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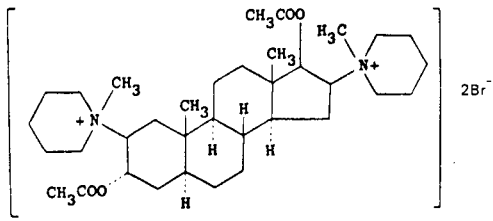
PANCURONIUM BROMIDE

Therapeutic Function: Muscle relaxant

Chemical Name: 1,1'-[3α,17β-bis(acetyloxy)-5α-androstane-2β,16β-diyl] bis[1-methylpiperidinium] dibromide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 15500-66-0

Trade Name	Manufacturer	Country	Year Introduced
Pavulon	Organon-Teknika	U.K.	1968
Pancuronium	Organon	W. Germany	1969
Pavulon	Organon-Teknika	France	1971
Pavulon	Organon	U.S.	1972
Myoblock	Organon-Sankyo	Japan	1973
Pavalon	Ravasini	Italy	1973

Raw Materials

3,17-Diacetoxy-5α-androstane-2,16-diene
m-Chlorperbenzoic acid
Piperidine
Sodium borohydride
Acetic anhydride
Methyl bromide

Manufacturing Process

A solution of 2α,3α,16α,17α-diepoxy-17β-acetoxy-5α-androstane (25 grams), prepared from 3,17-diacetoxy-5α-androstane-2,16-diene (*Chem. Abs.* 1960, 54, 8908) by treatment with m-chlor-per-benzoic acid, in piperidine (120 ml) and water (40 ml) was boiled under reflux for 5 days, the solution was concentrated and the product precipitated by the addition of water. The solid was collected, dissolved in dilute hydrochloric acid, filtered to give a clear solution and precipitated by the addition of sodium hydroxide solution. Crystalliza-

tion from acetone gave 2β,16β-bis-piperidino-5α-androstan-3α-ol-17-one (18.9 grams), MP 179°-185°C.

A solution of sodium borohydride (8 grams) in water (16 ml) was added to a stirred solution of 2β,16β-bis-piperidino-5α-androstan-3α-ol-17-one (17 grams) in tetrahydrofuran (70 ml) and methanol (30 ml) and the solution stirred at room temperature for 16 hours. The product was precipitated by the addition of water, filtered off, dried, and crystallized from acetone to give the diol (14.9 grams).

A solution of the piperidino-diol (9 grams) in acetic anhydride (18 ml) was heated at 90°C for 1 hour, the solution cooled, excess acetic anhydride destroyed by the careful addition of water, and the resulting solution carefully made alkaline with 2 N caustic soda solution to precipitate a solid product. The solid was dried, extracted with n-hexane and the solution filtered free of insoluble material before percolation down a column (4 x 1" diameter) of alumina. Elution with n-hexane gave a fraction (4.2 grams) which was crystallized twice from ether to give the diacetate, MP 176°-180°C.

Methyl bromide (17 grams) was added to a solution of the bis-piperidinodiacetate (4 grams) in methylene chloride (10 ml) and the resulting solution allowed to stand at room temperature for 4 days. The solution was evaporated to dryness, the residue triturated with ether, and filtered to give the bis-methobromide (5.2 grams), MP 206°C. Recrystallization from acetone-methylene chloride gave material MP 214°-217°C.

References

Merck Index 6870
Kleeman & Engel p. 681
PDR p. 1288
OCDS Vol. 2 p. 163 (1980)
DOT 5 (3) 104 (1969)
I.N. p. 726
REM p. 924
Hewett, C.L. and Savage, D.S.; U.S. Patent 3,553,212; January 5, 1971; assigned to Organon Inc.

PAPAIN

Therapeutic Function: Enzyme; used to prevent wound adhesions

Chemical Name: See Structural Formula

Common Name: –

Structural Formula: Has folded polypeptide chain of 212 residues with a molecular weight of about 23,400.

