and 50°C from the start of the introduction and was held there until the end of the reaction. It was left for 24 hours at ordinary temperature. Then the reaction mixture was poured into a large volume of ether, the precipitate which appeared was filtered off and washed with ether. The crude product was then dispersed in water and treated with dilute sodium hydroxide to pH 9.30-9.40. A light insoluble substance was filtered off, then the product was reprecipitated by the addition of hydrochloric acid to the alkaline solution to pH 2-3. It was filtered, washed with water, and then with ethanol. After drying, (+/-)-α-[[4-amino-5-[(3,4,5-trimethoxyphenyl)methyl]-2-pyrimidinyl]amino]-3-ethoxy-4-hydroxybenzenemethanesulfonic acid, was obtained, melting point 145°C. TLC of the product gave a single spot.

The sodium salt of the product was obtainable by treatment of the aqueous suspension of the acid form with dilute sodium hydroxide to a pH of 8.80. After evaporation of the solution under reduced pressure and drying, the sodium salt of the desired derivative of melting point 170°C was obtained.

References

Laruelle Claude, Lepant Marcel; US Paten No. 4,415,574; November 15, 1983; Assigned to S. A. Panmedica (Carros, FR)

VAPIPROST

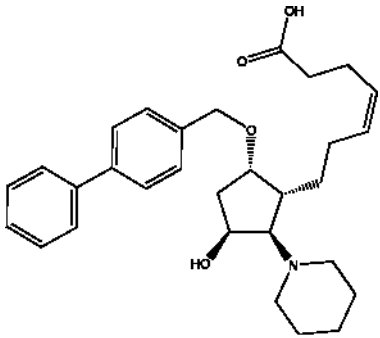
Therapeutic Function: Thomboxane A_2-antagonist

Chemical Name: [1R-[1α(Z),2β,3β,5α]]-7-[5-([1,1'-Biphenyl]-4-ylmethoxy)-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid

Common Name: Vapiprost

Chemical Abstracts Registry No.: 85505-64-2

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Vapiprost	GlaxoSmithKline	-	-

Raw Materials

Triethylamine
Benzyltriethylammonium chloride
Peracetic acid
4-(Bromomethyl)-4'-methoxy(1,1'-biphenyl)
Diisobutylaluminum hydride
Potassium t-butoxide
Methoxymethyltriphenylphosphonium chloride
3-(Carboxypropyl)triphenylphosphonium bromide
Pyridine-sulfur trioxide complex
1-[1R-(endo,anti)]-(+)-5-Hydroxy-7-(1-piperidinyl)bicyclo[2.2.1]heptan-2-one

Manufacturing Process

[1R-[1α(Z),2β,3β,5α]]-7-[5-([1,1'-Biphenyl]-4-ylmethoxy)-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid may be prepared in 9 steps:

1). [1R-(endo,anti)]-(+)-5-[[4'-Methoxy-(1,1'-biphenyl)-4-yl]methoxy]-7-(1-piperidinyl)bicyclo[2.2.1]heptan-2-one:

A mixture of 1-[1R-(endo,anti)]-(+)-5-Hydroxy-7-(1-piperidinyl)bicyclo[2.2.1]heptan-2-one (30.51 g), benzyltriethylammonium chloride (6.65 g) and 4-(bromomethyl)-4'-methoxy(1,1'-biphenyl) (52.6 g) in CH_2Cl_2 (365 ml) and 17 N NaOH (325 ml) was vigorously stirred at ambient temperature for 18 h. The mixture was diluted with water (1 L) and extracted with CH_2Cl_2 (3x150 ml). The combined extracts were dried and evaporated and the residue was purified by chromatography using ether-petroleum ether (boiling point 60°C) 1:1 followed by 7:3 as eluent to give the title compound (40.2 g). A portion was recrystallized from ether-petroleum ether (boiling point 60°C). MP: 109.5-110.5°C $[\alpha]_D^{23} = +22.7°$ ($CHCl_3$)

2). [1R-(endo,anti)]-(-)-6-[[4'-Methoxy(1,1'-biphenyl)-4-yl]methoxy]-8-(1-piperidinyl)-2-oxabicyclo[3.2.1]octan-3-one: A solution of peracetic acid in acetic acid (5.6 M, 124 ml) was added slowly to a stirred mixture of [1R-

(endo,anti)]-(+)-5-[[4'-Methoxy(1,1'-biphenyl)-4-yl]methoxy]-7-(1-piperidinyl)bicyclo[2.2.1]heptan-2-one

(42 g) in CH_2Cl_2 (235 ml), 2 N H_2SO_4 (29 ml) and water (159 ml) and the mixture stirred at ambient temperature for 24 h. The mixture was adjusted to ca. pH 7 using 5 N NaOH and pH 6.5 phosphate buffer then extracted with CH_2Cl_2 (3x200 ml). The combined organic extracts were added to an excess of sodium metabisulphite solution and stirred for 24 h. The mixture was extracted with ethyl acetate (1x500, 2x250 ml) and the combined organic extracts were dried and evaporated and the residue was purified by chromatography using 1:1 ethyl acetate-petroleum ether as eluent to give the title compound (24.4 g). A portion was recrystallized from ethyl acetate-petroleum ether MP: 116.5-117.5°C $[\alpha]_D^{23}$ =-24.5° ($CHCl_3$).

3). [1R-(1α,2β,3α,5α)]-(3-Hydroxy-5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(1-piperidinyl)cyclopentane acetaldehyde: Diisobutylaluminum hydride in hexane (1 M, 114 ml) was added slowly to a cold (-70°C) stirred solution of the above made compound from item 3 (24 g) in CH_2Cl_2 (240 ml). After 0.5 h methanol (240 ml) was added, slowly at first, and the mixture was stirred at ambient temperature for 16 h. The precipitate was filtered off and the filtrate evaporated to give the title compound as a foam (24.1 g).

4). [1R-(1α,2β,3α,5α)]-(+)-4-[[4'-Methoxy(1,1'-biphenyl)-4-yl]methoxy]-3-(3-methoxy-2-propenyl)-2-(1-piperidinyl)cyclopentanol, hydrochloride: A solution of [1R-(1α,2β,3α,5α)]-(3-Hyoroxy-5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(1-piperidinyl)cyclopentane acetaldehyde (24.1 g) in THF (75 ml) was added to a cooled (-5° to 0°C), stirred solution of the ylid derived from methoxymethyltriphenylphosphonium chloride (78 g) and potassium tert-butoxide (25.5 g) in THF (800 ml). After 1.5 h methanol (100 ml) was added and the solvents removed in vacuo. The residue in pH 6.5 phosphate buffer (600 ml) was extracted with CH_2Cl_2 (3x150 ml) and the combined extracts were dried and evaporated. The residue was purified by chromatography using 4:1 ethyl acetate-methanol as eluent to give the title compound, base as an oil (24.8 g). A portion was converted into the hydrochloride salt; m.p. 150-151°C (dec.), $[\alpha]_D^{23}$ = +38.1 ($CHCl_3$).

5). [1 R-(1α,2β,3α,5α)-(+)-3-Hydroxy-5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(1-piperidinyl)cyclopentanepropanol, hydrochloride: A solution of the end product from item4 (24.3 g) in 2 N HCl (55 ml) and acetone (250 ml) was stirred at ambient temperature for 1 h. Most of the acetone was removed in vacuo and the residue in water was extracted with CH_2Cl_2 (3x150 ml). The combined extracts were dried and evaporated to give a solid (23.6 g). A portion was triturated with ether to give the title compound as a powder; m.p.182-185°C (dec.) $[\alpha]_D^{23}$ =+51.5° ($CHCl_2$).

6). [1R-[1α(Z),2β,3α,5α]]-(+)-Methyl-7-[3-hydroxy-5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(1-piperidinyl)cyclopentyl]-4-heptenoate, hydrochloride: A suspension of [1 R-(1α,2β,3α,5α)-(+)-3-hydroxy-5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(1-piperidinyl)cyclopentanepropanal, hydrochloride (23.6 g) in THF (300 ml) was added to the derived from 3-(carboxypropyl)triphenylphosphonium bromide (69.5 g) and potassium tert-butoxide (36.3g) in THF (1000 ml). After 2 h water (200 ml) was added and the THF was removed in vacuo. The residue was diluted with water (250 ml)

and extracted with ether (3 x 200 ml; discarded). The aqueous layer was made neutral using 5 N HCl and extracted with CH_2Cl_2 (3 x 200 ml). The combined extracts were dried and evaporated and the residue was left to stand in methanol (250 ml) containing concentrated sulfuric acid (5 ml) for 19 h. Most of the methanol was removed in vacuo and the residue made neutral using 2 N NaOH and pH 6.5 phosphate buffer (150 ml). The mixture was extracted with ethyl acetate (3 x 150 ml) and the combined extracts were dried and evaporated. The residue was purified by chromatography using initially 9:1 ether-methanol followed by 4:1 ether-methanol as eluent to give the title compound, base as an oil (15.9 g). A portion was converted into the hydrochloride salt. MP: 122-125°C (dec.). $[\alpha]_D^{22}$ = +55.9° ($CHCl_3$).

7). [1 R-[1α(Z),2β,5α]]-(-)-Methyl-7-[5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-3-oxo-2-(1-piperidinyl)cyclopentyl]-4-heptenoate: A solution of pyridine-sulfur trioxide complex (10.33 g) in dry DMSO (17 ml) was added to a cold (0°C) solution of above compound (item 6), base (8.47 g) in Et_3N (13.5 ml), CH_2Cl_2 (30 ml) and DMSO (20 ml). After 1 h at 0°C, the mixture was diluted with pH 6.5 phosphate buffer (140 ml) and extracted with ethyl acetate (3x50 ml). The combined extracts were dried and evaporated and the residue was purified by chromatography using ethyl acetate-petroleum ether (1:3) as eluent to give the title compound as a solid (5.69 g). A portion was recrystallized from ether-petroleum ether. MP: 61.5-62.5°C. $[\alpha]_D^{22}$ =-19.8° ($CHCl_3$).

8). [1R-[1α(Z),2β,3β,5α]]-(+)-Methyl-7-[3-Hydroxy-5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(1-piperidinyl)cyclopentyl]-4-heptenoate: A solution of dibal in hexane (1 M, 93 ml) was added dropwise to a cold (-5°C) stirred solution of 2,6-di-tert-butyl-4-methylphenol (30.75 g) in dry toluene (350 ml). After 1 h at -5°C the mixture was cooled to -70°C and a solution of above compound from the item 7 (9.67 g) in toluene (50 ml) was added dropwise. After 1 h at -70°C and 1 h at -10°C the mixture was washed with 2 N HCl (7x60 ml) and the toluene was discarded. The acidic extracts were neutralised with 5 N NaOH solution (200 ml) and extracted with CH_2Cl_2 (4x80 ml). The combined extracts were dried and evaporated and the residue was purified by chromatography using 17:3 ether-methanol as eluent to give the title compound (7.02 g) as an oil. $[\alpha]_D^{21}$ =+63.2° ($CHCl_3$).

9). [1R-[1α(Z),2β,3β,5α]]-(+)-Methyl-7-[3-hydroxy-5-[[4'-methoxy(1,1'-biphenyl)-4-yl]methoxy]-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid, hydrochloride: A mixture of heptenoate from the item 8 (5.89 g) 5 N NaOH solution (6.77 ml) and methanol (40 ml) was vigorously stirred at ambient temperature for 18 h. Most of the methanol was removed in vacuo and the residue in pH 6.5 phosphate buffer (150 ml) was extracted with CH_2Cl_2 (3x40 ml). The combined extracts were dried and evaporated to give the title compound, base as a foam (5.79 g). A portion (0.67 g) in ether-CH_2Cl_2 was treated with an excess of ethereal HCl to give the title compound (0.61 g). MP: 122-124°C $[\alpha]_D^{22}$=+61.2° ($CHCl_3$).

References

Collington E.W. et al.; G.B. Patent No. 2,167,403 A; October 26, 1984

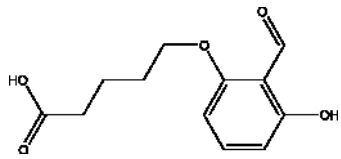
VELARESOL

Therapeutic Function: Antianemic

Chemical Name: Pentanoic acid, 5-(2-formyl-3-hydroxyphenoxy)-

Common Name: Velaresol

Structural Formula:



Chemical Abstracts Registry No.: 77858-21-0

Trade Name	Manufacturer	Country	Year Introduced
Velaresol	Wellcome (GSK)	-	-

Raw Materials

Sodium iodide
Sodium hydroxide
Potassium carbonate
Boron trichloride
Hydrochloric acid
Iodine
2-Hydroxy-6-methoxybenzaldehyde
Ethyl 5-bromopentanoate
Palladium on charcoal
2-Hydroxy-6-benzyloxybenzaldehyde
Hydrogen

Manufacturing Process

1st method of preparation of 5-(2-formyl-3-hydroxyphenoxy) pentanoic acid:

(A) 5-(2-Formyl-3-methoxyphenoxy)pentanoic acid:

2-Hydroxy-6-methoxybenzaldehyde (16.875 g, 0.111 M), ethyl 5-bromopentanoate (23.25 g, 17.6 ml, 0.111 M), anhydrous potassium carbonate (16.5 g), sodium iodide (0.675 g) and 95% ethanol (150 ml) were refluxed with stirring (16 hours). The cooled reaction mixture was filtered and the solid washed well with ethanol. The filtrate was evaporated to dryness and the residue partitioned between ether and water. The ethereal layer was separated and washed with 2 N sodium hydroxide solution, water, dried (sodium sulfate) and evaporated. The residue was dissolved in 95% ethanol (300 ml) and 0.66 N sodium hydroxide solution (450 ml) and stirred at ambient temperature (4 hours). The reaction mixture was evaporated to half volume and diluted with water. The mixture was extracted once with ether and the aqueous layer acidified with concentrated hydrochloric acid with cooling. The crystalline solid formed was filtered off and washed well with water. Recrystallisation from ethyl acetate-petrol gave 5-(2-formyl-3-methoxyphenoxy)pentanoic acid, melting point 99-101°C.

(B) 5-(2-Formyl-3-hydroxyphenoxy)pentanoic acid:

5-(2-Formyl-3-methoxyphenoxy)pentanoic acid (504 mg, 0.002 M) was dissolved in anhydrous dichloromethane (20 ml) and cooled to -70°C. A solution of boron trichloride in anhydrous dichloromethane (0.25 g/ml, 3.76 ml) was added dropwise over 10 min and the mixture stirred at -70°C (15 min). The reaction mixture was allowed to reach ambient temperature and stirred at that temperature (1.25 hours). After cooling to 10°C, 10% sodium acetate solution (15 ml) was added dropwise with stirring so that the temperature did not rise above 15°C. The resulting mixture was diluted with ethyl acetate (50 ml) and filtered. The filtrate was transferred to a separating funnel and the aqueous layer separated. The organic phase was extracted with 10% sodium carbonate solution (2 x 50 ml), the combined extracts acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The combined extracts were washed with water, dried (sodium sulfate) and evaporated to give a crystalline solid. This solid was dissolved in the minimum of chloroform-methanol (95:5) and passed through a pad of Kieselgel G. Evaporation of the filtrate and recrystallization from benzene-petrol gave 5-(2-formyl-3-hydroxyphenoxy)pentanoic acid, melting point 97-99°C.

2nd method of preparation of 5-(2-formyl-3-hydroxyphenoxy)pentanoic acid:

(A) Ethyl 5-(2-formyl-3-benzyloxypheoxy)pentanoate:

A mixture of 2-hydroxy-6-benzyloxybenzaldehyde (3.0 g, 0.013 M), ethyl 5-bromopentanoate (2.75 g, 0.013 M), anhydrous potassium carbonate (2.16 g, 0.0156 M), sodium iodide (0.195 g) and dry dimethylformamide (15 ml) were stirred at 60-80°C for 3 hours and then left to stir at room temperature overnight. The mixture was then poured into water (50 ml) and the product extracted with ether (2 x 80 ml) and the combined extracts washed with 10% aqueous sodium hydroxide (2 x 20 ml) and then with water to neutrality, dried, and evaporated to give ethyl 5-(2-formyl-3-benzyloxyphenoxy)pentanoate, (4.0 g, 86%) as a pale yellow oil.

(B) 5-(2-Formyl-3-benzyloxyphenoxy)pentanoic acid:

A mixture of ethyl 5-(2-formyl-3-benzyloxyphenoxy)pentanoate (3.61 g, 0.01 M), potassium hydroxide (1.19 g, 0.021 M) and ethanol (40 ml) were stirred at 50°-60°C for 5 hours. The ethanol was then removed in vacuum, the residue dissolved in water (50 ml) and the solution extracted with ether (2 x 80 ml). The aqueous layer was then acidified by the addition of 2 N aqueous hydrochloric acid and the product extracted with ether, and the combined extracts washed with water to neutrality, dried, and concentrated in vacuum to give 5-(2-formyl-3-benzyloxyphenoxy)pentanoic acid, 3.0 g, 91% as a yellow oil which crystallized on standing. The crude solid was crystallized from benzene/petroleum ether to give pale cream crystals, melting point 110°C.

(C) 5-(2-Formyl-3-hydroxyphenoxy)pentanoic acid:

A solution of 5-(2-formyl-3-benzyloxyphenoxy)pentanoic acid (1.0 g, 0.003 M) in ethanol containing 5% palladium on charcoal catalyst (0.61 g) was hydrogenated at atmospheric pressure. After 20 min the reaction was complete and the catalyst was filtered off and the ethanol removed in vacuum to give 5-(2-formyl-3-hydroxyphenoxy)pentanoic acid, m.p. 94°C.

3rd method of preparation of 5-(2-formyl-3-hydroxyphenoxy)pentanoic acid:

(A) Ethyl 5-(2-formyl-3-methoxyphenoxy)pentanoate:

2-Hydroxy-6-methoxybenzaldehyde (26.0 g, 0.17 M), ethyl 5-bromopentanoate (27.1 ml, 0.17 M), anhydrous potassium carbonate (25.4 g), sodium iodide (1.04 g) and ethanol (230 ml) were refluxed with stirring for 16 hours. The cooled reaction mixture was filtered and the solid washed well with ethanol. The filtrate was evaporated to dryness and the residue partitioned between ether (200 ml) and water (200 ml). The organic layer was separated and washed with 2 N sodium hydroxide solution, water, brine, dried (magnesium sulfate) and evaporated to yield ethyl 5-(2-formyl-3-methoxyphenoxy)pentanoate 32.97 g, 67% yield, as a pale yellow oil that solidified on standing in the refrigerator.

