V

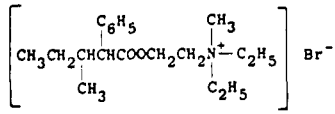
VALETHAMATE BROMIDE

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 Names	Manufacturer	Country	Year Introduced
Murel	Ayerst	U.S.	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

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

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-methyl-pentanoic 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 & 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.

VANCOMYCIN

Therapeutic Function: Antibacterial

Chemical Name: See structural formula

Common Name: –

Structural Formula: Not definitely known; has a molecular weight of about 3,300, a nitrogen content of about 7% and a carbohydrate content of 16 to 17%.

Chemical Abstracts Registry No.: 1404-90-6

Trade Name	Manufacturer	Country	Year Introduced
Vancocin	Lilly	U.S.	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 min-

utes 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.; U.S. Patent 3,067,099; December 4, 1962; assigned to Eli Lilly and Company

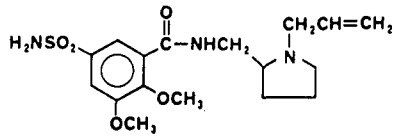
VERALIPRIDE

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
Carbondiimidazole
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 l'Ile-de-France

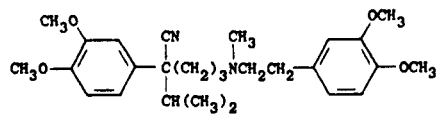
VERAPAMIL

Therapeutic Function: Coronary vasodilator; antiarrythmic

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)

Trade Name	Manufacturer	Country	Year Introduced
Isoptin	Knoll	W. Germany	1963
Isoptin	Knoll	Italy	1965
Isoptin	Knoll	Switz.	1965
Cordilox	Abbott	U.K.	1967
Isopine	Biosedra	France	1969
Calan	Searle	U.S.	1981
Isoptin	Knoll	U.S.	1981
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-aminopropyl]-3,4-dimethoxyphenolacetonitrile 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; n_D^{25} = 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-aminopropyl]-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 & Engel p. 940
PDR pp. 979, 1664, 1678
I.N. p. 1003
REM p. 862
Dengel, F.; U.S. Patent 3,261,859; July 19, 1966; assigned to Knoll A.G. Chemische Fabriken (Germany)

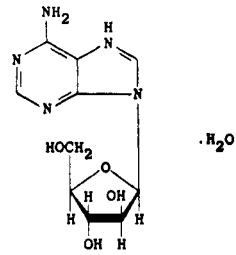
VIDARABINE

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	U.K.	1977
Vira-A	Parke Davis	U.S.	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 fermentor. 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 fermentors. The pH of the medium in each fermentor 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 fermentor 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 fermentor.

The fermentation mixtures from the four fermentors 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 & Company; British Patent 1,159,290; July 23, 1969

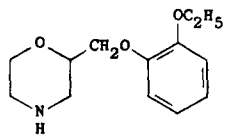
VILOXAZINE HYDROCHLORIDE

Therapeutic Function: Psychotropic

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

Common Name: –

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Vivalan	I.C.I.	U.K.	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 U.S. Patent 3,712,890.

References

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

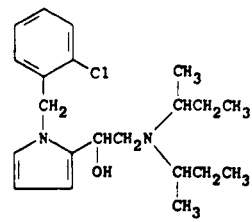
VIMINOL

Therapeutic Function: Analgesic

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

Common Name: Diviminol

Structural Formula:



Chemical Abstracts Registry No.: 21363-18-8

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

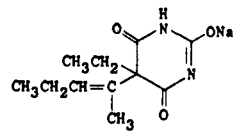
VINBARBITAL SODIUM

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	U.S.	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.; U.S. Patent 2,187,703; January 16, 1940; assigned to Sharp & Dohme, Inc.