Chemical Abstracts Registry No.: 9001-73-4

Trade Name	Manufacturer	Country	Year Introduced
Papain	Green Cross	Japan	1969
Panafil	Rystan	U.S.	–
Prevenzyme	Legere	U.S.	–

Raw Materials

Papaya fruit
Methanol

Manufacturing Process

Crude papain, obtained as the dried exudate of the fruit and leaves of *Carica papaya* L., Caricaceae, is usually found to have been contaminated during collection, drying, or storage by insects, rodent hair and excreta, botanical plant parts, sand, etc. and may thereby become further contaminated by harmful bacteria and enteric organisms.

Heretofore papain has been purified by dispersing the crude enzymes in water, filtering and spray-drying. In this procedure, however, the soluble contaminants are retained in the dried product. It has also been known to purify papain by dispersing it in water and adding acetone to reprecipitate the enzymes leaving many of the acetone-soluble and water-soluble impurities in the supernatant liquid. The material thus purified possesses a very disagreeable sulfidelike taste probably due to the reaction between the acetone and reactive sulfhydryl groups present in the papaya latex.

It has now been found that an enzyme mixture of high purity which contains none of the objectionable sulfidelike taste can be obtained by dispersing the crude enzymes in water, adding a quantity of a water-miscible lower-alkanol to the incipient precipitation point of the proteolytic enzymes thereby retaining the maximum proteolytic activity (i.e., the maximum amount of the proteolytic enzymes) in the solvent phase while precipitating the major portion of the lower-alkanol insoluble contaminants, removing the lower-alkanol insoluble contaminants and precipitated inert materials, for example, by filtration or centrifugation, and then adding an additional quantity of the water-miscible lower-alkanol sufficient to precipitate the proteolytic enzymes.

The following is a specific example of the conduct of the present process. 100 g of crude papain were stirred with 120 ml of 0.01 M cysteine hydrochloride for one hour during which time the papain was completely dispersed. To the dispersion was added slowly and with vigorous stirring 147 ml of methanol. The mixture, which contained 55% methanol by volume, was stirred for about thirty minutes and centrifuged and the clear supernatant liquid was removed and saved. The precipitate was washed with 50 ml of 55% aqueous methanol, and the mixture was centrifuged again. The precipitate containing the undesirable, insoluble contaminants was discarded, and the clear wash liquid was combined with the main supernatant. To the combined clear supernatant liquid was added slowly and with vigorous stirring 265 ml of methanol to give a mixture containing 75.5% methanol by volume. The enzymes were precipitated as a taffylike gum which was isolated by decantation of the supernatant liquid containing the undesirable, soluble contaminants and tray-drying. Alternatively, the precipitated enzymes can be redissolved in pure water and spray-dried.

References

Merck Index 6878
PDR pp. 1033, 1576
REM p. 1038
Lesuk, A.; U.S. Patent 3,011,952; December 5, 1961; assigned to Sterling Drug, Inc.

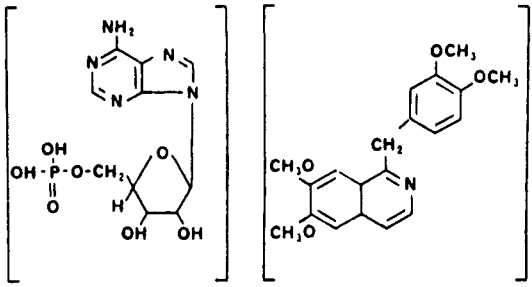
PAPAVERINE MONOPHOSADENINE

Therapeutic Function: Vasodilator and platelet aggregation inhibitor

Chemical Name: Papaverine adenosine 5-monophosphate

Common Name: Papaverine adenylate

Structural Formula:



Chemical Abstracts Registry No.: 58-74-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Lempav Ty-Med	Lemmon	U.S.	1975
Artegodan	Artesan	W. Germany	–
Cepaverin	Eurand	Italy	–
Cerespan	U.S.V.	U.S.	–
Dylate	Elder	U.S.	–
Omnopon	Roche	U.K.	–
Pameion	Simes	Italy	–
Panergon	Mack	W. Germany	–
Papaverlumin	Pidefe	Spain	–
Papaversan	Abello	Spain	–
Pavabid	Marion	U.S.	–
Pavacron	Cenci	U.S.	–
Pavagrant	Amfre-Grant	U.S.	–
Pavakey	Key Pharm.	U.S.	–
Pavatym	Everett	U.S.	–
Paver	Mulda	Turkey	–
Spastretten	Tropon	W. Germany	–
Sustaverine	I.C.N.	U.S.	–
Udip	Marion	U.S.	–