(B) 5-(2-Formyl-3-hydroxyphenoxy)pentanoic acid:

10 ml of a solution of iodine (40.3 g, 0.157 M) in ether (sodium dry, 500 ml) was added to a stirred mixture of magnesium metal (15.4 g, 0.636 GATOM) and ether (50 ml). When the reaction had commenced the remainder of the iodine solution was added dropwise at such a rate as to cause gentle refluxing. After the addition was complete the reaction mixture was heated to reflux until a colorless solution was obtained (1/2 hour). The cooled reaction mixture was filtered and the unreacted magnesium metal was washed with ether (100 ml). The colorless solution of magnesium iodide thus obtained was added dropwise to a solution of ethyl 5-(2-formyl-3-methoxyphenoxy)pentanoate (30.0 g, 0.106 M) in tetrahydrofuran (dried over molecular sieve, 300 ml) at such a rate as to cause gentle refluxing. A fine yellow precipitate dropped out of solution. The mixture was brought to reflux with stirring for 5 hours. The cooled reaction mixture was poured into 10% hydrochloric acid (400 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic phases, containing ethyl 5-(2-formyl-3-hydroxyphenoxy)pentanoate, were washed with water and then extracted into 2 N sodium hydroxide solution. The combined aqueous extracts were acidified with concentrated hydrochloric acid with ice-cooling. The precipitate was filtered, washed with water, sucked dry and then quickly washed with a petrol/ethanol mixture (6:1, 60 ml) to remove some of the color. The crude product was dried in a desiccator over phosphorus pentoxide to give a dark-peach colored solid which was then dissolved in ethyl acetate (250 ml); aluminum oxide (neutral, 10 g) and charcoal (5.0 g) were added and the mixture stirred vigorously for 1/2 hour and then filtered to give a pale-yellow solution. The solvent was removed in vacuum to give 5-(2-formyl-3-hydroxyphenoxy)pentanoic acid, melting point 98-99°C (from ethyl acetate/petrol).

References

Kneen Geoffrey; US Patent No. 4,410,537; October 18, 1983; Assigned to Burroughts Wellcome Co. (Research Triangle Park, NC)

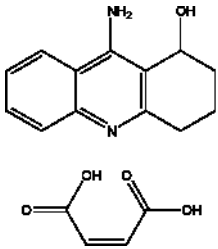
VELNACRINE MALEATE

Therapeutic Function: Cholinesterase inhibitor, Cognition activator

Chemical Name: 1-Acridinol, 9-amino-1,2,3,4-tetrahydro-, maleate (1:1)

Common Name: Velnacrine maleate

Structural Formula:



Chemical Abstracts Registry No.: 118909-22-1

Trade Name	Manufacturer	Country	Year Introduced
Velnacrine maleate	Hoechst-Roussel (Aventis)	-	-
SM 10.888	Sumitimo JPN	-	-

Raw Materials

9-Amino-3,4-dihydroacridin-1(2)-one
Lithium aluminum hydride
Potassium hydroxide
Hydrochloric acid

Manufacturing Process

In 100 ml of tetrahydrofuran was added 5.00 g of 9-amino-3,4-dihydroacridin-1(2)-one. The mechanically stirred suspension was cooled to -5°C and 21.4 ml (1 eq.) of 1.1 M $LiAlH_4$ solution in ether was added dropwise. After completion of the addition, the reaction mixture was stirred further for 2 hours, whereupon the reaction complete based on thin chromatography analysis. The $LiAlH_4$ was neutralized with 2 ml of saturated NH_4Cl and the salts were dissolved with 30% potassium hydroxide. The insoluble product was filtered off and rinsed with water. The precipitate was then dissolved in 3 N hydrochloric acid and the residual insoluble salts filtered off. The acid solution washed with ethyl acetate and made basic (pH 9) with 10% sodium hydroxide. The precipitated product was filtered and washed with water. After drying at 80°C under vacuum overnight, 4.15 g (82%) of (+/-)-9-amino-1,2,3,4-tetrahydro-1-acridinol was obtained, melting point 245°C. (+/-)-9-Amino-1,2,3,4-tetrahydro-1-acridinol maleate has melting point 171-173°C.

References

Shutske G.M., Pierrat F.A.; US Patent No. 4,631,286; Dec. 23, 1986; Assigned to Hoechst-Roussel Pharmaceuticals Inc., Somernille, N.J.

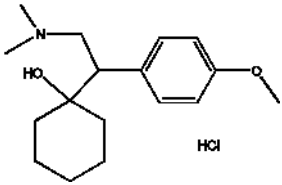
VENLAFAXINE HYDROCHLORIDE

Therapeutic Function: Antidepressant

Chemical Name: Cyclohexanol, 1-(2-(dimethylamino)-1-(4-methoxyphenyl)ethyl)-, hydrochloride

Common Name: Venlafaxine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 99300-78-4

Trade Name	Manufacturer	Country	Year Introduced
Efectin	Wyeth Medica Ireland	Ireland	-
Effexor	Wyeth-Ayerst Laboratories	-	-
Effexor XR	Southwood Pharmaceuticals Inc.	-	-
Trevilor	Wyeth	Germany	-

Raw Materials

p-Methoxyphenylacetonitrile
Cyclohexanone
Formaldehyde
Butyl lithium
Rhodium on alumina
Mallinckrodt Silicar CC7

Manufacturing Process

1-[Cyano(-methoxyphenyl)methyl]cyclohexanol

p-Methoxyphenylacetonitrile (50 gm, 0.3 mole) was added to dry tetrahydrofuran (250 ml) and the solution cooled to -70°C under nitrogen. n-Butyl lithium in hexane (210 ml, 0.3 mole) was added dropwise, with stirring. The temperature was maintained below -50°C and a yellow precipitate appeared. After the addition was complete, the reaction mixture was maintained below -50°C for 30 minutes and cyclohexanone (35 ml, 0.3 mole)

was added. After a further 45 minutes below -50°C the temperature was allowed to rise to 0°C and a saturated ammonium chloride solution was added. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulfate and evaporated. The product crystallized (25.2 gm, melting point 125°-127°C). The structure was confirmed by N.M.R. and mass spectral analysis.

1-[2-Amino-1-(p-methoxyphenyl)ethyl]cyclohexanol

1-[Cyano(p-methoxyphenyl)methyl]cyclohexanol (12 g, 0.05 mole) was dissolved on warming in a mixture of ammonia-ethanol (20% v/v, 250 ml) and hydrogenated in a Parr apparatus over 5% rhodium an alumina (2.8 gm). The catalyst was filtered, washed well with ethanol and the combined filtrate evaporated and dried under vacuum yielding an oil (12 gm). Thin layer chromatography: single spot, ninhydrin positive [chloroform-methanol-acetic acid (80:10:10 v/v)].

1-[-2-Dimethyl-amino)-1-(4-methoxyphenyl)-ethyl]cyclohexanol

1-[2-Amino-1-(p-methoxyphenyl)ethyl]cyclohexanol (12 gm; 0.048 mole) was treated with a mixture of formaldehyde (11 ml), formic acid (14.5 ml, 88%) and water (125 ml) and heated at 100°C for five hours. The reaction mixture was cooled and extracted with ethyl acetate. This extract was discarded. The aqueous residue was cooled in ice, rendered basic by the addition of solid potassium hydroxide, saturated with sodium chloride and extracted 3 times with ethyl acetate. The extract was washed with brine, dried over anhydrous potassium carbonate and evaporated to an oily residue (8 gm). This mixture of products was chromatographed on 1 kg of Mallinckrodt Silicar CC7 silica gel and the progress of the chromatography was monitored by thin layer chromatrography using a system comprising ethanol:2 N ammonia:ethyl acetate:cyclohexane 45:8:100:100 (v/v). Fractions containing the desired product were combined and the hydrochloride salt prepared using 4 N HCl in isopropanol. The yield of the free base was 4.6 gm of 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol. The hydrochloride (venlafaxine): melting point 215°-217°C. The structure was confirmed by mass spectral analysis and N.M.R. analysis.

References

Husband et al.; US Patent No. 4,761,501; Aug. 2, 1988; Assigned to American Home Products Corporation, New York, N.Y.

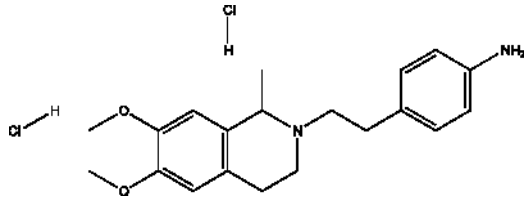
VERADOLINE HYDROCHLORIDE

Therapeutic Function: Analgesic

Chemical Name: (+/-)-2-(p-Aminophenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline dihydrochloride

Common Name: Veradoline hydrochloride

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Veradoline Hydrochloride	JINGTIAN PORTLINK Co., Ltd.	-	-

Chemical Abstracts Registry No.: 76448-47-0

Raw Materials

Triethylamine	2-(3,4-Dimethoxyphenyl)ethylamine
Acetyl chloride	Phosphorusoxychloride
Cyclohexane	Sodium borohydride
Palladium on carbon	Benzeneacetic acid, 4-nitro-
Borane	Dicyclohexylcarbodiimide

Manufacturing Process

Synthesis of N-(4-aminophenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline:

N-Acetyl-3,4-dimethoxyphenethylamine:

To a stirred solution of β-(3,4-dimethoxyphenyl)-ethylamine (100 g, 0.552 m) and triethylamine (66.6 g, 0,66 m) in $CHCl_3$ (1 liter) was added acetyl chloride (47.1 g, 0.60 mole) dropwise over a period of 30 min and the mixture stirred overnight. The mixture was washed with 3x500 ml H_2O, dried over $MgSO_4$ and evaporated to a solid. The solid was dissolved in 500 ml hot CCl_4, 300 ml cyclohexane added and allowed to cool slowly. The crystallized solid was collected by filtration and dried to afford N-acetyl-3,4-dimethoxyphenethylamine as a white solid, 112.1 g (91% yield). MP: 99-100°C.

3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline hydrochloride:

To a stirred solution of N-acetyl-3,4-dimethoxyphenethylamine (112.1 g, 0.502 m) in toluene (600 ml) maintained at 90-95°C was added dropwise phosphorusoxychloride (180.9 g, 112 ml, 1.179 mole) over a period of 1 hour. The mixture was heated to reflux for 2 hr, cooled to ambient temperature, and the solid hydrochloride salt collected by filtration, 170.4 g (wet with toluene). MP: (after drying) 202-203°C.

1,2,3,4-Tetrahydro-6,7-dimethoxy-l-methylisoquinoline:

To a stirred solution of 3,4-dihydro-6,7-dimethoxy-1-methylisoquioline hydrochloride (47.0 g, 0.229 m) and NaOH (5 g) in absolute methanol (500 ml) was added $NaBH_4$ (34.6g, 0.917 m) and the mixture stirred for 2 hr (TLC complete) and allowed to stand overnight. The mixture was cooled in an ice bath, treated carefully with 20% HCl until pH 1 was achieved and then heated to 500 for 1 hr. The solvent was then removed on the aspirator and the residue dissolved in 1 liter H_2O.The solution was basified to pH 11 with NaOH (20%) and extracted with 3 x 250 ml $CHCl_3$. The extracts were dried over $MgSO_4$ and evaporated to give 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline as an oil, 47.6 g (100% yield).

Alternative method:

A solution of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline hydrochloride (58.4 g, 0.24 m) in 1 liter of methanol and 5% Pd/C (5 g) were combined under nitrogen in a pressure bottle and the mixture hydrogenated at 40 psi and ambient temperature on a Parr apparatus for 18 hr. The catalyst was removed by filtration and the solvent evaporated. The residue was dissolved in H_2O (1 liter), basified to pH 11 with 50% NaOH and extracted with $CHCl_3$, (3x300 ml). The extracts were dried over $MgSO_4$ and evaporated to dryness (aspirator, then high vacuum) to give 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline, 35.2 g (70% yield).

N-(4-nitrophenylacetyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline:

To a stirred solution of 1,2,3,4-tetrahydro 6,7-dimethoxy-1-methyl-isoquinoline (35.2 g, 0.17 m) in methylene chloride (50 ml) under nitrogen at ambient temperature was added p-nitrophenylacetic acid (31.4 g,0.17 m) and then portionwise dicyclohexylcarbodiimide (37.0 g, 0.18 m) and the mixture stirred for 3 hr. The precipitated solid was removed by filtration and the filtrate evaporated to an oily residue. The residue was treated with 500 ml methanol and the solid precipitate collected by filtration to give, after drying, N-(4 nitro-phenylacetyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline as a yellow solid, 66.0 g (100% yield). The product contains a small amount of dicyclohexylurea.

The N-(4-aminophenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline may be obtained by either Method A or Method B:

Method A:

N-(4-Nitrophenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline N-(4-Nitrophenylacetyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline (62.9 g, 0.17 m) was added portion-wise to 500 ml of 1 M borane in THF which was diluted with 500 ml THF and maintained under nitrogen. The mixture was stirred at ambient temperature for 1 hr then heated to reflux for 4 hr. The mixture was then cooled in an ice bath and treated carefully with 20% HCl (250 ml). The mixture was refluxed for 1 hr, cooled and then the solvents evaporated on an aspirator. Water (1 liter) was added and the solution basified to pH 11 with 50% NaOH, then extracted with $CHCl_3$ (3 x 300 ml).

The extracts were dried over $MgSO_4$ and evaporated to an oily residue. The residue was dissolved in 300 ml of 1:1 methanol:isopropanol and treated with HCl gas until acidic. Upon cooling, a yellow solid was obtained which was collected by filtration and air dried to give 66.4 g (100%) N-(4-nitrophenethyl)-1,2,3,4-tetrahydro-1-methylisoquinoline hydrochloride. The product was slightly wet with isopropanol.

N-(4-Aminophenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline:

A solution of N-(4-nitrophenethyl)-1,2,3,4-tetrahydro-7,8-dimethoxy-1-methylisoquinoline hydrochloride (66.3 g, 0.17 m) in methanol (1 liter) and water (10 ml) was placed in an 1100 ml pressure bottle and 5% Pd/C catalyst (5.0 g) added under nitrogen. The mixture was hydrogenated at 40 psi in a Parr apparatus for 20 hr. The catalyst was removed by filtration and the solvent evaporated leaving an oily residue. The residue was dissolved in 95% ethanol (300 ml) and after 24 hr a solid had crystallized out which was collected by filtration and air dried giving 44.3 g (82%) of N-(4-aminophenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline monohydrochloride. The free base could be obtained by basifying a solution of this salt with NaOH and extracting with $CHCl_3$. Evaporation of the solvent and crystallization of the resulting oil from cyclohexane gives the base in 80% efficiency as a white solid. MP: 102-103°C on drying at 600 for 26 hr under high vacuum.

Method B:

N-(4-Aminophenylacetyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline:

A solution of N-(4-nitrophenylacetyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline (38.3 g, 0.1035 m) in a mixture of methanol (500 ml), ethylacetate (500 ml) and conc. HCl (8 ml) in a pressure bottle was treated with 5.0 g 5% Pd/C catalyst under nitrogen and the mixture hydrogenated on a Parr apparatus at 50 psi for 4 hr. The catalyst was removed by filtration and the solvent evaporated to a solid residue. The solid was dissolved in water (2 liters), filtered, then basified to pH with 50% NaOH. Extraction with $CHCl_3$ (3 x 250 ml) and evaporation of the extracts gave N-(4-aminophenylacetyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline as an off-white solid, 30.4 g (85% yield).

N-(4-Aminophenethyl)-1,2,3,4-tetrahydro-6,7-diemethoxy-1-methylisoquinoline:

N-(4-Aminophenylacetyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline (30.4 g, 0.0894 m) was added in small portions to a stirred solution of 1.0 M borane in THF (1-9 ml, 0.199 m) and the mixture stirred for 1 hr, then heated to reflux for 4 hr. The mixture was cooled with an ice bath and treated with THF (100 ml), then 10% HCl (200 ml). The mixture was refluxed for 1 hr, treated with an additional 100 ml 10% HCl, then the solvent removed on a rotary evaporator at 60°C. The residue was dissolved in water (1 liter) basified to pH 11 with 50% NaOH and extracted with $CHCl_3$ (3 x 200 ml), the extracts dried over $MgSO_4$, then evaporated to dryness. 100 ml

ether was added and then evaporated leaving a solid residue which was air dried to provide 21.4 g (74% yield) of N-(4-aminophenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline, MP: 102-103°C.

References

Devidson T.A. et al.; European Patent No. 0,051,190; October 10, 1981

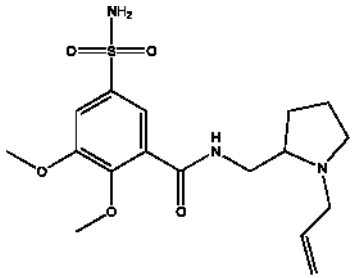
VERALIPRIDE

Therapeutic Function: Menopause treatment

Chemical Name: N-(1'-Allyl-2'-pyrrolidylmethyl)-2,3-dimethoxy-5-sulfamoylbenzamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 66644-81-3

Trade Name	Manufacturer	Country	Year Introduced
Agreal	Delagrange	France	1980
Agradil	Vita	Italy	1982
Veralipral	Finadiet	Argentina	-

Raw Materials

2,3-Dimethoxy-5-sulfamoylbenzoic acid
Carbonyldiimidazole
1-Allyl-2-aminomethylpyrrolidine

Manufacturing Process

7.8 g (0.03 mol) of 2,3-dimethoxy-5-sulfamoylbenzoic acid, 200 ml of tetrahydrofuran and 7.3 g (0.045 mol) of carbonyldimidazole are placed in a 500 ml flask fitted with an agitator, a thermometer and a condenser.

The mixture is agitated for 30 minutes at normal temperature, then 6.7 g (0.948 mol) of 1-allyl-2-aminomethylpyrrolidine is added. The mixture is left under agitation for 5 hours at 20°C, then the solvent is evaporated under vacuum and the residue treated with 150 ml of water. The crystals are washed and dried.

6.9 g of N-(1'-allyl-2'-pyrrolidyl-methyl)-2,3-dimethoxy-5-sulfamoyl-benzamide is obtained. Yield is 60%; melting point 113°C to 114°C.