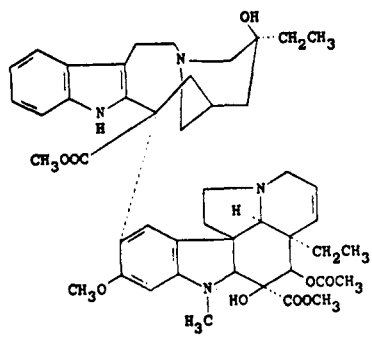
VINBLASTINE SULFATE

Therapeutic Function: Cancer chemotherapy

Chemical Name: Vincaleukoblastine sulfate

Common Name: –

Structural Formula:



(base)

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

Trade Name	Manufacturer	Country	Year Introduced
Velban	Lilly	U.S.	1961
Velbe	Lilly	U.K.	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 U.S. 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.

1½ 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 2% 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 & 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.; U.S. Patent 3,097,137; July 9, 1963; assigned to Canadian Patents and Development, Ltd., Canada
Svoboda, G.H.; U.S. Patent 3,225,030; December 21, 1965; assigned to Eli Lilly and Co.

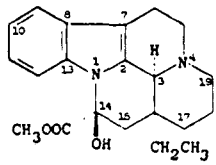
VINCAMINE

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	–
Cincuental	Nemi	Argentina	–
Equipur	Fresenius	W. Germany	–

Trade Name	Manufacturer	Country	Year Introduced
Esberidin	Schaper & 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	Radiumfarma	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

Vincadiformine
Trimethylphosphite
Sodium hydride
Oxygen

Manufacturing Process

The following route is described in U.S. Patent 4,145,552: At ambient temperature, over a period of thirty minutes, a solution of 33.8 g (0.1 mol) 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 & Engel p. 944
I.N. p. 1008
Kuehne, M.E.; U.S. Patent 3,454,583; July 8, 1969; assigned to U.S. Secretary of Health, Education and Welfare
Heymes, A.; U.S. 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: The N-methyl group in vinblastine (which see) is replaced by N-CHO.

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

Trade Name	Manufacturer	Country	Year Introduced
Oncovin	Lilly	U.S.	1963
Oncovin	Lilly	France	1964
Vincristin	Lilly	W. Germany	1965
Vincristina	Lilly	Italy	1966
Oncovin	Lilly	U.K.	1966
Cristovin	Teva	Israel	–
Kyocristine	Kyorin	Japan	–
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 U.S. 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 U.S. Patent 3,899,493.

References

Merck Index 9788
Kleeman & 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.; U.S. Patent 3,205,220; September 7, 1965; assigned to Eli Lilly & Co.
Jovanovics, K., Szasz, K., Fekete, G., Bittner, E., Dezseri, E. and Eles, J.; U.S. Patent 3,899,493; August 12, 1975; assigned to Richter Gedeon Vegyeszeti Gyar R.T.

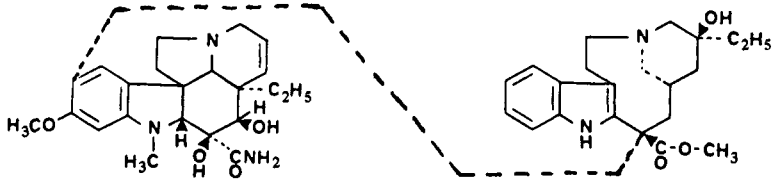
VINDESINE

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

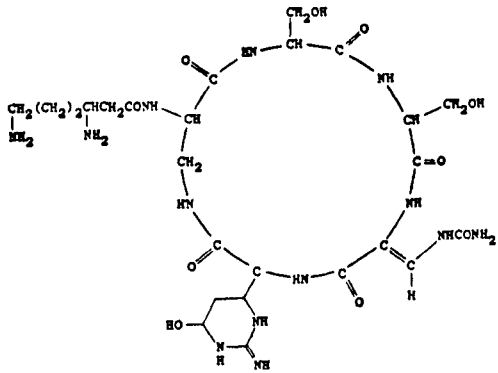
VIOMYCIN

Therapeutic Function: Antitubercular

Chemical Name: See structural formula

Common Name: —

Structural Formula:



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

Trade Name	*Manufacturer*	Country	Year Introduced
Vinactane	Ciba	U.S.	1953
Viocin	Pfizer	U.S.	1953
Panto-Viocine	Pfizer	France	—
Viomicin	Parke Davis Sankyo	Japan	—
Viomycin	Parke Davis	U.S.	—
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 U.S. 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 & Engel p. 949
I.N. p. 1010
REM p. 1212
Marsh, W.S., Mayer, R.L., Mull, R.P., Scholz, C.R. and Townley, R.W.; U.S. Patent 2,633,445; March 31, 1953; assigned to Ciba Pharmaceutical Products, Inc.