Raw Materials

Adenosine-5'-monophosphoric acid
Papaverine base

Manufacturing Process

To 3.65 g (0.01 mol) of monohydrated adenosine-5'-monophosphoric acid, brought into suspension in a mixture of 45 ml of water and 5 ml of ethanol, are added 3.39 g (0.01 mol) of papaverine base (melting point, 147°C). The mixture is gently heated until a final temperature of 40°C is reached. The solution obtained is then filtered and the filtrate is concentrated under vacuum. The remaining product quickly crystallizes. After drying to 50°C to constant weight, there are obtained 6.68 g of desired product, in the monohydrated state, as a white crystalline powder, which melts at 140°C and is very soluble in water.

References

Merck Index 6880
Kleeman & Engel p. 683
PDR pp. 830, 875, 993, 1079, 1569, 1606, 1810
OCDS Vol. 1 p. 347 (1977)
DOT 11 (8) 315 (1975)
I.N. p. 728
REM p. 852

Mauvernay, R.Y.; U.S. Patent 3,823,234; July 9, 1974; assigned to Centre Europeen de Recherches Mauvernay C.E.R.M.

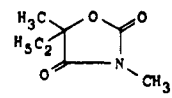
PARAMETHADIONE

Therapeutic Function: Anticonvulsant

Chemical Name: 5-ethyl-3,5-dimethyl-2,4-oxazolidinedione

Common Name: Isoethadione

Structural Formula:



Chemical Abstracts Registry No.: 115-67-3

Trade Name	Manufacturer	Country	Year Introduced
Paradione	Abbott	U.S.	1949

Raw Materials

Methyl ethyl ketone
Urea
Methanol
Sodium cyanide
Sodium
Dimethyl sulfate

Manufacturing Process

About 143.1 grams (one mol) of 5-methyl-5-ethyloxazolidine-2,4-dione is dissolved in 300 cc of methanol containing 23 grams of sodium. To the above mixture is added 126 grams of dimethyl sulfate in 10 cc portions while the temperature is maintained at about 50°C by external cooling. The mixture is then heated briefly to boiling, cooled, diluted with about 500 cc of water and extracted with two 250 cc portions of benzene. The benzene extract is separated, washed once with sodium bicarbonate solution and once with water. The benzene is removed by evaporation on a steam bath and the residue is fractionally distilled. The material boiling at 112° to 116°C at 25 mm pressure is taken; $n_D^{25} = 1.4495$. Upon further fractionation, a very pure specimen boils at 101°-102°C at 11 mm.

The 5-methyl-5-ethyloxazolidine-2,4-dione may be prepared by reacting methyl ethyl ketone with sodium cyanide and with ammonium thiocyanate followed by desulfurization. This intermediate may also be prepared by condensing α-hydroxy-α-methylbutyramide with ethyl chlorocarbonate or by condensing ethyl α-hydroxy-α-methylbutyrate with urea. Another method described (Traube and Aschar, *Ber.*, 46, 2077-1913) consists in the condensation of ethyl α-hydroxy-α-methylbutyrate with guanidine followed by hydrolysis.

References

Merck Index 6890
Kleeman & Engel p. 685
PDR p. 545
OCDS Vol. 1 p. 232 (1977)
I.N. p. 730
REM p. 1080

Spielman, M.A.; U.S. Patent 2,575,693; November 20, 1951; assigned to Abbott Laboratories

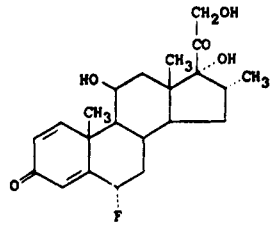
PARAMETHASONE ACETATE

Therapeutic Function: Glucocorticoid

Chemical Name: 6α-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 1597-82-6; 53-33-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Haldrone	Lilly	U.S.	1961
Dilar	Cassenne	France	1962
Paramezone	Recordati	Italy	1962
Monocortin	Gruenenthal	W. Germany	1963
Stemex	Syntex	U.S.	1970
Cortidene	I.F.L.	Spain	—
Metilar	Syntex	U.K.	—
Paramesone	Tanabe	Japan	—
Sintecort	Medicamenta	Portugal	—
Triniol	I.F.L.	Spain	—