References

Merck Index 9745
DFU 6 (1) 46 (1981)
DOT 17 (3) 96 (1981)
I.N. p. 1003
Thominet, M.L. and Perrot, J.; British Patent 1,539,319; January 31, 1979; assigned to Societe d'Etudes Scientifiques et Industrielles de I'Ile-de-France

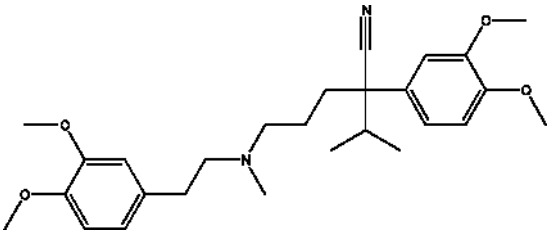
VERAPAMIL

Therapeutic Function: Coronary vasodilator, Antiarrhythmic

Chemical Name: α-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl)benzeneacetonitrile

Common Name: Iproveratril

Structural Formula:



Chemical Abstracts Registry No.: 52-53-9; 152-11-4 (Hydrochloride salt)

Trade Name	Manufacturer	Country	Year Introduced
Isoptin	Knoll	W. Germany	1963
Isoptin	Knoll	Italy	1965
Isoptin	Knoll	Switz.	1965
Cordilox	Abbott	UK	1967
Isopine	Biosedra	France	1969
Calan	Searle	US	1981
Isoptin	Knoll	US	1981

Trade Name	Manufacturer	Country	Year Introduced
Cardibeltin	Pharma-Schwarz	W. Germany	-
Dilacoran	Knoll	W. Germany	-
Ikacor	Ikapharm	Israel	-
Manidon	Medinsa	Spain	-
Vasolan	Eisai	Japan	-
Veramil	Yurtoglu	Turkey	-
Verpamil	Erco	Denmark	-

Raw Materials

Veratryl cyanide
Sodium amide (N-Methyl-N-homoveratryl)-γ-aminochloropropane
Isopropyl bromide

Manufacturing Process

177.2 g (1 mol) of veratryl cyanide are dissolved in 1 liter of toluene in a three-neck flask. 42.9 g (1.1 mols) of pulverized sodium amide are added. The mixture is heated to boiling under reflux for one hour while stirring and excluding moisture. A solution of the base (N-methyl-N-homoveratryl)-γ-aminochloropropane, freshly prepared from 339.2 g (1.1 mols) of the hydrochloride, in 1.2 liters of toluene is added drop by drop into this boiling mixture within two hours while stirring vigorously. Heating and stirring are continued for four more hours. After cooling, the reaction mixture is poured into 3 liters of ice water while stirring, The mixture is acidified with 20% hydrochloric acid. The acidified aqueous layer is separated, neutralized by the addition of sodium hydroxide solution, and rendered alkaline by the addition of concentrated potassium carbonate solution. The precipitated oily base is taken up in benzene. On evaporating the solvent, 402 g of the crude base are obtained in the form of a reddish-brown, viscous oil.

The crude base is dissolved in a mixture of 550 ml of isopropanol and 650 ml of ethyl acetate; Gaseous hydrogen chloride is introduced into the solution until it is of weakly acidic reaction. On allowing the mixture to stand at 0°C, 365 g of α-[(N-methyl-N-homoveratryl)-γ-amino-propyl]-3,4-dimethoxyphenyl acetonitrile hydrochloride precipitate as a slightly yellowish crystal powder of the melting point 136°C to 139°C (corr.). Yield: 81% of the theoretical yield. The pure, white hydrochloride melting at 140°C to 142°C (corr.) is obtained on recrystallizing the crude salt twice from isopropanol with the addition of decolorizing carbon. The salt is very soluble in water. The base prepared from the hydrochloride in the form of an almost colorless, very viscous oil boils at 233°C to 235°C/0.01 mm Hg; nD25= 1.5532. Dioxalate, melting point: 123°C to 125°C (corr.), on recrystallization from acetone and isopropanol.

61.9 g (0.15 mol) of α-[(N-methyl-N-homoveratryl)-γ-aminopropyl]-3,4-dimethoxyphenyl acetonitrile are dissolved in 300 ml of toluene. The solution is heated to boiling under reflux with 8.5 g (1.45 x 0.15 mols) of pulverized sodium amide for one hour while stirring. Thereafter, a solution of 31.4 g (1.7 x 0.15 mols) of isopropyl bromide in 50 ml of toluene is added drop by drop thereto within 90 minutes and the mixture is kept boiling for four more hours while stirring. The cooled reaction mixture is allowed to run into 1.5 liters of ice water and the mixture is acidified with 20% hydrochloric acid. The

aqueous layer is separated and is rendered alkaline by the addition of a solution of potassium carbonate. The base is taken up in warm benzene. The solvent is evaporated and the residue is distilled in a vacuum. 62.6 g of α-isopropyl-α-[(N-methyl-N-homoveratryl)-γ-aminopropy]-3,4-dimethoxyphenyl acetonitrile are obtained in the form of a light yellow, very viscous oil. Boiling point: 232°C to 235°C/0.01 mm Hg; n_D^{25} = 1.5460. Yield: 91.8% of the theoretical yield. Hydrochloride: melting point: 139.5°C to 140.5°C (corr.), on recrystallization from a mixture of isopropanol and ethyl acetate.

References

Merck Index 9747
Kleeman and Engel p. 940
PDR pp. 979, 1664, 1678
I.N. p. 1003
REM p. 862
Dengel, F.; US Patent 3,261,859; July 19, 1966; assigned to Knoll A.G. Chemische Fabriken (Germany)

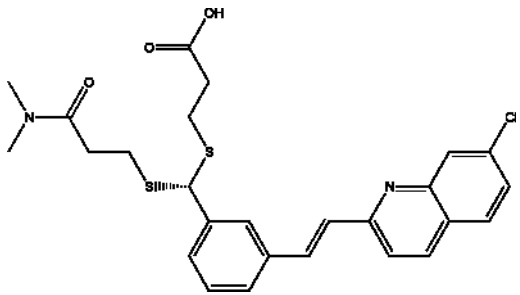
VERLUKAST

Therapeutic Function: Anti-asthmatic, Antiallergic

Chemical Name: [R-(E)]-3-[[[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propanoic acid

Common Name: Verlukast; L 668019; MK-679; Venzair

Structural Formula:



Chemical Abstracts Registry No.: 120443-16-5

Trade Name	Manufacturer	Country	Year Introduced
Verlukast	Merck Frosst (Merck and Co.)	-	-

Raw Materials

7-Chloroquinaldine
N-Bromosuccinimide

Benzoyl peroxide	Triphenylphosphine
Isophthalaldehyde	Methyl 3-mercaptopropanoate
Trimethylsilyl chloride	Butyl lithium
Trimethylaluminum	Dimethylamine
Lithium hydroxide	1,2-Dimethoxyethane

Manufacturing Process

5-(3-(2-(7-Chloroquinolin-2-yl)ethenyl)phenyl)-8-dimethylcarbamyl-4,6-dithiaoctanoic acid was prepared in 7 steps:

Step 1: Preparation of 2-bromomethyl-7-chloroquinoline:

A solution of 7-chloroquinaldine (177 g, 1 mole) N-bromosuccinimide (178 g, 1 mole), benzoylperoxide (1 g) in 2 L CCl_4 were heated at reflux for 2 days under a sun lamp. The reaction mixture was cooled, and passed through a plug of SiO_2 (approx. 1 Kg) using toluene as eluent. Chromatography on 2 x 1 kg SiO_2 columns using toluene as eluent afforded 110-120 g of the title compound, MP: 112°C.

Step 2: Preparation of (7-chloroquinolin-2-yl)-methyltriphenylphosphonium bromide:

To a suspension of 2-bromomethyl-7-chloroquinoline (120 g, 0.5 mol) in 800 ml of CH_3CN at 60°C was added triphenylphosphine (183 g). The reaction mixture was heated overnight at 60°C, cooled and 400 ml ether was added. The solid was filtered and dried to yield 170 g phosphonium salt.

Step 3: Preparation of dimethyl 5-(3-formylphenyl)-4,6-dithianonanedioate:

To a solution of isophthalaldehyde (40 g, 0.3 mol.) in chloroform (400 ml) and methyl 3-mercaptopropanoate (68 ml, 0.6 mol) was added dropwise trimethylsilyl chloride (48 ml, 0.38 mol) over 30 min. The reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched with 25% aq. NH_4OAc, extracted with ethyl acetate, dried and evaporated. Flash chromatography of the residue afforded 50 g of the title compound.

Step 4: Preparation of dimethyl 5-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-4,6-dithianonanedioate:

To a suspension of 190 g phosphonium salt from Step 2 (0.36 mol.) in THF (2 L) at -78°C were added 1.6 M BuLi (220 ml) dropwise over 1.5 hrs. The resulting brown suspension was stirred 30 min at -78°C. To the suspension was added the aldehyde (Step 3) (11.7 g, 0.32 mol.) in THF (400 ml) dropwise over 1.5 hrs. The reaction mixture was allowed to warm to room temperature and quenched with pH 7 buffer (approx. 2 L). Ethyl acetate (1 L) was added. The organic phase was separated, dried and evaporated. Flash chromatography of the residue using 30% ethyl acetate hexane; followed by crystallization with 3:1 hexane/ether afforded 135 g of the title compound as a white solid. MP: 53°C.

Step 5: Preparation of methyl 5-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-

8-dimethylcarbamyl-4,6-dithiaoctanoate:

A solution of the aluminum reagent was prepared by adding dropwise 150 ml of 2 M trimethylaluminum in hexane at -20°C to a solution of 2 M dimethylamine in toluene (300 ml). The solution was allowed to warm to room temperature. To the diester (step 4) (95 g) in CH_2Cl_2 (1 L) was added dropwise 150 ml of the aluminum reagent. The reaction was stirred 7-8 hrs at room temperature. The reaction was carefully quenched at 0°C with 2 N HCl (until the vigorous reaction subsided); then pH 7 buffer (25% NH_4OAc in H_2O) (1 L) and CH_2Cl_2 (1 L) were added. The organic phase was separated, dried and evaporated. Flash chromatography of the residue using first 50% ethyl acetate hexane followed by ethyl acetate afforded 38 g recovered di-ester and 38 g desired amide. The recovered di-ester was recycled through the sequence to give 18 g di-ester and 14 g desired amide. Total yield: 52 g of amide.

Step 6: Preparation of 5-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-8-dimethylcarbamyl-4,6-dithiaoctanoic acid:

To the amide (30 g) in 800 ml 1,2-dimethoxyethane (DME) was added 1.5 eq 1 N LiOH (75 ml). The reaction mixture was stirred one hour under N_2. The DME was evaporated. The residue was partitioned between H_2O (500 ml) and ethyl acetate (1 L). The aqueous phase was reextracted with ethyl acetate (500 ml). The aqueous phase was acidified with AcOH and a little 2 N HCl to pH 4 and extracted with ethyl acetate (2 x 600 ml). The organic phase was dried and evaporated. The residue was co-evaporated with toluene (300 ml) and triturated with cold ethyl acetate to give 18 g of the acid. MP: 153-155°C. Recrystallization from 2-butanone gave MP: 157-158°C.

References

Young R.N. et al.; European Patent No. 0,233,763 A2; February 13, 1987

VEROFYLLINE

Therapeutic Function: Bronchodilator, Anti-asthmatic

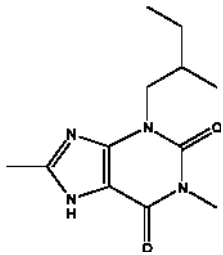
Chemical Name: (+/-)-3,7-Dihydro-1,8-dimethyl-3-(2-methylbutyl)-1H-purine-2,6-dione

Common Name: Verofylline

Chemical Abstracts Registry No.: 66172-75-6

Trade Name	Manufacturer	Country	Year Introduced
Verofylline	Berlex Labs	-	-

Structural Formula:



Raw Materials

2-Methyl-1-butylamine	Methyl isocyanate
Cyanoacetic acid	Acetic anhydride
Sodium nitrite	Sodium dithionite

Manufacturing Process

Synthesis of 1,8-dimethyl-3-(2-methyl-1-butyl)xanthine included 7 steps:

1). 1-Methyl-3-(2-methyl-1-butyl)urea:

1.03 kg (11.8 mole) of 2-methyl-1-butylamine was added to 4.5 L of chloroform and the solution cooled to 0-5°C. Then 674.0 g (11.8 mole) of methyl isocyanate was added slowly while maintaining the temperature at 0.5°C. After the addition was complete the reaction was allowed to reach room temperature. Stirring was continued for 18 hours. The chloroform was removed under vacuum to yield 1.7 kg of 1-methyl-3-(2-methyl-1-butyl)urea as an oil. Yield 100%.

2). 1-Methyl-1-cyanoacetyl-3-(2-methyl-1-butyl)urea:

To 1.7 kg (11.8 mole) of 1-methyl-3-(2-methyl-1-butyl)urea were added 4.3 L of methyl isocyanate and 1.18 kg (13.9 mole) of cyanoacetic acid. This was heated for 2 hours at 60-70°C. The acetic anhydride was removed under vacuum to yield 2.9 kg of oil. This material is a mixture of cyanoacetic acid and 1-methyl-1-cyanoacetyl-3-(2-methyl-1-butyl)urea. No attempt was made at purification; the crude oil was used immediately in the next step.

3). 1-Amino-1-methyl-3-(2-methyl-1-butyl)uracil:

10.3 L of 10% NaOH solution was slowly added to 2.9 kg (11.8 mole) of crude 1-methyl-1-cyanoacetyl-3-(2-methyl-1-butyl)urea with stirring. The oil dissolved and shortly another oil precipitated. The temperature rose to about 60°C and then dropped. After stirring for a while at room temperature the oil crystallized. After cooling the product was filtered. The crude product was slurred in water and dried at 50°C in vacuum to yield 2.1 kg of 4-amino-1-methyl-3-(2-methyl-1-butyl)uracil. MP: 121-124°C. Yield 85%.

4). 4-Amino-5-nitroso-1-methyl-3-(2-methyl-1-butyl)uracil:

21 kg (9.9 mole) of 4-amino-1-methyl-3-(2-methyl-1-butyl)uracil was suspended in 22.0 L of water. A solution of 745.5 g (10.8 mole) of sodium nitrite in 5.7 L of water was added to the suspension. Then 1.2 L of glacial acetic acid was added dropwise and the suspension was stirred for 18 hours at room temperature. After cooling the precipitate was filtered. The crude product was slurred in water and dried at 80°C in vacuum to yield 1.9 kg of 4-amino-5-nitroso-1-methyl-3-(2-methyl-1-butyl)uracil. MP: 202-204°C. Yield 80%.

5). 4,5-Diamino-1-methyl-3-(2-methyl-1-butyl)uracil:

8.65 L of conc. ammonium hydroxide (58%) was added to 1.9 kg (7.9 mole) of 4-amino-5-nitroso-1-methyl-3-(2-methyl-1-butyl)uracil. An orange salt formed. The suspension was placed in an oil bath at 80-90°C and a solution resulted. 5.6 kg (32.3 mole) of sodium dithionite was added in portions over about 30 min. When the addition was complete stirring was continued for 30 min. The reaction was allowed to cool to room temperature and stirred overnight. After cooling the precipitate was filtered, slurred with water and dried at 80°C in vacuum to yield 1.25 kg of 4,5-diamino-1-methyl-3-(2-methyl-1-butyl)uracil. MP: 161-163°C. Yield 70%.

6). 4-Amino-5-acetylamino-1-methyl-3-(2-methyl-1-butyl)uracil:

1.25 kg (5.5 mole) of 4,5-diamino-1-methyl-3-(2-methyl-1-butyl)uracil was added to 4.5 L of glacial acetic acid and heated to reflux for 2 hours. The acetic acid was evaporated and the residue triturated with ether. The solid was filtered and dried at 60°C in vacuum to yield 1.26 kg of 4-amino-5-acetylamino-1-methyl-3-(2-methyl-1-butyl)uracil. MP: 178-182°C. Yield 85%.

7). 1,8-Dimethyl-3-(2-methyl-1-butyl)xanthine:

1.26 kg (4.7 mole) of 4-amino-5-acetylamino-1-methyl-3-(2-methyl-1-butyl)uracil was added to 3.9 L of 10% sodium hydroxide solution and heated at reflux for 30 min. The solution was filtered and the filtrate cooled to room temperature. The pH of the filtrate was adjusted to 5.0 with glacial acetic acid. After cooling the precipitate was filtered. The crude product was slurred twice with water and dried at 80°C in vacuum to yield about 1.0 kg of 1,8-dimethyl-3-(2-methyl-1-butyl)xanthine. MP: 189-191°C. Yield 85%.

References

G.B. Patent No. 1,561,005; February 13, 1980; Cooper laboratoties, INC., New Jersey USA

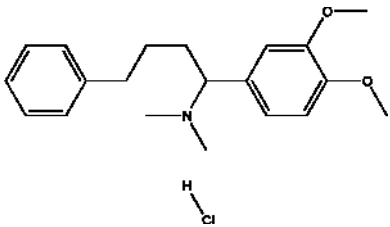
VETRABUTINE HYDROCHLORIDE

Therapeutic Function: Uterine relaxant

Chemical Name: Benzenebutanamine, α-(3,4-dimethoxyphenyl)-N,N-dimethyl- hydrochloride

Common Name: Dimephebumine; Profenveramine hydrochloride; Revatrine hydrochloride; Vetrabutine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 3735-45-3 (Base); 5974-09-4

Trade Name	Manufacturer	Country	Year Introduced
Monzal	Boenhringer Ingelheim	-	-
Monzaldon	Boenhringer Ingelheim	-	-

Raw Materials

Magnesium
3-Phenylpropyl bromide
(3,4-Dimethoxyphenyl)dimethylaminoacetonitrile

Manufacturing Process

1.5 mole magnesium and 1 mole 3-phenylpropyl bromide were used for preparing of ester solution of Grignar reagent. 1 mole (3,4-dimethoxyphenyl)dimethylaminoacetonitrile in absolute ester was added to above reagent dropwise. Then the mixture was heated for 3 hours to reflux. On cooling it was poured into ice with 12% hydrochloric acid. The ester layer was separated. The water layer was alkalized with concentrate ammonia and ammonium chloride. The precipitated oil was dissolved in ester, dried over sodium sulfate and distilled in vacuum after removing of ester to give α-(3,4-dimethoxyphenyl)-N,N-dimethylbenzenebutanamine (vertabutine); BP: 166°-168°C/0.1 mm Hg. Yield 85%. The free base may be turn into colorless hydrochloride by adding of equivalent of hydrochloric acid in ester; MP: 146°-148°C.