Freaney, T.E.; U.S. Patent 2,828,245; March 25, 1958; assigned to Commercial Solvents Corporation

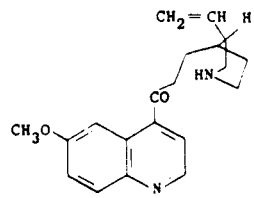
VIQUIDIL

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

N-Benzoylhomomeroquinene ethyl ester
Sodium ethoxide
Ethyl quininate
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.; U.S. Patent 2,500,444; March 14, 1950; assigned to Polaroid Corp.

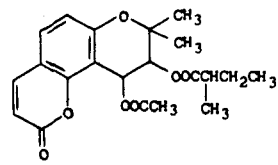
VISNADINE

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 & Engel p. 950
I.N. p. 1011
Le Men, J.G.; U.S. Patent 2,995,574; August 8, 1961; assigned to Laboratoire Roger Bellon S.A. (France)

W

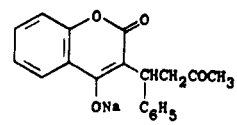
WARFARIN SODIUM

Therapeutic Function: Anticoagulant

Chemical Name: 3-(α-acetonylbenzyl)-4-hydroxycoumarin sodium salt

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 129-06-6; 81-81-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Coumadin	Endo	U.S.	1954
Prothromadin	Harvey	U.S.	1956
Athrombin	Purdue Frederick	U.S.	1959
Coumadine	Merrell	France	1959
Panwarfin	Abbott	U.S.	1960
Adoisine	Delalande	France	–
Aldocumar	Aldo Union	Spain	–
Dicusat	Ferrosan	Denmark	–
Marevan	Orion	Finland	–
Tintorane	A.C.F.	Neth.	–
Waran	Nyegaard	Norway	–
Warcoumin	Harvey	Australia	–
Warfilone	Merck-Frosst	Canada	–

Raw Materials

4-Hydroxycoumarin
Benzalacetone
Sodium hydroxide

Manufacturing Process

About 0.1 mol each of 4-hydroxycoumarin and benzalacetone are dissolved, in any desired order, in about three times their combined weight of pyridine. The solution is refluxed for about 24 hours, and then allowed to cool; after which it is poured into about 15 volumes of water, and acidified to about pH 2 by the addition of hydrochloric acid. An oil separates, and on cooling and standing overnight solidifies. The solid product is recovered, as by filtration, and recrystallized from ethanol, according to U.S. Patent 2,427,578.

The base melts at about 161°C. It is a white crystalline solid, soluble in hot ethyl alcohol

and substantially insoluble in cold water; it dissolves in alkali solutions with formation of the salt. The yield is about 40%.

Then, as described in U.S. Patent 2,777,859, warfarin may be reacted with NaOH to give a sodium salt solution. Crystalline warfarin sodium may be prepared as described in U.S. Patent 2,765,321.

References

Merck Index 9852
Kleeman & Engel p. 950
PDR pp. 545, 852, 1606
OCDS Vol. 1 p. 331 (1977)
I.N. p. 1015
REM p. 827
Stahmann, M.A., Ikawa, M. and Link, K.P.; U.S. Patent 2,427,578; September 16, 1947; assigned to Wisconsin Alumni Research Foundation
Schroeder, C.H. and Link, K.P.; U.S. Patent 2,765,321; October 2, 1956; assigned to Wisconsin Alumni Research Foundation
Link, K.P.; U.S. Patent 2,777,859; January 15, 1957; assigned to Wisconsin Alumni Research Foundation