Raw Materials

5α,11β,17α,21-Tetrahydroxy-6β-fluoro-16α-methylallopregnane-3,20-dione-21 acetate 3-ethylene glycol ketal
Hydrogen chloride

Manufacturing Process

A solution of 0.144 g of the 3-ethylene glycol ketal of 5α,11β,17α,21-tetrahydroxy-6β-fluoro-16α-methylallopregnane-3,20-dione 21-acetate in 12 ml of chloroform and 0.1 ml of absolute alcohol was cooled to -10°C in an ice-salt bath and a stream of anhydrous hydrochloric acid was gently bubbled through the solution for 2.5 hours while the temperature was maintained between -5°C and -15°C. The solution was then diluted with 25 ml of chloroform, washed with dilute sodium bicarbonate and water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure at 60°C or less to give 6α-fluoro-11β,17α,21-trihydroxy-16α-methyl-4-pregnene-3,20-dione 21-acetate.

References

Merck Index 6891

Kleeman & Engel p. 686
OCDS Vol. 1 p. 200 (1977)
I.N. p. 730
REM p. 969
Lincoln, F.H., Schneider, W.P. and Spero, G.B.; U.S. Patent 3,557,158; January 19, 1971; assigned to The Upjohn Co.

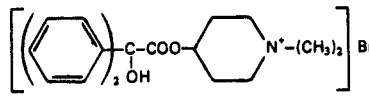
PARAPENZOLATE BROMIDE

Therapeutic Function: Antiulcer

Chemical Name: N-Methyl-4-piperidylbenzilate methobromide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: –

Trade Name	Manufacturer	Country	Year Introduced
Spacine	Unilabo	France	1968
Vagopax	Essex	Italy	1976
Vagopax	Centrane	France	–

Raw Materials

N-Methyl-4-piperidinol HCl
Diphenylchloroacetyl chloride
Methyl iodide
Silver bromide

Manufacturing Process

N-methyl-4-piperidyl benzilate and the methiodide: An intimate mixture of 0.1 mol of N-methyl-4-piperidinol hydrochloride and 0.1 mol diphenylchloroacetyl chloride is heated at 160°C to 180°C until the evolution of hydrogen chloride ceases (usually about 4 to 5 hours). The melt is then dissolved in 500 ml of water and the resultant mixture heated on a steam bath for about ½ hour, after which time complete solution is effected. The acid solution is cooled and rendered alkaline with ammonium hydroxide solution whereupon the ester is precipitated. The ester is purified either by removal by filtration and recrystallization from benzene petroleum ether or by extracting the mixture with benzene and precipitating the ester by the addition of petroleum ether. After recrystallization there is obtained about 0.06 mol of N-methyl-4-piperidyl benzilate, melting point 162°C to 163°C.

To a solution of 0.05 mol of the above-obtained ester in about 100 ml of anhydrous benzene there are added 15 ml of methyl iodide. The ensuing mixture is refluxed for several hours whereupon the quaternary salt is deposited and removed by filtration. Recrystallization from ethanol or ethanol-ether yields the quaternary salt, melting point 199°C to 200°C.

N-methyl-4-piperidyl benzilate methobromide: To a suspension of 0.15 mol of freshly prepared silver bromide in 300 ml of anhydrous methanol is added a solution of 0.1 mol of quaternary iodide obtained as above. The mixture is stirred and refluxed for several hours after which time transhalogenation is complete. The mixture is cooled, the insoluble silver

salt removed by filtration and the methanolic solution of the quaternary bromide is concentrated in vacuo. The residue is recrystallized from methanol or methanol-ether yielding the quaternary bromide in quantitative amounts, melting point 237°C to 238°C.

References

OCDS Vol. 2 p. 75 (1980)
DOT 6 (3) 92 (1970)
I.N. p. 731
Papa, D.; British Patent 788,126; December 23, 1957; assigned to Schering Corp.