References

Seeger E., Kottler A.; D.B. Patent No. 963,424; Sept. 24, 1954; Dr. Karl Thomae Gesellschaft mit beschranker Haftung Bierach/Ris

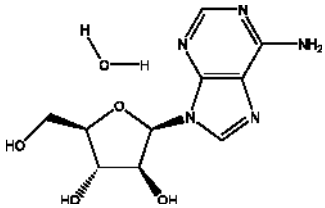
VIDARABINE

Therapeutic Function: Antiviral

Chemical Name: 9-β-D-Arabinofuranosyl-9H-purine-6-amine monohydrate

Common Name: Adenine arabinoside; Spongoadenosine

Structural Formula:



Chemical Abstracts Registry No.: 5536-17-4

Trade Name	Manufacturer	Country	Year Introduced
Vidarabin	Thilo	W. Germany	1975
Vira-A	Parke Davis	UK	1977
Vira-A	Parke Davis	US	1977
Vira-A	Substantia	France	1981

Raw Materials

Bacterium Streptomyces antibioticus
Nutrient medium

Manufacturing Process

Sterile agar slants are prepared using the Streptomyces sporulation medium of Hickey and Tresner, J. Bact., vol. 64, pages 891-892 (1952). Four of these slants are inoculated with lyophilized spores of Streptomyces antibioticus NRRL 3238, incubated at 28°C for 7 days or until aerial spore growth is well-advanced, and then stored at 5°C. The spores from the four slants are suspended in 40 ml of 0.1% sterile sodium heptadecyl sulfate solution. A nutrient medium having the following composition is then prepared: 2.0% glucose monohydrate; 1.0% soybean meal, solvent extracted, 44% protein; 0.5% animal peptone (Wilson's protopeptone 159); 0.2% ammonium chloride; 0.5% sodium chloride; 0.25% calcium carbonate; and water to make 100%.

The pH of the medium is adjusted with 10-normal sodium hydroxide solution to pH 7.5. 12 liters of this medium is placed in a 30-liter stainless steel fermenter. The medium is sterilized by heating it at 121°C for 90 minutes, allowed to cool, inoculated with the 40 ml spore suspension described above, and incubated at 25° to 27°C for 32 hours while being agitated at 200 rpm with air being supplied at the rate of 12 liters per minute. About 38 grams of a mixture of lard and mineral oils containing mono-and diglycerides is added in portions during this time to prevent excessive foaming.

16 liters of a nutrient medium having the composition described above is placed in each of four 30-liter stainless steel fermenters. The pH of the

medium in each fermenter is adjusted with 10-normal sodium hydroxide solution to pH 7.5, and each is sterilized by heating at 121°C for 90 minutes. Upon cooling, the medium in each fermenter is inoculated with 800 ml of the fermentation mixture described above, and each is incubated at 25° to 27°C for 96 hours while being agitated at 200 rpm with air being supplied at the rate of 16 liters per minute. About 170 grams of the antifoam mixture described above is added in portions during this time to the medium in each fermenter.

The fermentation mixtures from the four fermenters are combined and filtered with the aid of diatomaceous earth, A material such as Celite 545 can be used. The filtrate is concentrated under reduced pressure to a volume of 10 liters, and the concentrate is treated with 200 grams of activated charcoal (for example, Darco G-60), stirred at room temperature for one hour, and filtered. The charcoal cake is washed with 7.5 liters of water, and then extracted with three 10-liter portions of 50% aqueous acetone. The three aqueous acetone extracts are combined, concentrated under reduced pressure to approximately one liter, and chilled at 5°C for 48 hours. The solid 9-(β-D-arabinofuranosyl)adenine that precipitates is isolated and purified by successive crystallizations from boiling methanol and from boiling water; MP 262° to 263°C.

In the foregoing procedure, when the temperature of incubation in the two fermentation stages is raised from 25° to 27°C to 36° to 38°C, the same 9-(β-D-arabinofuranosyl)adenine product is obtained in higher yields.

References

Merck Index 9779
DFU 7 (8) 588 (1982)
PDR p. 1395
DOT 13 (9) 387 (1977)
I.N. p. 1006
REM p. 1232
Parke, Davis and Company; British Patent 1,159,290; July 23, 1969

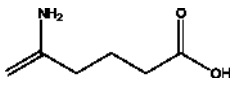
VIGABATRIN

Therapeutic Function: Antiepileptic

Chemical Name: 5-Hexenoic acid, 4-amino-

Common Name: γ-vinyl-GABA; Vigabatrin

Structural Formula:



Chemical Abstracts Registry No.: 60643-86-9

Trade Name	Manufacturer	Country	Year Introduced
Sabril	Hoechst Marion Roussel	-	-
Sabril	Aventis Pharma	-	-
Vigabatrin	Hoechst Marion Roussel	-	-

Raw Materials

Erythritol
Propionic acid
Trichloroacetonitrile
Formic acid
Triethylorthoacetate
Sodium hydride

Manufacturing Process

Step A: 4-Formyloxy-3-hydroxy-1-butene

A solution of erythritol (50 g, 0.5 mole) in aqueous formic acid (150 g, 75%) was heated above 100°C, 12 hours, then water and formic acid were distilled off and the reaction mixture was heated above 200°C with a Bunsen burner. The product was collected by distillation (b.p. 230°C, 30 g) and should be rectified (b.p. 90°C, 15 mm).

Step B: Ethyl 6-formyloxy-4-hexanoate

A solution of 4-formyloxy-3-hydroxy-1-butene (1.06 g, 10 mmol) and propionic acid (1 drop) in triethylorthoacetate (6 g, 40 mmol) was heated at 140°C under conditions for distillative removal of ethanol. After 2 hours, the excess of ethylorthoacetate was removed by distillation in vacuo. The residue was hydrolysed with water and extracted with AcOEt. The product was purified by flash chromatography on SiO_2 (eluant AcOEt:hexane, 2:8) (1 g, 60%) but distillative purification is preferred when larger quantities are involved.

Step C: Ethyl 6-hydroxy-4-hexanoate

A solution of 6-formyloxy-6-hexanoate (0.9 g, 5 mmol) in absolute EtOH (10 mL) containing few drops of a saturated solution of alcoholic HCl gas was left 2 hours at 20°C. The solvent was removed in vacuo and the residue was used for the next step without further purification (0.7 g, quantitative). This compound was found to be partially decomposed by flash chromatography on SiO_2.

Step D: Ethyl 4-trichloroacetamido-5-hexanoate

Sodium hydride (0.03 g of a 50% dispersion in oil, 0.5 mmol, was added to a solution of ethyl 6-hydroxy-4-hexanoate (0.7 g, 5 mmol) and trichloroacetonitrile (0.6 g, 5 mmol) in anhydrous ether (50 mL) under N2at0°C. After 1hour, ethanol (0.5 mmol) was added and the solvent was removed in vacuo. The formation of the imidate was controlled by NMR (NH, about.8.5 ppm). A solution of the crude imidate in xylene (30 mL) was heated at reflux 48 hours. Then the solvent was removed in vacuo and the residue was purified by flash chromatography on SiO_2 (eluant AcOEt:hexane, 2:8) to

give the title product (1.1 g, about 70%). A sample was distilled for analysis (b.p. 150°C, 0.5 mm Hg).

Step E: 4-Amino-5-hexenoic acid

A suspension of ethyl 4-trichloroacetoamido-5-hexanoate (0.3 g, 1 mmol) in 6 N HCl (10 mL) was heated under reflux 6 hours. Then the mixture was concentrated in vacuo, diluted with water (10 mL), washed twice with AcOEt, and dried in uacuo to give the title product (0.18 g, 100%). NMR, TLC (NH_4OH:EtOH, 3:7) are identical with those of an authentic sample of 4-amino-5-hexenoic acid.

References

Casara P.; US Patent No. 5,380,936; Jan. 10, 1995; Assigned to Merrell Dow Pharmaceuticals Inc., Cincinnati, Ohio

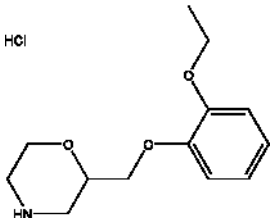
VILOXAZINE HYDROCHLORIDE

Therapeutic Function: Psychotropic

Chemical Name: 2-[(2-Ethoxyphenoxy)methyl]morpholine hydrochloride

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 35604-67-2; 46817-91-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Vivalan	I.C.I.	UK	1974
Vivalan	I.C.I.	France	1977
Vivalan	I.C. Pharma	Italy	1977
Vivalan	I.C.I.	W. Germany	1978
Emovit	Farmakhim	Bulgaria	-
Vicilan	I.C.I.	Japan	-
Viloksan	Dif-Dogu	Turkey	-

Raw Materials

2-Ethoxyphenol
Epichlorohydrin
2-Aminoethyl hydrogen sulfate

Manufacturing Process

2-Ethoxyphenol is first reacted with epichlorohydrin to give 1,2-epoxy-3-(o-ethoxyphenoxy)-propane.

A mixture of crude (83%) 1,2-epoxy-3-(o-ethoxyphenoxy)propane (19.4 grams), 70.5 grams 2-aminoethyl hydrogen sulfate, 40.0 grams sodium hydroxide, 400 ml ethanol and 200 ml water is stirred at 60°C for 18 hours and is then evaporated to dryness. The residue is dissolved in 200 ml water and the mixture is extracted three times with 150 ml of diethyl ether each time. The combined extracts are dried over magnesium sulfate and evaporated to dryness, The crude product (21.5 grams) is dissolved in isopropanol (20 ml), 10.5 ml concentrated aqueous hydrochloric acid and 75 ml ethyl acetate are added and the mixture is cooled. The mixture is filtered and there is thus obtained as solid product 2-(o-ethoxyphenoxymethyl) morpholine hydrochloride, MP 179° to 182°C (8.6 grams; 38% yield based on total epoxide used), according to US Patent 3,712,890.

References

Merck Index 9781
Kleeman and Engel p. 941
OCDS Vol. 2 p. 306 (1980) and 3, 32 (1984)
DOT 11 (2) 72 (1975)
I.N. p. 1007
Lee, SA.; US Patent 3,712,890; January 23,1973; assigned to Imperial Chemical Industries Limited, England
Mallion, K.B., Turner, R.W. and Todd, A.H.; US Patent 3,714,161; January 30,1973; assigned to Imperial Chemical Industries Limited, England

VIMINOL

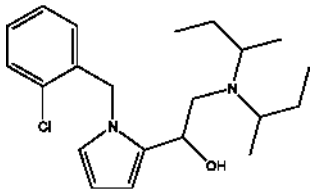
Therapeutic Function: Analgesic

Chemical Name: α-[[Bis(1-methylpropyl)amino]methyl]-1-[(2-chlorophenyl)methyl]-1H-pyrrole-2-methanol

Common Name: Diviminol

Chemical Abstracts Registry No.: 21363-18-8

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Dividol	Zambon	Italy	1974
Lenigesial	Inpharzam	W. Germany	1978

Raw Materials

1-(o-Chloro)-benzyl-2-di-sec-butylaminoacetyl-pyrrole
Lithium aluminum hydride

Manufacturing Process

10 g (0.0278 mol) of 1-(o-chloro)-benzyl-2-di-sec-butylaminoacetyl-pyrrole and 300 ml of anhydrous diethyl ether are placed in a 500 ml four-necked flask with a mercury-sealed stirrer, a thermometer, a dropping funnel and a reflux condenser topped with a tube containing anhydrous calcium chloride. The solution is stirred and a mixture of 1g (0.0264 mol) of lithium aluminum hydride in 20 ml of diethyl ether is added slowly through the dropping funnel at such a rate that the solvent refluxes gently without external heating. When the addition is complete and the initial reaction subsides, the mixture is stirred and heated at gentle reflux for two hours.

The mixture is cooled and the excess of lithium aluminum hydride is decomposed with cracked ice. The water layer is separated and washed with diethyl ether. The combined ether extracts are dried over anhydrous magnesium sulfate and the solvent is removed by distillation under reduced pressure. Yield, 8.8 g; boiling point, 160°C to 165°C/0.1 mm Hg.

References

Merck Index 9782
Kleeman and Engel p. 942
DOT 10 (3) 101 (1974)
I.N. p. 1007
Teotino, U.M. and Della Bella, D.; US Patent 3,539,589; November 10, 1970; assigned to Whitefin Holding S.A. (Switz.)

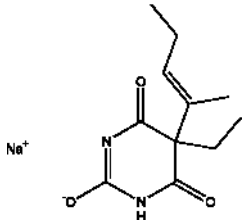
VINBARBITAL SODIUM

Therapeutic Function: Sedative

Chemical Name: 5-Ethyl-5-(1-methyl-1-butenyl)-2,4,6-(1H,3H,5H)-pyrimidinetrione sodium salt

Common Name:

Structural Formula:



Chemical Abstracts Registry No.: 125-44-0

Trade Name	Manufacturer	Country	Year Introduced
Delvinal	MSD	US	1943

Raw Materials

Ethyl (1-methyl-δ(1)-butenyl)cyanoacetic acid ethyl ester
Sodium
Ethanol
Urea

Manufacturing Process

6.9 parts of sodium are dissolved in 100 parts of absolute ethyl alcohol in a vessel provided with a reflux condenser. After the sodium is dissolved, 9.6 parts of urea and 20.9 parts of the ethyl ester of ethyl (1-methyl-δ_1-butenyl)cyanoacetic acid are added. The mixture is refluxed for twelve hours, after which the alcohol is removed by vacuum distillation and the residue is dissolved in 100 parts of water. The resulting solution is extracted with ether in three successive 25 part portions. The nitrile which is formed as a by-product from the cyanoacetate used is recovered from the ether extract by washing with water, evaporating the ether and distilling. The combined water solutions containing 5-ethyl-5-(1-methyl-δ_1-butenyl)-4-imino barbituric acid, are acidified until acid to Congo red with concentrated hydrochloric acid, after which the mixture is transferred, if necessary, to another vessel, and an equal volume of concentrated hydrochloric acid is added. The solution is then refluxed for one hour to hydrolyze the imino compound. The 5-ethyl-5-(1-methyl-δ_1-butenyl)barbituric acid crystallizes out on cooling. It is filtered and washed with two 25 part portions of ice water. By this process, 8 parts of the crude product (35% yield) have been obtained. After two crystallizations from 50% alcohol, the yield of the purified product is 6.5 parts (29%). The product melts at 160°C to 162°C.

The sodium salt of 5-ethyl-5-(1-methyl-δ_1-butenyl)barbituric acid is prepared by dissolving 23 parts of sodium in 350 parts of absolute alcohol in a vessel

provided with a reflux condenser containing a drying tube, and adding the resulting solution to a solution of 224 parts of 5-ethyl-5-(1-methyl-δ_1-butenyl)barbituric acid dissolved in 300 to 400 parts of absolute alcohol. The resulting solution is concentrated in vacuo, with heating on a warm water bath. About 200 parts of dry benzene are then added and the mixture is again concentrated, If this evaporation is carried out to an extent such that all of the solvent is removed, no further washing is required. If all of the solvent is not removed by evaporation, the residue is washed with dry ether. The resulting sodium salt is then dried in an oven at 90°C and then is dried in vacuo (2 mm) at 78°C. The yield is 97% to 99%.

References

Merck Index 9783
OCDS Vol. 1 p. 269 (1977)
I.N. p. 1007
Cope, A.C.; US Patent 2,187,703; January 16, 1940; assigned to Sharp and Dohme, Inc.

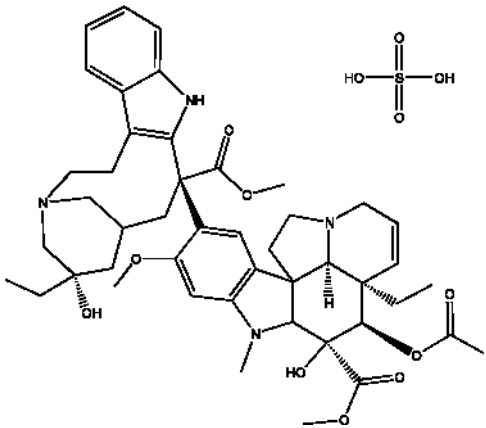
VINBLASTINE SULFATE

Therapeutic Function: Cancer chemotherapy

Chemical Name: Vincaleukoblastine sulfate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 143-67-9; 865-21-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Velban	Lilly	US	1961
Velbe	Lilly	UK	1961
Velbe	Lilly	France	1963
Velbe	Lilly	Italy	1965
Blastovin	Teva	Israel	-
Exal	Shionogi	Japan	-
Periblastine	Petersen	S. Africa	-

Raw Materials

Vinca rosea plants
Benzene
Sulfuric acid

Manufacturing Process

According to US Patent 3,225,030, 1,500 grams of dried ground plant of Vinca rosea were intimately mixed with 1,000 ml of a 2% tartaric acid solution, and the mixture was extracted with three 9-liter portions of benzene. The benzene extracts were combined and were concentrated in vacuo to about 1,500 ml. The concentrate was mixed with 1 liter of 2% tartaric acid and the mixture was steam-distilled under reduced pressure until all of the benzene had distilled over. The insoluble residue was dissolved in hot methanol, a second 1-liter portion of 2% tartaric acid solution was added, and the mixture was steam-distilled under reduced pressure until all of the methanol had distilled.

The undistilled aqueous tartaric acid solution was extracted with three 1-liter portions of ethylene dichloride, and was then brought to a pH of about 8.5 to 9.5 by the addition of 28% aqueous ammonium hydroxide. The ammoniacal solution was extracted with three 1-liter portions of ethylene dichloride; the ethylene dichloride extracts were combined, were dried, and were evaporated in vacuo, yielding a residue of 3.35 grams of a light-brown powder.

1 1/2 grams of the residue were dissolved in 10 ml of benzene, and the solution was passed over a chromatographic adsorption column containing 50 grams of alumina (Alcoa activated alumina, Grade F-20) which had previously been shaken for about 20 minutes with a mixture of 100 ml of benzene containing 1.5 ml of 10% acetic acid.

The column was developed by washing it with 2,100 ml of benzene. The column was then washed sequentially with 300 ml of benzene-chloroform solvent (95:5 by volume) and 800 milliliters of benzene-chloroform solvent (75:25) to remove indeterminate impurities. The leurosine was eluted from the alumina by passing over the column 900 ml of benzene chloroform solvent (50:50).

The eluate was evaporated to dryness in vacuo, leaving an amorphous residue of 113 mg of leurosine. The residue was treated with a few ml of methanol in which it quickly dissolved, but from which leurosine quickly precipitated in crystalline form. Because of the affinity of leurosine for water, and the presence of traces of water in the solvents, the leurosine was obtained in the form of its octahydrate. Although the material as obtained was substantially

pure, it was further purified by recrystallizing it from hot methanol solution. The hydrated leurosine obtained decomposed at about 200° to 205°C.

Further elution of the above chromatographic column with a 50:50 benzene-chloroform solvent mixture or with a 25:75 benzene-chloroform solvent mixture serves to elute vincaleukoblastine. Vincaleukoblastine also occurs in the latter fractions containing leurosine. Vincaleukoblastine is obtained from vincaleukoblastine-containing fractions by evaporation to dryness, either of a filtrate from which leurosine has previously been isolated, or from a chromatographic eluate fraction. The resulting residue is dissolved in ethanol and 286 ethanolic sulfuric acid is added until the pH is lowered to about 4. The solution is seeded with crystals of vincaleukoblastine sulfate and is chilled for about 24 hours. Vincaleukoblastine sulfate, if present, precipitates during this period and can be separated by filtration. Vincaleukoblastine sulfate melts at about 284° to 285°C.