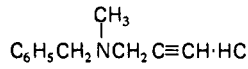
PARGYLINE HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: N-methyl-N-2-propynylbenzenemethanamine hydrochloride

Common Name: N-methyl-N-propargylbenzylamine hydrochloride

Structural Formula:



$$C_6H_5CH_2\overset{\overset{CH_3}{|}}{N}CH_2C{\equiv}CH\cdot HCl$$

Chemical Abstracts Registry No.: 306-07-0; 555-57-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Eutonyl	Abbott	U.S.	1963

Raw Materials

N-Methylbenzylamine
Propargyl bromide
Sodium carbonate
Hydrogen chloride

Manufacturing Process

A mixture of 23.8 grams (0.2 mol) of propargyl bromide, 24.2 grams (0.2 mol) of N-methyl benzylamine and 400 ml of anhydrous ethanol in the presence of 42.4 grams (0.4 mol) of anhydrous sodium carbonate was heated at the boiling temperature and under reflux for a period of 17 hours.

The sodium carbonate was then removed by filtration and the alcohol was removed by distillation under reduced pressure. The residue was treated with 300 ml of dry ether and the resulting solution was filtered to remove sodium bromide.

The filtrate was dried and fractionally distilled under reduced pressure to obtain the desired N-methyl-N-propargylbenzylamine which boiled at 96°-97°C at 11 mm pressure.

Analysis calculated for $C_{11}H_{13}N$: C = 82.97%; H = 8.23%; N = 8.80%. Found: C = 82.71%; H = 8.51%; N = 8.93%.

The hydrochloride salt of this amine was prepared by dissolving the amine in ether and adding ethereal hydrogen chloride to the ether solution. The solid hydrochloride salt which precipitated was recrystallized from an ethanol-ether mixture and was found to melt at 154°-155°C.

References

Merck Index 6902
Kleeman & Engel p. 688
PDR p. 523
OCDS Vol. 1 p. 54 (1977) & 2, 27 (1980)
DOT 9 (6) 217 (1973)
I.N. p. 732
REM p. 850
Martin, W.B.; U.S. Patent 3,155,584; November 3, 1964; assigned to Abbott Laboratories

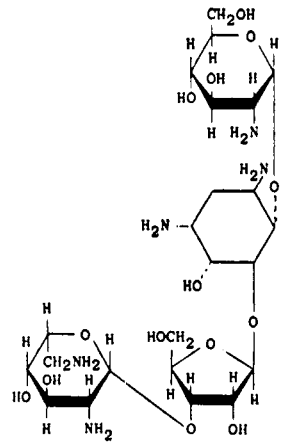
PAROMOMYCIN

Therapeutic Function: Amebacidal

Chemical Name: O-2,6-diamino-2,6-dideoxy-β-L-idopyranosyl-(1→3)-O-β-D-ribofuranosyl-(1→5)-O-[2-amino-2-deoxy-α-D-glucopyranosyl-(1→4)]-2-deoxystreptamine

Common Name: Catenulin, aminosidine, crestomycin, hydroxymycin, neomycin E, paucimycin

Structural Formula:



Chemical Abstracts Registry No.: 7542-37-2

Trade Name	Manufacturer	Country	Year Introduced
Humatin	Parke Davis	U.S.	1960
Humatin	Parke Davis	W. Germany	1961
Humatin	Parke Davis	Italy	1961
Humagel	Parke Davis	France	1963
Aminosidine	Kyowa	Japan	–
Aminoxidin	Farmalabor	Italy	–
Gabbromycin	Montedison	Italy	–
Gabbroral	Farmalabor	Italy	–
Paramicina	Ragionieri	Italy	–

Raw Materials

Bacterium *Streptomyces rimosus* forma *paromomycinus*

Glucose
Soybean meal

Manufacturing Process

As described in U.S. Patent 2,916,485: 12 liters of a nutrient medium having the following composition is placed in a 30 liter fermentor equipped with stainless steel fittings including sparger, impeller, baffles and sampling lines and the medium is sterilized by heating at 121°C for two hours.