References

Merck Index 9784
Kleeman and Engel p. 943
PDR p. 1072; DOT 16 (5)169 (1980)
I.N. p. 1007
REM p. 1154
Beer, C.T., Cutts, J.H. and Noble, R.L.; US Patent 3,097,137; July 9,1963; assigned to Canadian Patents and Development, Ltd., Canada
Svoboda, G.H.; US Patent 3,225,030; December 21, 1965; assigned to Eli Lilly and Co.

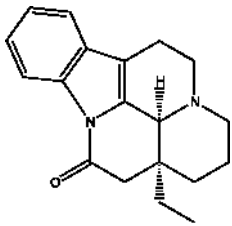
VINBURNINE

Therapeutic Function: Cerebrotonic

Chemical Name: (3α,16α)-Eburnamenin-14(15H)-one

Common Name: (-)-Eburnamonine; Vinburnine; Vincamon

Structural Formula:



Chemical Abstracts Registry No.: 4880-88-0

Trade Name	Manufacturer	Country	Year Introduced
Euburnamonine	Shanghai Lansheng Corporation	-	-
Atrican	Montpellier	-	-
Cervoxan	Pharmapharm	-	-
Cervoxan	Almirall	-	-
Cervoxan	SmithKline	-	-
Cervoxan	COVEX	-	-
Eburnal	Chiesi	-	-
Eburnal	COVEX	-	-
Eburnoxin	Astra	-	-
Scleramin	Ibirn	-	-
Tensiplex	Francia Farm	-	-
Zedec	Zambeletti	-	-
Scleramin	Ibirn	-	-

Raw Materials

cis-1-Ethyl-1-(2'-hydroxy-2'-carboxyethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine
Celite reagent, containing 50% of silver carbonate
Tartaric acid, dibenzoate, (-)-

Manufacturing Process

200 g (0.087 moles) of cis-1-ethyl-1-(2'-hydroxy-2'-carboxyethyl)-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-a]quinolizine were suspended in 100 ml of xylene. 12 g of supported silver carbonate (a silver carbonate-Celite reagent, containing 50% of silver carbonate) were added to the suspension, and the system was boiled for 8 hours under a nitrogen atmosphere, with constant stirring. Thereafter the hot solution was filtered, washed with 3 x 30 ml to 5% sodium carbonate solution, dried over magnesium sulfate, and evaporated under reduced pressure. 1.05 g of a solid residue, which was a mixture of racemic vincamone and racemic vincanol, was obtained. 40 ml of ethyl ether were added to the mixture, and the insoluble crystals were filtered off. The crystals were recrystallized from methanol, to yield 0.5 g of (+/-)-eburnamonine (vincamone). Yield: 29.5%. MP: 201°-202°C. The value was identical with the literature value (J. Mokry et al.: Coll. Czech, Chem. Comm. 28, 1309, 1963). The etheral mother liquor was processed by preparative layer chromatography (adsorbent: Kieselgel $PF_{254+366}$, developing agent: a 14:2 mixture of benzene and methanol). The obtained substance was recrystallized from ether to yield 0.2 g (16%) of (+/-)-vincanol (eburnamine). MP: 163-164°C, under decomposition. The IR spectrum of the obtained substance was identical with that of the authentic sample.

Resolution of (+/-)-vincamone:

10.0 g (0.0342 moles) of (+/-)-vincamone and 12.2 g (0.0342 moles) of (-)-dibenzoyl tartaric acid were dissolved in 150 ml of dichloromethane, the solution was seeded with crystalline (-)-vincamone-(-)-dibenzoyl-tartarate, and the mixture was left to stand. The separated crystals were filtered off, dissolved in dimethylformamide, and the pH of the solution was adjusted to 9

with aqueous ammonia. The separated substance was filtered off, washed with water, and dried. This way 4.2 g (84%) of (-)-vincamone were obtained; MP: -176°C; α_D^{20} = -96°. The mother liquor of resolution was evaporated and (+)-vincamone was separeted as described above. The obtained substance had MP: 173°-176°C.; α_D^{20} = +96°.

References

GB Patent No. 1,440,634; Dec. 7, 1973; Richter Gedeon Vegyeszeti Gyar RT., Hungary, Budapest

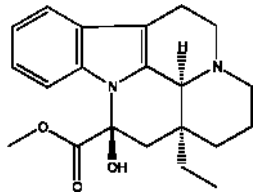
VINCAMINE

Therapeutic Function: Vasodilator

Chemical Name: 14,15-Dihydro-14-hydroxyeburnamenine-14-carboxylic acid methyl ester

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 1617-90-9

Trade Name	Manufacturer	Country	Year Introduced
Pervancamine	Dausse	France	1969
Vincadar	Roussel Maestretti	Italy	1974
Vincadil	Richter	Italy	1974
Vincapront	Mack	W. Germany	1976
Vincamin	A.G.M.	W. Germany	1976
Aethroma	Mepha	Switz.	-
Alfavinca	Alfar	Spain	-
Anasclerol	Fardeco	Italy	-
Artensen	Cusi	Spain	-
Arteriovinca	Farma-Lepori	Spain	-
Asnai	Durban	Spain	-
Ausomina	Ausonia	Italy	-
Branex	Galepharma Iberica	Spain	-
Centractiva	Larma	Spain	-
Cetal	Parke Davis	W. Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Cincuental	Nemi	Argentina	-
Equipur	Fresenius	W. Germany	-
Esberidin	Schaper and Brunner	W. Germany	-
Horusvin	Horus	Spain	-
Novicet	Schwarzhaupt	W. Germany	-
Oxygeron	Syntex-Pharm	Switz.	-
Perphal	Laphal	France	-
Pervone	Millot	France	-
Tripervan	Roger Bellon	France	-
Vasculogene	Negma	France	-
Vascumine	Pharma	France	-
Vinca	Millot	France	-
Vincabiomar	Biologia Marina	Spain	-
Vincabrain	Bouchara	France	-
Vincachron	Eurand	Italy	-
Vinca-Ecobi	Ecobi	Italy	-
Vincafarm	Radiumpharma	Italy	-
Vincafolina	Lampugnani	Italy	-
Vincafor	Clin-Comar-Byla	France	-
Vincagalup	Galup	Spain	-
Vincagil	Sarsa	Brazil	-
Vincahexal	Durachemie	W. Germany	-
Vincalen	Firma	Italy	-
Vincamidol	Magis	Italy	-
Vincanor	Theranol	France	-
Vinca-Tablinen	Sanorania	W. Germany	-

Raw Materials

Sodium hydride
Oxygen
Vincadiformine
Trimethylphosphite

Manufacturing Process

The following route is described in US Patent 4,145,552: At ambient temperature, over a period of thirty minutes, a solution of 33.8g (0.1mol) of (-)-vincadiformine in a mixture of 140 ml of anhydrous dimethylformamide and 140 ml of anhydrous toluene is added to a suspension of 2.64 g (0.11 mol) of sodium hydride in a mixture of 200 ml of anhydrous tetrahydrofuran, 20 ml of anhydrous hexamethylphosphotriamide (EMPT) and 18.7 ml (0.14 mol) of trimethyl phosphite. When the release of hydrogen has finished (about two hours later), the solution is cooled to -10°C and then stirred under an oxygen atmosphere until absorption ceases (duration: 3 hours). Still at -10°C, 136 ml of glacial acetic acid are added, and the mixture is then left at ambient temperature for two hours. After the addition of 500 ml of 1 N sulfuric acid, the aqueous phase is isolated, reextracted with 150 ml of isopropyl ether, made alkaline with 350 ml of 11 N ammonia, then extracted 3 times with 300 ml aliquots of methylene chloride. After drying over calcium

chloride and evaporating the solvent, 30.2 g of crude product are obtained which, when chromatographed on a column of silica gel (1.5 kg) yield, 9.9 g of vincamine (yield: 28%) melting point (decomp.): 250°C.

References

Merck Index 9785
Kleeman and Engel p. 944
I.N. p. 1008 Kuehne, M.E.; US Patent 3,454,583; July 8, 1969; assigned to US Secretary of Health, Education and Welfare
Heymes, A.; US Patent 4,145,552; March 20, 1979; assigned to Parcor (France)

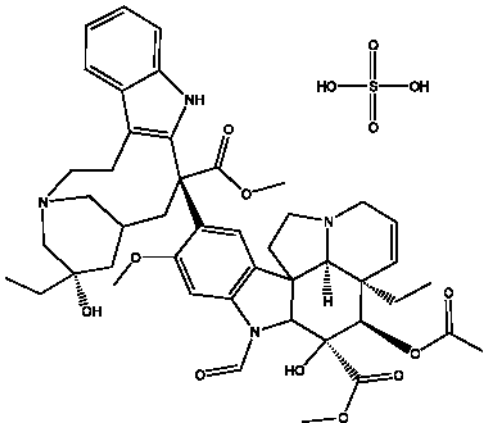
VINCRISTINE SULFATE

Therapeutic Function: Cancer chemotherapy

Chemical Name: Leurocristine sulfate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 2068-78-2; 57-22-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Oncovin	Lilly	US	1963
Oncovin	Lilly	France	1964
Vincristin	Lilly	W. Germany	1965
Vincristina	Lilly	Italy	1966
Oncovin	Lilly	UK	1966
Cristovin	Teva	Israel	-
Kyocristine	Kyorin	Japan	-

Trade Name	Manufacturer	Country	Year Introduced
Leucid	Leo	Sweden	-
Pericristine	Petersen	S. Africa	-
Vincosid	Leo	Sweden	-

Raw Materials

Vinca rosea plants
Benzene
Sulfuric acid

Manufacturing Process

The alkaloid mixture from the extraction of Vinca rosea plants (as in vinblastine extraction) was chromatographed to give vincristine which was then converted to the sulfate, according to US Patent 3,205,220.

Vincristine may also be prepared in a semisynthetic process starting from vinblastine. Vinblastine or a salt thereof, preferably the sulfate, is oxidized with chromic acid or with one of its salts at a low temperature, the reaction mixture is neutralized or rendered alkaline and the product is separated therefrom by extraction, the extract is evaporated to dryness, the dry residue is optionally formylated, vincristine, and optionally N-demethylvinblastine also, are isolated from the product, and the product(s) are optionally converted into their salts; preferably into the sulfates, according to US Patent 3,899,493.

References

Merck Index 9788
Kleeman and Engel p. 948
PDR p. 1066
DOT 16 (5) 173 (1980)
I.N. p. 1009
REM p. 1154
Svoboda, G.H., Barnes, A.J. Jr. and Armstrong, R.J.; US Patent 3,205,220; September 7, 1965; assigned to Eli Lilly and Co.
Jovanovics, K., Szasz, K., Fekete, G., Bittner, E., Dezseri, E. and Eles, J.; US Patent 3,899,493; August 12, 1975; assigned to Richter Gedeon Vegyeszeti Gyar R.T.

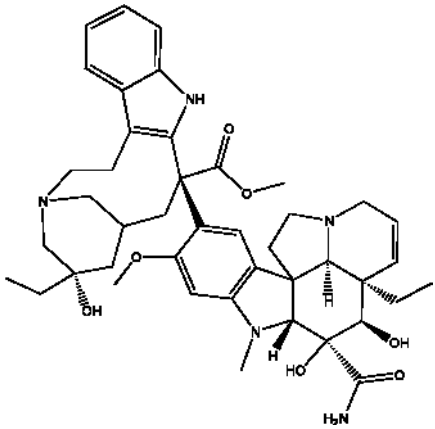
VINDESINE

Therapeutic Function: Antineoplastic

Chemical Name: 4-Desacetyl-vinblastine-C-3-carboxamide

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 53643-48-4

Trade Name	Manufacturer	Country	Year Introduced
Eldisine	Lilly	France	1980
Eldisine	Lilly	UK	1980
Eldisine	Lilly	W. Germany	1980
Eldisin	Serum Impfinst.	Switz.	1982

Raw Materials

Vinblastine
Ammonia

Manufacturing Process

About 10 g of VLB (vincaleucoblastine or simply vinblastine) sulfate were converted by standard procedures to VLB free base. The free base, obtained as a residue after evaporation of the dried ethereal solvent, was dissolved in about 200 ml of anhydrous methanol. Anhydrous liquid ammonia (300 ml) was added, and the reaction mixture sealed and maintained at about 100°C for 60 hours. The reaction vessel was opened, and the contents removed and evaporated to dryness in vacuo. The resulting residue, containing 4-desacetyl VLB C-3 carboxamide, as shown by thin layer chromatography, were combined and the solvent evaporated therefrom in vacuo, yielding asa residue purified 4-desacetyl VLB C-3 carboxamide free base. The NMR and IR spectra of the solid free base confirmed the structure indicated. The free base showed a band in the infrared at 1,687 cm^{-1}, characteristic of the amide function. The molecular weight of the free base determined by mass spectroscopy was 753 which is in agreement with theoretical value calculated for $C_{43}H_{55}N_5O_7$.

References

Merck Index 9789
DFU 3 (5) 401 (1978)

Kleeman and Engel p. 948
DOT 16 (5) 173 and (6) 198 (1980)
I.N. p. 1009
REM p. 1157
Cullinan, G.J. and Gerzon, K.; US Patent 4,203,898; May 20, 1980; assigned to Eli Lilly and Company

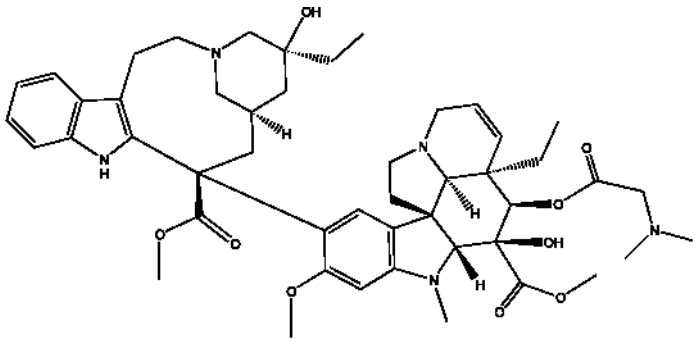
VINGLICINATE

Therapeutic Function: Antineoplastic

Chemical Name: 4'-Deacetylvincaleukoblastine 4-ester with N,N-dimethylglycine

Common Name: Vinglycinate

Structural Formula:



Chemical Abstracts Registry No.: 865-24-7

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

Raw Materials

Alkaloid from Vinca rosea (Catharanthus roseus) (Apocynaceae)
Desacetyl VLB chloroacetate
Dimethylamine

Manufacturing Process

N,N-Dimethyldesacetyl vincaleukoblastine (VLB) glycinate: Five hundred milligrams of desacetyl VLB chloroacetate (were dissolved in 10 ml of tetrahydrofuran. Four milliliters of a 25% solution of dimethylamine in tetrahydrofuran were added, and the resulting mixture was allowed to remain overnight at room temperature. A precipitate of dimethylamine hydrochloride, produced as a by-product of the reaction, was removed by filtration and the

filtrate, containing N,N-dimethyl desacetyl VLB glycinate, was evaporated to dryness in vacuum. Fifty milliliters of water were added to the residue, and the aqueous solution was made basic by the addition of an excess of 14 N ammonium hydroxide. N,N-dimethyl desacetyl VLB glycinate was insoluble in the alkaline layer and was extracted into methylene dichloride. The methylene dichloride layer was separated and dried, and the solvent removed by evaporation in vacuum. The residue, comprising N,N-dimethyl desacetyl VLB glycinate, was crystallized from ether. MP: 180-182°C (Et_2O-solvate). MP: 216°C (dry). Thin layer chromatography on alumina indicated that this product was pure and differed from the starting material. Infrared and nuclear magnetic resonance spectra of the crystalline material were obtained, and these spectral data were completely consistent with the assigned structure.

Crystalline N,N-dimethyl desacetyl VLB glycinate was dissolved in a mixture of methanol and water. The pH of the solution was adjusted to about 1.8 with 1% sulfuric acid. Evaporation of the resulting solution to dryness in vacuum yielded N,N-dimethyl desacetyl VLB glycinate sulfate as a residue. The residue was crystallized from a mixture of methanol and ethanol. MP: 284-285°C. Nuclear magnetic resonance and infrared spectra of sulfate salt were entirely consistent with the assigned structure.

References

Hargrove W.W.; US Patent No. 3,387,001; June 4, 1968; Assigned to Eli Lilly and Company, Indianapolis, Ind., a corporation of Indiana

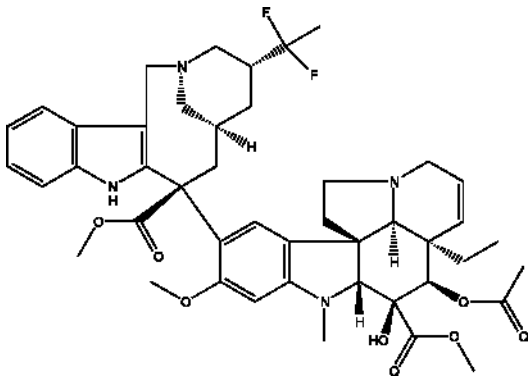
VINORELBINE

Therapeutic Function: Antineoplastic

Chemical Name: 3',4'-Didehydro-4'-deoxy-C'-norvincaleukoblastine

Common Name: Noranhydrovinblastine; Vinorelbine

Structural Formula:



Chemical Abstracts Registry No.: 71486-22-1

Trade Name	Manufacturer	Country	Year Introduced
VINBINE	Cadila Pharmaceuticals Ltd.	-	-
VINELBINE	Dabur Pharmaceuticals Ltd.	-	-
Vinorelbine	SK Energy and Chemical	-	-
Vinorelbine	China Pharm Chemical Co., Ltd.	-	-

Raw Materials

5-Ethyl-1,2,3,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester, (+/-)-
Tartaric acid, L-
Lithium bromide
N-Phenylsulfonyl indole
1,2-Dibromoethane
Trifluoroacetic acid
1-Chloroethyl chloroformate
Formaldehyde
Allyl bromide
Lithium aluminum hydride
Methanesulfonic acid
Magnesium
Sodium naphthalenide
Vindoline
Acetic acid
Triethylamine
Butyl lithium

Manufacturing Process

(+/-)-5-Ethyl-1,2,3,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester and (+)-tartaric acid were dissolved in hot 95% ethanol. The resulting solution was allowed to slowly cool to room temperature and refrigerated overnight. The crystals were filtered, washed with cold ethanol, and recrystallized from 95% ethanol, cooling as before to give the (+)-tartrate salt of (+)-5-ethyl-1,2,3,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester.

The salt of (+)-5-ethyl-1,2,3,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester was dissolved in on ice, and 3 N sodium hydroxide was slowly added until the pH reached 11-12. The solution was extracted with chloroform, dried (Na_2SO_4) and evaporated in vacuum to give (+)-5-ethyl-1,2,3,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester as a mobile oil.

Reduction of (+)-5-ethyl-1,2,3,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester with $LiAlH_4$ in THF, using the usual protocols associated with this reagent gave the (+)-5-ethyl-1,2,3,6-tetrahydro-pyridine-3-ol. This material was used directly in the next step.

To a solution of the (+)-5-ethyl-1,2,3,6-tetrahydro-pyridine-3-ol in ethanol and triethylamine water, cooled equiv.) was added allyl bromide and the mixture heated at reflux for 12 h. The mixture was evaporated in vacuo and the residue dissolved in chloroform and washed with 5% aqueous K_2CO_3. The chloroform layer was dried ($MgSO_4$) and evaporated in vacuo to give the (+)-1-allyl-5-ethyl-1,2,3,6-tetrahydro-pyridin-3-ol.

The (+)-1-allyl-5-ethyl-1,2,3,6-tetrahydro-pyridin-3-ol was converted into its methanesulfonate ester in the standard manner by treatment with methanesulfonic acid.

To a solution of the (+)-1-allyl-5-ethyl-1,2,3,6-tetrahydro-pyridin-3-

methanesulfonate in acetone was added lithium bromide (6.9 g, 0.08 mol) and the suspension heated at reflux. The acetone was evaporated in vacuo, and the residue partitioned between chloroform and cold aqueous 5% K_2CO_3 solution. The chloroform layer was dried ($MgSO_4$), filtered, and evaporated in vacuo to give a brown oil. Fractional distillation gave the (+)-1-allyl-5-ethyl-1,2,3,6-tetrahydro-pyridin-3-bromide.

To a solution of N-phenylsulfonyl indole (5.14 g, 20 mmol) in dry THF (100 ml) under argon, and cooled to -65°C., was added t-butyl lithium (13 ml, 22 mmol, 1.7 M in pentane). The solution was allowed to warm to 0°C and stirred for 1 h. The above solution was added via canula to a stirred solution of dimethyloxalate (9.5 g, 80 mmol) in THF (250 ml) at 0°C. After 4 h at 0°C the mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 times 100 ml). The dried ($MgSO_4$) extract was evaporated in vacuum, and the residue purified by chromatography over silica gel eluting with hexane/ethyl acetate (b 10:1) to give the N-phenylsulfonyl-2-methoxalyl indole (2.3 g, 34%). Melting point 111°-112°C (from ethyl acetate).

To the (+)-1-allyl-5-ethyl-1,2,3,6-tetrahydro-pyridin-3-bromide in a flame dried flask under argon was added Mg powder and dry THF. The mixture was heated at reflux and two drops of 1,2-dibromoethane added to initiate Grignard reagent formation. After 3 h the turbid suspension was cooled to room temperature and added to a solution of the N-phenylsulfonyl-2-methoxalyl indole in THF, at 0°C under argon. After 30 min the solution was quenched with saturated aqueous NH_4Cl solution, and diluted with ethyl acetate. The dried ($MgSO_4$) extract was evaporated in vacuo to give the (+)-methyl 2-[2-(N-phenylsulfonyl)indolyl]-2-hydroxy-3-[3-(N-allyl 5-ethyl-1,2,3,6-tetrahydro-peridine)]propionate consisting of a mixture of diastereomers at C-2 (1:1). For the purpose of characterization, one of the diastereomers was purified by chromatography over silica gel eluting with hexane/ethyl acetate/10% aqueous NH_4OH/MeOH (15:3:1) to give the (+)-methyl 2-[2-(N-phenylsulfonyl)indolyl]-2-hydroxy-3-[3-(N-allyl-5-ethyl-1,2,3,6-tetrahydro-pyridine)]propionate.

To a solution of the (+)-methyl 2-[2-(N-phenylsulfonyl)indolyl]-2-hydroxy-3-[3-(N-allyl-5-ethyl-1,2,3,6-tetrahydropyridine)]propionate (a mixture of diastereomers at C-2) in dry dimethoxyethane at -50°C under argon was added sodium naphthalenide (1 M in THF). The mixture was quenched with trifluoroacetic acid, and extracted with ethyl acetate (3 times 10 ml). The extract was washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated in vacuo to give the (+)-methyl 2-(2-indolyl)-2-hydroxy-3-[3-(N-allyl-5-ethyl-1,2,3,6-tetrahydro-pyridine)]propionate. The mixture of diastereomers was not separated but chromotagraphed over silica gel eluting with hexane/ethyl acetate/10% aqueous NH_4OH/MeOH (5:1:1) to remove more polar impurities.

A solution of the (+)-methyl 2-(2-indolyl)-2-hydroxy-3-[3-(N-allyl-5-ethyl-1,2,3,6-tetrahydro-pyridine)]propionate (mixture of diastereomers), and vindoline in 1% HCl/MeOH was heated at reflux for 2 h. The solution was evaporated in vacuo and the residue dissolved in chloroform and washed with saturated aqueous $NaHCO_3$ solution. The chloroform layer was dried over $MgSO_4$, filtered, and evaporated to give a foam consisting of a mixture of S-

and R-diastereomers. The diastereomeric mixture was separated by preparative HPLC eluting with hexane/CH_2Cl_2/MeOH/10% aqueous NH_4OH to give S-(+)-4-acethoxy-9-[2-(1-allyl-5-ethyl-1,2,3,6-tetrahydro-pyridin-3-yl)-1-(1H-indol-2-yl)-1-methoxycarbonyl-ethyl]-3a-ethyl-5-hydroxy-8-methoxy-6-methyl-3a,4,5,5a,6,11,12,12b-octahydro-1H-6,12a-diaza-indeno[7,1-ca]fluorene-5-carboxylic acid methyl ester.

The S-(+)-4-acethoxy-9-[2-(1-allyl-5-ethyl-1,2,3,6-tetrahydro-pyridin-3yl)-1-(1H-indol-2-yl)-1-methoxycarbonyl-ethyl]-3a-ethyl-5-hydroxy-8-methoxy-6-methyl-3a,4,5,5a,6,11,12,12b-octahydro-1H-6,12a-diaza-indeno[7,1-ca]fluorene-5-carboxylic acid methyl ester in 1,2-dichloroethane, containing proton sponge at 25°C, was treated with 1-chloroethyl chloroformate (0.056 ml, 0.512 mmol, 2.0 equiv.) and the resulting solution stirred for 3 h. The mixture was evaporated in vacuo, and the residue dissolved in methanol and heated at reflux for 3 h. The methanol was evaporated and the residue dissolved in chloroform and purified by chromatography over silica gel eluting with $CHCl_3$, MeOH, 10% aqueous NH_4OH (20:1) to give S-(+)-4-acethoxy-9-[2-(5-ethyl-1,2,3,6-tetrahydro-pyridin-3yl)-1-(1H-indol-2-yl)-1-methoxycarbonyl-ethyl]-3a-ethyl-5-hydroxy-8-methoxy-6-methyl-3a,4,5,5a,6,11,12,12b-octahydro-1H-6,12a-diaza-indeno[7,1-ca]fluorene-5-carboxylic acid methyl ester.

To a solution of the S-(+)-4-acethoxy-9-[2-(5-ethyl-1,2,3,6-tetrahydro-pyridin-3yl)-1-(1H-indol-2-yl)-1-methoxycarbonyl-ethyl]-3a-ethyl-5-hydroxy-8-methoxy-6-methyl-3a,4,5,5a,6,11,12,12b-octahydro-1H-6,12a-diaza-indeno[7,1-ca]fluorene-5-carboxylic acid methyl ester in dioxane and glacial acetic acid was added 37% aqueous formaldehyde and the mixture stirred at 35°C for 24 h. The solution was evaporated in vacuo and the residue suspended in chloroform and washed with cold aqueous 5% K_2CO_3 solution. The chloroform layer was dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed eluting with EtOAc/MeOH, 10% NH_4OH to give the product navelbine.

References

Magnus P.D., Thurston L.S.; US Patent No. 5,220,016; June 15, 1993; Assigned: Board of Regents, The University of Texas System, Austin, Tex.

Andriamialisoa R.Z. et al.; Tetrahedron, Vol. 36, p.3053-3060, 1980

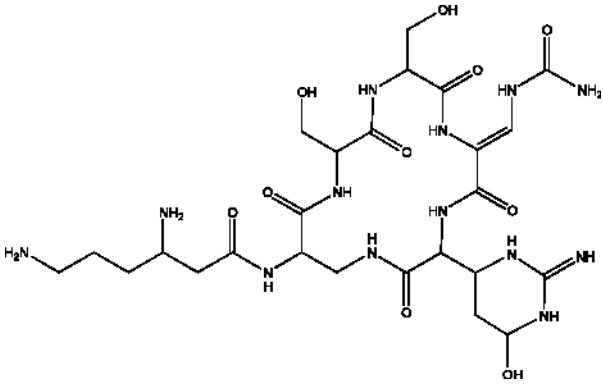
VIOMYCIN

Therapeutic Function: Antitubercular

Chemical Name: Viomycin

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 32988-50-4; 37883-00-4 (Sulfate)

Trade Name	Manufacturer	Country	Year Introduced
Vinactane	Ciba	US	1953
Viocin	Pfizer	US	1953
Panto-Viocine	Pfizer	France	-
Viomicin	Parke Davis Sankyo	Japan	-
Viomycin	Parke Davis	US	-
Viomycin Pfizer	Taito Pfizer	Japan	-

Raw Materials

Bacterium Actinomyces vinaceus
Nutrient medium

Manufacturing Process

Viomycin is produced by inoculating a nutrient medium with a viable strain of the organism Actinomyces vinaceus. A method for the production of viomycin is set forth in US Patent 2,663,445 comprising inoculating a medium containing soy peptone, beef extract, dextrose, sodium chloride and a silicone antifoaming agent with a spore suspension of Actinomyces vinaceus and incubating the inoculated medium for 120 hours at a temperature of 26°C while passing sterile air through the medium at a rate of 500 ml per liter of medium per minute.

References

Merck Index 9805
Kleeman and Engel p. 949
I.N. p. 1010
REM p. 1212 Marsh, W.S., Mayer, R.L., Mull, R.P., Scholz, C.R. and T ownley, R.W.; US Patent 2,633,445; March 31, 1953; assigned to Ciba Pharmaceutical Products, Inc.
Freaney, T.E.; US Patent 2,828,245; March 25, 1958; assigned to Commercial Solvents Corporation

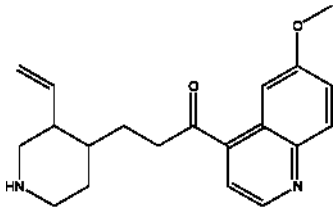
VIQUIDIL

Therapeutic Function: Vasodilator, Antiarrhythmic

Chemical Name: 3-(3-Ethenyl-4-piperidinyl)-1-(6-methoxy-4-quinolinyl)-1-propanone

Common Name: Quinotoxine; Mequiverine; Chinicine; Quinotoxol

Structural Formula:



Chemical Abstracts Registry No.: 84-55-9

Trade Name	Manufacturer	Country	Year Introduced
Desclidium	Spret	France	1972
Desclidium	Rorer	Italy	1973
Desclidium	Badische	W. Germany	1979
Chinotoxin	Badische	W. Germany	-
Permiran	Lab. Franc. Therap.	France	-

Raw Materials

Ethyl quininate
Sodium ethoxide
N-Benzoylhomomeroquinene ethyl ester
Hydrogen chloride

Manufacturing Process

2.70 g of N-benzoylhomomeroquinene ethyl ester (0.0086 mol) are mixed with 4.0 g of ethyl quininate (0.0173 mol = 100% excess). 1.4 g of absolutely dry pulverulent sodium ethoxide (0.0207 mol -140% excess, based on N-benzoylhomomeroquinene ethyl ester) is added, and the reaction mixture is heated to about 80°C with continuous stirring. As the ethyl quininate melts, and the materials become thoroughly mixed, the initial yellow color changes to brown and then gradually to deep red. The reaction mixture is maintained at about 82°C for fourteen hours with continuous stirring. It is then cooled, and the resulting very hard, dark red mass is decomposed with ice water and benzene. The (not entirely clear) combined aqueous layers are extracted with a small amount of ether. The clear, deep red, aqueous layer is then made just acid to litmus. The precipitated oil is taken up in ether. Evaporation of solvent, finally in vacuo, gives 2.56 g of a red glass. The combined benzene and ether extracts from above, containing largely neutral material, are extracted with 10% aqueous sodium hydroxide. The alkaline extract is made just acid to litmus, and extraction with ether followed by removal of solvent gives a further small quantity of β-ketoester, 0.16 g.

Total weight of N-benzoylquinotoxine carboxylic acid ethyl ester thus obtained was 2.72 g, equivalent to 63.4% of the theoretical.

2.72 g of N-benzoylquinotoxine carboxylic acid ethyl ester are dissolved in 30 cc of 1:1 aqueous hydrochloric acid (from 15 cc concentrated hydrochloric acid and 15 cc water). The clear, reddish-orange solution is then boiled under reflux for four hours. The very dark reddish-brown solution is extracted with ether (from this extract 0.50 g of benzoic acid is obtained on evaporation). The aqueous solution is then made strongly alkaline and extracted with ether. 0.23 g of ether-insoluble interface material is dissolved in benzene and set aside. Removal of solvent from the above ether extract gives 1.39 g of crude quinotoxine as a dark red viscous oil.

References

Merck Index 9808
DOT 8 (4) 156 (1972)
I.N. p. 1010
Woodward, R.B. and Doering, W.V.; US Patent 2,500,444; March 14, 1950; assigned to Polaroid Corp.

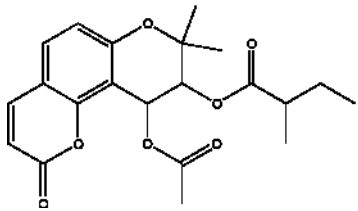
VISNADINE

Therapeutic Function: Coronary vasodilator

Chemical Name: 2-Methylbutyric acid 9-ester with 9,10-dihydro-9,10-dihydroxy-8,8-dimethyl-2H,8H-benzo[1,2-b:3,4-b']dipyran-2-one acetate

Common Name: -

Structural Formula:



Chemical Abstracts Registry No.: 477-32-7

Trade Name	Manufacturer	Country	Year Introduced
Vibeline	Bellon	France	1960
Carduben	Madaus	W. Germany	1968
Provismine	Bellon	France	-
Visnamine	Chinoin	Japan	-

Raw Materials

Ammi visnaga plants

Manufacturing Process

Ammi visnaga is a plant of the Umbelliferae family, which has been known and used for its therapeutic properties by the peoples of the Mediterranean basin since time immemorial.

Visnadine may be extracted from the umbels of Ammi visnaga by an organic solvent having a boiling point less than 110°C. The resulting solution is concentrated first by heating in a water bath and then is allowed to stand some time at a temperature of about 20°C and if necessary is treated for separation of gummy constituents therefrom, after which the solution is concentrated under reduced pressure. Finally, the crude product is crystallized and separated by retaining it on a filter.

This crude product may then, according to the process, be purified by mixing it with petroleum ether and allowing it to stand at ordinary temperature, then filtering it to obtain the pure visnadine.

References

Merck Index 9815
Kleeman and Engel p. 950
I.N. p. 1011
Le Men, J.G.; US Patent 2,995,574; August 8, 1961; assigned to Laboratoire Roger Bellon S.A. (France)

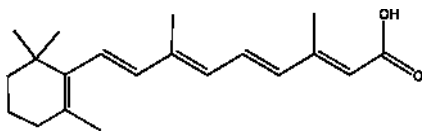
VITAMIN A

Therapeutic Function: Vitamin

Chemical Name: Retinol, all trans-

Common Name: Antixerophthalmic Vitamin; A-Vitamin; Axeroftolo; Axerophthol; Axerophthylium; Gadol; Oleovitamin A; Retinol; Vitamin A; Vitamin A_1; Xerophthol

Structural Formula:



Chemical Abstracts Registry No.: 68-26-8

Trade Name	Manufacturer	Country	Year Introduced
Acon	Endo	-	-
Audax	Faran	-	-
Vitamin A	Roche	Switz.	-
Vitamin A	Roche Vitamins	USA	-
Vitamin A	Vitec America Corp.	USA	-
Vitamin A	Sanavita	Germany	-
Vitamin A	Roche Vitamins	France	-
Vitamin A	BASF Corporation	USA	-
Vitamin A	Hoffmann - La Roche Inc.	USA	-

Raw Materials

Ethynyl-β-ionol
Dimethyl sulfoxide
Ethyl bromide
Copper chloride
Alumina (Alcoa F-20)
Palladium on calcium carbonate
Ethyl sulfate
Magnesium
Hexamethyl phosphoric triamide
1-Chloro-4-acetoxy-2-methyl-2-butene
Sodium amide

Manufacturing Process

Preparation of ethyl ether of ethynyl-β-ionol.

Ethynyl-beta-ionol has been converted to its lower alkyl ethers by use of alkyl sulfates, using an aprotic solvent such as dimethyl sulfoxide (DMSO) or dimethyl formamide (DMF) in a basic medium, using a base such as NaOH or $Ba(OH)_2$.The yields around 90%. In one example, the following components were used: ethynyl-β-ionol 65.7 g (0.3 mole); ethyl sulfate 138.6 g (0.9 mole) sodium hydroxide (97%) pellets 37.0 g (0.9 mole) dimethyl sulfoxide 200 ml.

The components were placed in a one liter, 3-neck flask equipped with a stirrer, thermometer and nitrogen inlet tube. The mixture was stirred gently with sufficient speed to move the pellets of NaOH about. Heat was slowly evolved. The temperature was maintained at about 35°C (33°-37°C). After 6 hours of stirring, a second liquid phase appeared and the reaction was stopped by decanting the liquids from the unreacted NaOH. At this point, about 5 to 10 grams of unreacted NaOH remained. The flask was washed with acetone and the washings added to the reaction product. To the mixture was then added 75 ml of concentrated aqueous NH_4OH and the whole allowed to stand overnight to destroy unreacted ethyl sulfate.

The following morning the mixture was poured into two liters of brine and the precipitated oil taken up in hexane. The aqueous layer was re-extracted once with more hexane. The combined hexane extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under vacuum to an oil. This oil was then distilled through a 10 inch jacketed Vigreaux column at 0.1 mm pressure. The following fractions were obtained: Fraction I 70°-71°C/0.1 mm - 9 g; n_D^{20} 1.4834. Fraction II 71°C/0.1 mm - 58.3 g. n_D^{20} 1.4880; Fraction III 71°-72°C/0.1 mm - 7.6 g. n_D^{20} 1.4898. The infrared spectrum analysis of the main fraction II showed no free hydroxyl group. The

ultraviolet spectrum analysis showed only a single maximum λ_m236 mμ, characteristic of the β-ionol chromophore. However, some ethynyl-β-ionol may be present in the crude product and, if so, may be removed by the next procedure.

Separation of the ether was also obtained by percolating a pentane or hexane solution of the reaction product through a column having granular alumina (Alcoa F-20) in an amount of 4 to 5 times the weight of the crude product. Unreacted ethynyl-β-ionol is retained on the column while desired ether passes through on washing with pentane or hexane. Unchanged ethynyl-β-ionol was then recovered by eluting the column of alumina with diethyl ether.

Coupling Reaction.

Alkylation of ethyl ether of ethynyl-β-ionol having a terminal acetylene group with a chloro-ester via the acetylenic Grignard derivative is impractical, since the Grignard reagent reacts more readily with the ester group, such as contained in the chloroacetate. The acetylene moiety is first converted to the copper derivative. Such compounds are inert toward esters but can displace the halide from organic halides. In this example, the following components were used: 12.3 g (0.05 mole) ethynyl-β-ionol ethyl ether; 1.4 g magnesium; 7.5 g ethyl bromide; 50 ml tetrahydrofuran; 6.6 g cuprous chloride; 100 ml hexamethyl phosphoric triamide; 12.5 g 1-chloro-4-acetoxy-2-methyl-2-butene.

In a three-necked flask fitted with a mechanical stirrer, condenser, thermometer and nitrogen inlet tube, the ethyl magnesium bromide was prepared in 40 milliliters of the tetrahydrofuran in a conventional manner. The acetylenic ether was then added at room temperature using the last 10 milliliters of tetrahydrofuran. Evolution of ethane started at once, and the mixture was stirred and heated for two hours when gas evolution ceased. To the solution of acetylenyl Grignard reagent thus formed, the hexamethyl phosphoric triamide was added at room temperature. The reaction flask was then flushed with nitrogen and under a positive pressure of nitrogen, the cuprous chloride was added at room temperature. It dissolved immediately. The mixture was then stirred at 65°C for 30 minutes and the chloroacetoxy methylbutene added at once. The mixture was then stirred at 83° to 92°C for 6 hours under nitrogen. The reaction was quenched by pouring the mixture into one liter of an aqueous solution of 10% NH_4Cl and 5% NH_4OH, layered with 300 ml of pentane. After thorough mixing, the pentane layer was separated, dried over sodium sulfate and concentrated under vacuum. To remove unreacted chloroisopentenyl acetate, 50 ml of diethyl amine were added and the solution allowed to stand at room temperature overnight.

The following morning a precipitate of Et_2NHHCl was present. The mixture was washed twice with brine, five times with 15% acetic acid, then with water, and finally with $NaHCO_3$ solution. After drying with sodium sulfate, the product was concentrated under vacuum. Unchanged starting ether was removed by treatment with neutral alumina (Alcoa F-20).

The infrared spectrum of the product obtained showed the presence of the acetate group and the ether group. Its ultraviolet spectrum showed a single maximum at 236 mμ, characteristic of the β-ionol group diene. The reaction

product at the stage indicated was passed through a column of neutral alumina without making any attempt at chromatographic fractionation. The chloride was removed and the product recovered by washing the column of alumina with diethyl ether. The wash product was then distilled under high vacuum and collected at 98° to 105°C at 0.001 mm/Hg, n_D^{22} 1.4950. This product was the acetate form. The infrared spectrum showed allylic ester bands at 5.75 mμ, 8.16 mμ, and 9.77 mμ. The ether doublet was at 9.1 mμ and 9.21 mμ. The ultraviolet showed the β-ionyl chromophore at λ_m236 mμ.

This example illustrates a further technique for treating the crude reaction product, obtained from the coupling reaction. Such reaction product was concentrated under vacuum and dissolved in 2 % methanolic sodium hydroxide. The solution was then allowed to stand at room temperature under a blanket of nitrogen for 12 hours. The unreacted chloride present and the ester groups on the coupling product were thereby hydrolyzed.

The mixture was next quenched with water and the resulting precipitated oil taken up in pentane, dried with sodium sulfate, and distilled under vacuum. The product was collected at 100° to 110°C at 0.001 mm/Hg, $n_D^{24.5}$ 1.5060. The infrared and ultraviolet spectrum corresponded to 10,11-didehydro-9-ethoxy-9,12-dihydroretinol acetate, using carotenoid nomenclature based on the parent compound retinol.

Semi-Hydrogenation of Coupling Product.

A solution of 2.6 grams of an above prepared acetate in 50 ml of hexane was stirred under hydrogen with 1.56 grams of 5 % Pd on $CaCO_3$ at 22°C. Absorption of hydrogen ran at about 6.0 ml/min. At the theoretical end-point, 176 milliliters of hydrogen at 22°C, the rate of absorption had fallen to 0.8 ml/min. The catalyst was filtered off and the hexane removed under vacuum. The product was a light yellow oil; the yield was 2.52 g.

Hydrolysis of Semi-Hydrogenated Coupling Product.

The semi-hydrogenated acetate coupled product was dissolved in a 1% solution of sodium hydroxide in methyl alcohol. The solution was allowed to stand about 12 hours at room temperature under a blanket of nitrogen. The hydrolysis was complete as shown by the total absence of ester bands in an infrared analysis.

De-ethanolation of the Semi-Hydrogenated, Hydrolyzed Coupling Product, Preparation of Vitamin A.

The product of hydrolysis was placed in anhydrous ether solution and the mixture added to a suspension of freshly prepared sodamide in liquid ammonia in a weight ratio of about 2.28 product; 25 ether; 1.36 sodamide; 100 ammonia. At -40°C no reaction appeared to take place other than the formation of the alkoxide of the starting material. On raising the temperature to -30°C, the reaction mixture turned a deep opaque purple which remained for the duration of the run. After two hours the reaction mixture was quenched with ammonium chloride.

Separation of Vitamin A from the product obtained was achieved by

acetylating the total reaction product using pyridine-acetic anhydride at room temperature and chromatographing on alumina neutralized with acetic acid. A fairly clean separation was achieved. The Vitamin A acetate fraction was sufficiently pure to become crystallized from pentane at -15°C when seeded with a pure Vitamin A acetate crystal.

When the Vitamin A acetate was converted to the alcohol form of Vitamin A, the final product showed the characteristic infrared and ultraviolet absorption curves for Vitamin A. Similar results were obtained using as co-solvents (with the liquid ammonia) ethylene diamine and ether; pentane; tetrahydrofuran; diethylamine and hexamethylphosphoramide.

References

Oroshnik W.; US Patent No. 3,949,006; Apr. 6, 1976; Assigned to SCM Corporation, New York, N.Y.

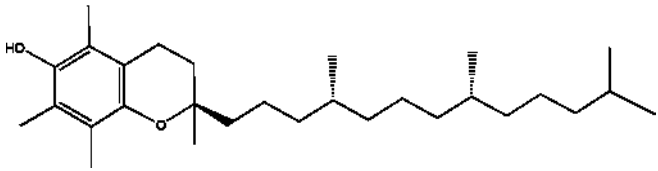
VITAMIN E

Therapeutic Function: Antioxidant

Chemical Name: 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)-, (2R)

Common Name: Antisterility Vitamin; Tocoferolum; α-Tocopherol; Vitamin E; Witamina E

Structural Formula:



Chemical Abstracts Registry No.: 59-02-9

Trade Name	Manufacturer	Country	Year Introduced
Doppelherz Vitamin E forte	Queisser Pharma GmbH and Co. KG	Germany	-
Evitol	Krka	Slovenia	-
Forvitale	Deva	-	-
Pura	D'Franssia	-	-
Tocopher-400	Torrent	India	-
Vitamin E	Sagmel, Inc.	USA	-
Vitamin E	Slovakofarma	Slovakia	-
Vitamin E	Roche Vitamins	USA	-
Vitamin E	BASF AG	Germany	-

Trade Name	Manufacturer	Country	Year Introduced
Vitamin E	Helm AG	Germany	-
Vitrum Vitamin E	Unipharm	USA	-

Raw Materials

Lithium	Hexahydropseudoionone
Copper chloride	Trimethylhydroquinone
Isoprene	Acetylenic chloride or propargylic chloride
Zinc	Methyl magnesium chloride
Sodium amide	Isoprene chloroacetate
Lindlar catalyst	Palladium on barium sulfate
Ferric nitrate nonahydrate	Boron trifluoride platinum catalyst

Manufacturing Process

The synthesis of Vitamin E, that is, α-tocopherol (5,7,8-trimethyltocol) in the past has been accomplished primarily by reacting trimethylhydroquinone (TMHQ) with isophytol (3,7,11,15-tetramethylhexadec-1-en-3-ol) or phytol (3,7,11,15-tetramethylhexadec-2-en-1-ol) in a condensation reaction. The reaction is well known and has been practiced for many years (Stalla-Bourdillon, Ind. Chim. Belg., 35, 13 (1970); "The Vitamins" Vol. 5, pages 168-223, Academic Press, New York, 1967).

Hexahydropseudo-ionone is an available material produced by complete catalytic hydrogenation of the double bonds of pseudo-ionone. The hexahydropseudo-ionone is reacted with a metal acetylide such as lithium or sodium acetylide, in a known condensation reaction using conventional chemistry to provide 3,7,11-trimethyl-3-hydroxy-1-dodecyne (1), a C_{15} acetylenic (ethynyl) carbinol compound having a terminal acetylene group and methyl and hydroxyl groups on the adjacent carbon atom. Again, the numbering system applied in the drawing for this formula and succeeding formulate follows the conventional numbering system for the tocopherols, each carbon atom being given the number it will eventually have in the alpha;-tocopherol molecule.

The carbinol of formula (1) [prepared by F. G. Fisher and K. Lowenberg, Liebigs Ann. Chem., 475, 183 (1929)] is converted to the corresponding chloride, 3,7,11-trimethyl-3-chloro-1-dodecyne (2) by dissolving the carbinol in a concentrated hydrochloric acid solution saturated with dry hydrogen chloride at about -25° to -10°C. The conversion is carried out at -10° to 0°C, under atmospheric pressure, preferably in the presence of cuprous chloride resulting in a substantially quantitative recovery of the chloride. The product, an acetylenic chloride or propargylic chloride, is a clean water-white oil. In a particular example, 78.8 grams (0.351 mole) of the C_{15} ethynylcarbinol is added at -25°C to a mixture of 550 ml concentrated HCl and 18.5 grams of CuCl into which HCl gas has been bubbled until in excess. After warming to 0°-5°C and at the end of a reaction period of about 2 hours, the reaction mixture was extracted with pentane and worked-up following conventional procedures to yeild 87.3 grams of crude product.

Dehalogenation to Allene (3). The chloride (2) is reductively dehalogenated to the corresponding C_{15}-allene, 3,7,11-trimethyldodeca-1,2-diene, by dissolving and stirring the chloride in a mixture of glacial acetic acid mixed with zinc

dust, using the following proportions: 87.3 grams the crude product from the halogenation step (C_{15}-propargylic chloride), 87.3 grams Zn dust (activated with dilute HCl), HOAC (glacial) 850 ml.

The reaction is exothermic but is carried out at room temperature by cooling. Quenching in water after filtering off the unreacted zinc dust, taking up the oil precipate with a solvent such as hexane, further washing, drying and concentrating, results in a crude product of 80% purity. This is then distilled at 0.5 mm pressure with very little or no polymerization to give a product of 84% purity. The yeild of desired product was 85% of theoretical yield.

Rearrangement to C_{15} Acetylene.

The isomerization of allene to acetylene with a solution of sodium amide in ethylene diamine produces an 87% by weight yield of distilled product of 70% purity. The bulk of the impurity is a conjugated diene.

The reaction is carried out by adding the allene dropwise to a solution of sodium amide in ethylene diamine-ether (30:70) maintained at room temperature. The reaction mixture is agitated during addition and for about two to three hours thereafter, followed by quenching with aqueous ammonium chloride and distillation. The presence of the diene does not interfere in the subsequent coupling reaction of the acetylene with "isoprene chloroacetate" (1-acetoxy-4-chloro-3-methylbut-2-ene) (3), as it is merely an inert component in the reaction mixture.

The resultant C_{15} acetylene product is 3,7,11-trimethyldodeca-1-yne (4)

In a particular example, the following components were employed: the crude product of dehalogenation step (C_{15} allene) 76.2 grams; Na 13.5 grams (0.59 gram-atoms); NH_3 700 ml; ether (anhydrous) 700 ml, $NH_2CH_2CH_2NH_2$ 280 ml (dried over molecular sieves).

The ammonia and sodium are combined in the presence of a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ at the boiling temperature of NH_3 to obtain a solution of $NaNH_2$ in liquid NH3. The ether, ethylene diamine and allene are then added in that order. After a reaction period of about 4.5 hours, quenching and work up, 54.4 grams of distilled product (63.5% acetylene) was obtained.

The compound of formula (4) is coupled with isoprene chloroacetate (1-acetoxy-4-chloro-3-methylbut-2-ene) (4a) to form the basic C_{20} skeleton of dehydrophytol. The chloroacetate is known and prepared by the chlorhydrination of isoprene in glacial acetic acid as described in an article by W. Oroshnik and R. A. Mallory, J. Amer. Chem. Soc. 72, 4608 (1950). The coupling reaction results in the preparation of 3,7,11,15-tetramethyl-1-acetoxyhexadec-2-en-5-yne (5), a C_{20} enyne. The coupling reaction may be carried out employing several methods. The following methods are preferred.

This coupling reaction involves pre-forming a cuprous salt of the C_{15} acetylene compound of formula (4) and then reacting the salt with the coupling reactant "isoprene chloroacetate" (4a) in an aprotic solvent such as dimethyl formamide (DMF). The cuprous salt is formed by reacting the C_{15} acetylene

compound (67.2% purity) 9.9 grams (0.0317 mole) with a Grignard reagent such as methyl magnesium chloride (1.25 M, 27 ml, 0.0388 mole) in 36 ml of tetrahydrofuran (THF) giving off methane as a gas to form an acetylenic Grignard compound and then adding cuprous chloride, 3.52 grams (0.0356 mole), copper replacing the magnesium chloride group. Following this, isoprene chloroacetate 6.4 grams (0.0396 mole) in 35 ml DMF is added; and the tetrahydrofuran is driven off under vacuum leaving a DMF solution in which all the reactants are dissolved. This solution is heated for several hours at 80°C under nitrogen giving the C_{20} enyne.

The Grignard reagent was added dropwise to a solution of 11 ml of THF and the acetylene at less than 30°C, followed by warming to 60°C and maintaining this temperature for 2 hours. This was followed by cooling, addition of CuCl, and addition of the chloroacetate with the remaining THF. The DMF is then added and the THF removed under vacuum heating up to 50°C. The coupling reaction was carried out at about 90°C for 6 hours, producing 3.0 grams of pure product (28% of theoretical yield).

The compound of formula (5) is next subjected to selective hydrogenation to convert the acetylenic bond to an ethylenic bond. This can be readily accomplished by a number of different catalysts, such as a nickel catalyst prepared from a nickel salt and $NaBH_4$, Lindlar catalyst, or 5% palladium on barium sulfate in the presence of qunioline. The reaction was run at one atmosphere. Analyses by nuclear magnetic resonance and vapor phase chromatography showed the correct structure in good quantity. The product obtained was 3,7,11,15-tetramethylhexadeca-2,5-dien-1-acetate (6), a C_{20} dienolacetate.

Saponification of the C_{20} Dienol Acetate to Dehydrophytol.

The acetate (6) is dissolved in 1-2% methanolic NaOH and allowed to stand for 12 hours at room temperature under nitrogen. The reaction mixture is then quenched with water, and the precipitated oil is taken up in hexane. The hexane solution after drying with anhydrous sodium sulfate or magnesium sulfate is concentrated under vacuum, and the residual oil can either be distilled under high vacuum or used as such in the subsequent steps. High yields of dehydrophytol [3,7,11,15-tetramethylhexadeca-2,5-dien-1-ol (7)] were obtained. UV absorption showed no detectable conjugation. The product was chromatographed on alumina, which gave a pure material.

Condensation of Dehydrophytol with TMHQ to yield Dehydro-Vitamin E.

For the synthesis of dehydro-Vitamin E, 0.45 grams (1.54 millimoles) dehydrophytol of formula (7) is reacted with 0.23 grams (1.51 millimoles) trimethylhydroquinone to yeild dehydro-Vitamin E following the procedure published in the Journal of Organic Chemistry, Volume 36, (19) pages 2910-12 (1971), by Wehrli, Fryer and Metlesics. Essentially the method involves first forming a TMHQ-BF_3 complex in methylene chloride (2 ml) containing one equivalent of nitromethane (0.090 ml) and no excess BF_3, by bubbling in the BF_3 and precipitating the complex. The dehydrophytol is then added with 3.5 ml of methylene chloride at -20°C; and the reaction is carried out for a period at -20°C, then at -10°C, and finally at room temperature to yeild dehydro-Vitamin E.

The dehydro-Vitamin E obtained is hydrogenated with a platinum catalyst in methanol. Good yields of Vitamin E (8) (α-tocopherol) are obtained.

References

Close R. et al.; US Patent No. 4,115,466; Sept. 19, 1978; Assigned to SCM Corporation, New York, N.Y.
Close R. et al.; US Patent No. 4,055,575; Oct. 25, 1977; Assigned to SCM Corporation, New York, N.Y.

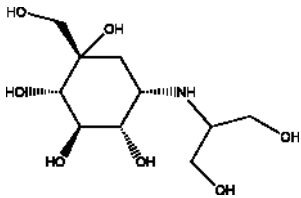
VOGLIBOSE

Therapeutic Function: Antidiabetic, Antiobesity

Chemical Name: 3,4-Dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-C-(hydroxymethyl)-D-epiinositol

Common Name: Voglibose; Voglistat

Structural Formula:



Chemical Abstracts Registry No.: 83480-29-9

Trade Name	Manufacturer	Country	Year Introduced
Voglibose	Takeda	-	-

Raw Materials

Valiol amine
Dowex
Amberlite
Dihydroxyacetone
Sodium cyanoborohydride

Manufacturing Process

N-(1,3-Dihydroxy-2-propyl)valiolamine:

To a solution of 2.0 g of valiol amine in 50 ml of N,N-dimethylformamide are added 3.4 g of dihydroxyacetone, 1.5 ml of 2 N hydrochloric acid and 2.6 g of sodium cyanoborohydride, followed by stirring at 60 to 70°C for 16 hours. The reaction solution is concentrated under reduced pressure to distill off the N,N-dimethylformamide as much as possible, and the residue is dissolved in 100

ml of water. The solution is made acid with 2 N hydrochloric acid, stirred for 30 to 40 minutes under ice-cooling, adjusted to pH 4.5 with 1 N sodium hydroxide solution and subjected to column chromatography (250 ml) on Dowex 50W x 8 (H^+ type) (produced by Dow Chemical of the United States of America). After the washing with water, the elution is carried out with 0.5 N aqueous ammonia. The eluate is concentrated under reduced pressure, and the concentrate is chromatographed on a column (250 ml) of Amberlite CG-50 (NH_4^+ type) (produced by Rohm and Haas Co. of the United States of America), followed by the elution with water. The eluate is concentrated under reduced pressure, and the concentrate is lyophilized to give 2.0 g of white powder of N-(1,3-dihydroxy-2-propyl)valiol amine.

Ethanol (about 60 ml) is added to the above lyophilized product (1.2 g) of N-(1,3-dihydroxy-2-propyl)valiol amine, and the mixture is warmed for 30 minutes in a hot water bath (the bath temperature: 90-95°C), followed by leaving on standing in a refiegerator. The resultant crystalline substance is recovered by filtration, washed with ethanol and then dried in a desiccator under reduced pressure. Yield of 0.95 g. MP: 162-163°C. $[\alpha]_D^{25}$ = +26.2° (c = 1, H_2O).

References

Miller J.C. et al.; US Patent No. 4,096,148; June 20, 1978; Assigned to Eli Lilly and Company, Indianapolis, Ind.

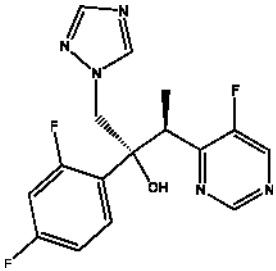
VORICONAZOLE

Therapeutic Function: Antifungal

Chemical Name: 4-Pyrimidineethanol, α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1H-1,2,4-triazol-1-ylmethyl)-, (R-(R*,S*))-

Common Name: Voriconazole

Structural Formula:



Chemical Abstracts Registry No.: 137234-62-9

Trade Name	Manufacturer	Country	Year Introduced
Vfend	Pfizer	-	-

Raw Materials

3-(4-Chloro-5-fluoropyrimidin-6-yl)-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, enantiomeric
Palladium on charcoal
Hydrogen

Manufacturing Process

A solution of 3-(4-chloro-5-fluoropyrimidin-6-yl)-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, enantiomeric pair B (0.307 g, 0.8 mmol) in ethanol (20 ml) was hydrogenated at atmospheric pressure and at room temperature in the presence of 10% palladium-on-charcoal (30 mg) and sodium acetate (0.082 g, 1 mmol). After 5 hours a further 10 mg of 10% palladium-on-charcoal was added and hydrogenation was continued for an additional 1 hour. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. 'Flash' chromatography of the residue on silica using 97:3 ethyl acetate/methanol as the eluent provided, after combination and evaporation of appropriate fractions and trituration with diethyl ether, the 2-(2,4-difluorophenyl-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-I-yl)butan-2-ol enantiomeric pair B, (0.249 g, 89%), m.p. 127°C.

2-(2,4-Difluorophenyl-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol enantiomeric pair A was prepared by a similar method using 3-(4-chloro-5-fluoropyrimidin-6-yl)-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, enantiomeric pair A as a starting material. This gave the product with m.p. 137°C.

References

Ray St.J. et al.; EP Patent No. 0,440,372; 24.01.91; Assigned to Pfizer Limited, Ramsgate Road Sandwich Kent CT13 9NJ (GB)

VOROZOLE

Therapeutic Function: Antineoplastic

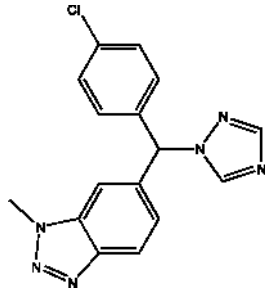
Chemical Name: 1H-Benzotriazole, 6-((4-chlorophenyl)-1H-1,2,4-triazol-1-ylmethyl)-1-methyl- (S)

Common Name: Vorozole; Rivizor

Chemical Abstracts Registry No.: 129731-10-8

Trade Name	Manufacturer	Country	Year Introduced
Vorozole	Janssen Pharmaceutica	-	-

Structural Formula:



Raw Materials

1H-1,2,4-Triazole
Sodium hydride
6-[Chloro(4-chlorophenyl)-methyl]-1-methyl-1H-benzotriazole

Manufacturing Process

To a stirred solution of 28.4 parts of 1H-1,2,4-triazole in 135 parts of N,N-dimethylformamide were added 11.4 parts of a sodium hydride dispersion 80% under nitrogen atmosphere. After stirring for 1 hour at room temperature, a solution of 40 parts of 6-[chloro(4-chlorophenyl)-methyl]-1-methyl-1H-benzotriazole in 90 parts of N,N-dimethylformamide was added to the mixture. The whole was stirred for 1 hour at 60°C. The reaction mixture was diluted with 50 parts of water and the whole was evaporated. The residue was extracted with ethyl acetate. The extract was washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (99:1 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from a mixture of 2-propanone and 1,1'-oxy-bis-ethane (ether). The product was filtered off and dried, yielding 13 parts (29.2%) of 6-[(4-chlorophenyl)-(1H-1,2,4-triazol-1-yl)methyl]-1-methyl-1H-benzotriazole; MP: 178.9°C. A resolution of enantiomers any usual method gave crystals from 2-propanol, MP: 130-135°C. $[\alpha]_D^{20}$ = 8.0° (plus or minus) (c = 10 in CH_3OH).

References

Bayermaekers A. H. M. et al.; European Patent No. 0,293,978 A2; May 26, 1988

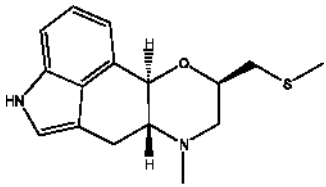
VOXERGOLIDE

Therapeutic Function: Anti-anoxic, Anti-ischemic

Chemical Name: (8β)-(+/-)-6-Methyl-8-[(methylthio)methyl]-9-oxaergoline

Common Name: Voxergolide

Structural Formula:



Chemical Abstracts Registry No.: 89651-00-3

Trade Name	Manufacturer	Country	Year Introduced
Voxergolide	Roussel-Uclaf (Aventis)	-	-

Raw Materials

Lithium aluminum hydride
Aluminum chloride
Methyl chloroformate
Ethyl glycidate
Tosyl chloride
N-Chlorodiisopropylamine
Diazomethane
Hexamethylphosphoramine
Palladium on carbon
Sodium borohydride
Methyl mercaptan
Dimethylacetamide
4RS-trans-1,2,2a,3,4,5-Hexahydro-4-methylamino-1-benzyl-benz[c,d]indo-5-ol

Manufacturing Process

Voxergolide was prepared in 9 steps:

Methyl [6aRS-(6aα,9β,10aβ)]-4,6,6a,8,9,10a-hexahydro-7-methyl-7H-indolo[3,4-g,h][1,4]benzoxazine-9-carboxylate hydrochloride:

STEP 1: 4RS-trans-1,2,2a,3,4,5-hexahydro-4-methylamino-1-benzylbenz[c,d]indo-5-ol:

26 g of 4RS-trans-4-amino-1-benzoyl-1,2,2a,3,4,5-hexahydrobenz[c,d]indol-5-ol were slowly added under an inert atmosphere with stirring to a mixture of 26 g of lithium aluminum hydride, 13 g of aluminum chloride and 800 ml of dioxane and the mixture was refluxed for 2 hours and cooled in an ice bath while adding dropwise 300 ml of 10% hydrated tetrahydrofuran and 300 ml of 2 N sodium hydroxide solution. The mixture was vacuum filtered and the filter was washed with methylene chloride. The filtrate was added to 1.5 liters of methylene chloride and the organic phase was washed with water, dried and evaporated to dryness to obtain 20 g of 4RS- trans-4-amino-1,2,2a,3,4,5-hexahydro-1-benzylbenz[c,d]indol-5-ol melting at 166°C after crystallization from methylene chloride.

10 g of the said product were dissolved in 100 ml of chloroform and 10 ml of sodium hydroxide and after cooling the mixture to 0° to 5°C, 25 ml of water were added thereto. Then, 4 ml of methyl chloroformate were added thereto

dropwise and the mixture was stirred at room temperature for 30 minutes and was extracted with ethyl acetate containing 10% methanol. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness to obtain 11.8 g of product melting at 200°C, which was used as is. A solution of 11.7 g of said product in 250 ml of tetrahydrofuran was added over 10 minutes at 0° to °C to a suspension of 11.7 g of lithium aluminum hydride in 250 ml of tetrahydrofuran and the mixture was refluxed for 2 hours. 250 ml of 20% aqueous tetrahydrofuran were added thereto and the mixture was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness to obtain 10 g of raw product. The said product was dissolved in 100 ml of methylene chloride and the mixture was stirred with activated carbon for 20 minutes. The methylene chloride phase was rinsed and concentrated to a volume of 100 ml. 100 ml of isopropyl ether were added thereto and the mixture stood at room temperature for 30 minutes and for 30 minutes in an ice bath to obtain 5.5 g of 4RS- trans-1,2,2a,3,4,5-hexahydro-4-methylamino-1-benzylbenz[c,d]indol-5-ol melting at 148°C.

STEP 2: Ethyl 4RS-trans-2-hydroxy-3-[(5-hydroxybenzyl)-1,2,2a,3,4,5-hexahydro-benz[c,d]indol-4-yl)-methylamino]-propanoate:

A mixture of 24.2 g of the product of Step 1, 1.2 liters of ethanol and 19.2 g of ethyl glycidate was refluxed under an inert atmosphere for 4 hours and was then evaporated to dryness under reduced pressure. The oil was chromatographed over silica gel and was eluted with a 7-3 benzene-ethyl acetate mixture to obtain 28.2 g of ethyl 4RS-trans-2-hydroxy-3-[(5-hydroxybenzyl)-1,2,2a,3,4,5-hexahydro-benz[c,d]indol-4-yl)-methylamino]-propanoate.

STEP 3: Ethyl [6aRS-(6aα,9β,10aβ)] and [6aRS-(6aα,9β,10aβ)]-7-methyl-4,5,5a,6,6a,8,9,10a-octahydro-4-benzyl-7H-indolo[3,4-g,h][1,4]-benzoxazine-9-carboxylate:

31.8 ml of hexamethylphosphoramine were added dropwise under an inert atmosphere at -40° to -45°C to a solution of 22.6 g of the product of Step 2, 17.25 g of N-chlorodiisopropylamine, and 200 ml of methylene chloride and the mixture was stirred for 15 minutes and then allowed to stand for one hour at room temperature. The mixture was poured into 250 ml of water and the organic phase was extracted with aqueous 2 N hydrochloric acid. The aqueous phase was made alkaline with sodium hydroxide solution and was extracted with methylene chloride. The organic extract was washed with water, dried and evaporated to dryness under reduced pressure. The residue was added to a few ml of isopropyl ether and was vacuum filtered. The product was dried to obtain 9.6 g of the 9α-isomer of the desired compound melting at 156°C. The mother liquors were chromatographed over silica gel and eluted with a 7-3 benzene-ethyl acetate mixture to obtain another 2.2 g of the 9α-isomer melting at about 157°C and 3.4 g of the 9β-isomer melting at about 110°C.

STEP 4: Methyl-[6aRS-(6aα,9β,10aβ)]-7-methyl-4,5,5a,6,6a,8,9,10a-octahydro-4-benzyl-7H-indolo[3,4-g,h]benzoxazine-9β-carboxylate:

A mixture of 14.5 g of the isomer mixture of Step 3, 1 liter of ethanol, 3.6 g of sodium in 200 ml of ethanol was refluxed for one hour under an inert atmosphere and was evaporated to dryness under reduced pressure. The

residue was added to 50 ml of water and concentrated hydrochloric acid was added thereto to adjust the pH to 6.5. The mixture was evaporated to dryness under reduced pressure at 50°C and the residue was taken up in 1.2 liters of methylene chloride and 50 ml of methanol. 300 ml of a solution of 12 g/l of diazomethane in methylene chloride was added dropwise at 5° to 10°C to the mixture, which was then stirred at 4°C for 16 hours. Excess diazomethane was destroyed by addition of a few drops of acetic acid and the mixture was washed with 2 N sodium hydroxide solution, with water, dried and evaporated to dryness under reduced pressure. The residue was added to a few ml of ether and the mixture was vacuum filtered. The product was dried to obtain 11.8 g of methyl [6aRS-(6aα,9β,10aβ)]-7-methyl-4,5,5a,6,6a,8,9,10a-octahydro-4-benzyl-7H-indolo[3,4-g,h]benzoxazine-9β-carboxylate melting at 127°C and at 130°C after crystallization from isopropyl ether.

STEP 5: Methyl-[6aRS-(6aα,9β,10aβ)]-7-methyl-4,5,5a,6,6a,8,9,10a-octahydro-7H-indolo [3,4-g,h][1,4]benzoxazine-9-carboxylate:

A mixture of 12.75 g of methyl [6aRS-(6aα,9β,10aβ)]-4,5,5a,6,6a,8,9,10a-octahydro-7-methyl-4-benzyl-7H-indolo[3,4-g,h][1,4]-benzoaxazine-9-carboxylate, 600 ml of acetic acid and 3.2 g of 10% Pd/C was hydrogenated for 4 hours and the mixture was filtered. The filter was rinsed with acetic acid and the filtrate was evaporated to dryness at 30-35°C under reduced pressure. The residue was added to 200 ml of water and the mixture was adjusted to a pH of 9 by addition of ammonium hydroxide. The mixture was extracted with methylene chloride and the organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The residue was added to a few ml of ether and the mixture was vacuum filtered. The product was dried at 50°C under reduced pressure to obtain 8.28 g of methyl [6aRS-(6aα,9β,10aβ)]-7-methyl-4,5,5a,6,6a,8,9,10a-octahydro-7H-indolo[3,4-g,h][1,4]benzoazine-9-carboxylate melting at 178°C. Chromatography of the mother liquors over silica gel and elution with a 95;5 chloroform/methanol mixture yielded another 0.475 g of the product melting at about 178°C.

STEP 6: Methyl [6aRS-(6aα,9β,10aβ)]-4,6,6a,8,9,10a-hexahydro-7-methyl-7H-indolo[3,4-g,h][1,4]benzoxazine-9-carboxylate:

A mixture of 33.5 g of manganese dioxide and a solution of 8.4 g of the product of Step 5 in 840 ml of methylene chloride was stirred under an inert atmosphere for 16 hours and was filtered. The filtrate was washed and evaporated to dryness under reduced pressure. The residue was added to a few ml of ether and the mixture was vacuum filtered. The product was dried to obtain 2 crops of 3.9 and 0.91 g of methyl [6a-RS (6aα,9β,10aβ)]-4,6,6a,8,9,10a-hexahydro-7-methyl-7H-indolo[3,4-g,h][1,4]benzoxazine-9-carboxylate melting at 174°C and an additional 1.1 g of product melting at 174°C by chromatography of the mother liquors.

Step 7: [6aRS-(6aα,9β,10aβ)]-4,6,6a,8,9,10a-hexahydro-7-methyl-7H-indolo[3,4-g,h][1,4]benzoxazine-9-methanol and its hydrochloride:

A mixture of 2.2 g of the free base of the product of step 6, 30 ml of dioxane, 15 ml of methanol and 2.2 g of 95% sodium borohydride was refluxed with stirring under an inert atmosphere for one hour and after cooling the mixture, 150 ml of water were added thereto. The mixture was extracted with methylene chloride and the organic phase was washed with water, dried and

filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was added to a few ml of ether. The mixture was vacuum filtered and the product was dried at 50°C under reduced pressure to obtain 1.82 g and then 0.08 g of [6aRS-(6aα,9β,10aβ)]-4,6,6a,8,9,10a-hexahydro-7-methyl-7H-indolo[3,4-g,h][1,4]benzoxazine-9-methanol melting at 208°C. 2 g of the free base were dissolved in 80 ml of methanol and 5 ml of methanolic 2 N hydrochloric acid were added thereto. The mixture stood for 16 hours and was vacuum filtered. The product was rinsed with ether and dried at 50°C under reduced pressure to obtain 1.97 g of the hydrochloride of the said base melting at 320°C.

STEP 8: [6aRS-(6aα,9β,10aβ)]-4,6,6a,8,9,10a-hexahydro-7-methyl-7H-indolo[3,4-g,h][1,4]benzoxazine-9-p-toluenesulfonatemethanol:

A solution of 9.5 g of tosyl chloride in 125 ml of pyridine was added to a mixture of 6.6 g of the product of step 7 and 66 ml of pyridine and the mixture was stirred at 20°C for 17 hours and was then poured into methylene chloride. The mixture was washed with aqueous saturated sodium bicarbonate solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 95-5 methylene chloride-methanol mixture to obtain 7.7 g of [6aRS-(6aα,9β,10aβ)]-4,6,6a,8,9,10a-hexahydro-7-methyl-7H-indolo[3,4-g,h][1,4]benzoxazine-9-p-toluenesulfonate-methanol which after crystallization from an isopropyl ether-methylene chloride mixture melted at 180°C.

STEP 9: [6aRS-(6aα,9β,10aβ)]-4,6,6a,8,9,10a-hexahydro-7-methyl-9-methylthiomethyl-7H-indolo[3,4-g,h][1,4]benzoxazine and its hydrochloride:

50 ml of condensed methyl mercaptan were added to 150 ml of dimethylacetamide at 0°C.and then 12.6 g of sodium hydride as a 50% mineral oil mixture were added thereto. A solution of 6.6 g of the product of Step 8 in 40 ml of dimethylacetamide was added over 15 minutes at 20°C to the mixture and the mixture was stirred for 2 hours and was poured into iced water. The mixture was extracted with methylene chloride and the organic phase was washed with water, dried and evaporated to dryness. The residue was chromatographed over silica gel and eluted with a 95-5 methylene chloride-methanol mixture to obtain a 4.2 g of [6aRS-(6aα,9β,10aβ)]-4,6,6a,8,9,10a-hexahydro-7-methyl-9-methylthiomethyl-7H-indolo[3,4,-g,h][1,4]benzoxazine which melted at 150°C after crystallization from methylene chloride. 3.96 g of the said base were dissolved in 150 ml of methylene chloride and 7 ml of hydrochloric acid in ether were added thereto. Crystallization was effected at 20°C and the mixture was vacuum filtered. The crystals were washed with methylene chloride and dried to obtain 4.1 g of the hydrochloride of the base, which melted at 250°C (decomposition) after crystallization from methanol.

References

Nedelec L. et al.; US Patent No. 4,493,836; January 15,1985; Assigned to Uclaf, Paris, France