	Percent
Glucose monohydrate	0.5
Glycerol	0.5
Casein, acid hydrolyzed	0.3
Peptone	0.25
Brewer's yeast	0.1
Cornsteep solids	0.25
Soybean oil meal	0.25
Acetone-butanol fermentation residue	0.25
Sodium chloride	0.5
Calcium carbonate	0.1
Water sufficient to make	100%

The medium is cooled and inoculated with 20 ml of a suspension of the spores from two Moyer's sporulation agar slant cultures of *Streptomyces rimosus* forma *paromomycinus* in sterile 0.1% sodium heptadecyl sulfate solution. The inoculated culture mixture is incubated at 26°C for sixty hours during which time the mixture is stirred at 200 rpm and sterile air is passed into the medium through the sparger at the rate of 12 liters per minute. A portion of the resulting incubated culture mixture is employed for inoculation of 16 liters of a nutrient medium having the following composition:

	Percent
Glucose monohydrate	1.0
Soybean oil meal	1.0
Sodium chloride	0.5
Calcium carbonate	0.1
Ammonium chloride	0.167
Hog stomach residue, saline extracted	0.5
Water sufficient to make	100%

The pH of the latter nutrient medium is adjusted to 7.5 with 10 N sodium hydroxide solution and is placed in a 30 liter glass fermentor equipped with sparger, impeller, baffles and sampling line. The medium is sterilized by heating at 121°C for two hours, is allowed to cool and is then inoculated with 800 ml of the culture mixture obtained as described above.

The resulting culture mixture is incubated at 26°C for 94 hours during which time the mixture is stirred at 200 rpm and sterile air is passed into the medium through the sparger at the rate of 16 liters per minute. During the incubation, foaming is avoided by the addition, as needed, of crude lard and mineral oils containing mono- and diglycerides.

At the end of the incubation period the fermentation culture mixture is adjusted to pH 2 with concentrated hydrochloric acid, the solid material present is removed by filtration, and the filter cake is washed with water. The washings are combined with the main filtrate, adjusted to pH 7.0, and 15.5 liters of the filtered culture liquid is introduced into a columnar exchanger (1½" i.d.) packed with 380 ml of carboxylic acid resin which has been preliminarily washed in succession with two liters of an aqueous solution of 37.5 grams of sodium hydroxide and with two liters of water. The column containing paromomycin is washed with two hold-up volumes of water and is eluted with 0.5 N hydrochloric acid.

The first 19.4 liters of percolate contains little or no paromomycin and varies in pH from 6 to 7.3. When the pH of the eluate begins to fall below 6.0, two liters of the eluate are collected.

The two liter portion of the eluate, collected as indicated, is neutralized to pH 6 with 10 N sodium hydroxide solution and is filtered. The filtrate is concentrated by evaporation in vacuo to a volume of approximately one liter.

An adsorption column is prepared by pouring a slurried aqueous mixture of 65 grams of acid-washed activated charcoal (Darco G-60) and 50 grams of diatomaceous earth in a 1½" column and 300 ml of the concentrated filtrate is added. The column is washed with 400 ml of water and eluted successively with 325 ml of water, 425 ml of 1% aqueous acetone and 400 ml of 10% aqueous acetone. The water and acetone eluates are concentrated and lyophilized to give paromomycin hydrochloride as a powder. The product is purified by taking up the powder in methanol, adding a large excess of acetone to the solution, recovering the precipitate which forms by filtration. The product, paromomycin hydrochloride, has an optical rotation $[\alpha]_D^{25} = +56.5°$ (1% in water). By analysis it contains 35.71% carbon, 6.95% hydrogen, 8.24% nitrogen and 21.5% chlorine.

In order to obtain paromomycin in free base form, the hydrochloride is dissolved in water as a 3% solution, the solution is poured into an adsorption column containing an anion exchange resin (Amberlite IR-45 or preferably IRA-411 or IRA-400) in the hydroxyl form and the column is washed with a small amount of water.

The aqueous percolate is concentrated to dryness by lyophilization, and the solid product obtained is purified by taking up in boiling absolute ethanol, cooling and recovering the solid product paromomycin; $[\alpha]_D^{25} = +64°$ (1% in water). By analysis it contains 45.17% carbon, 7.44% hydrogen and 10.35% nitrogen.

References

Merck Index 6903
Kleeman & Engel p. 688
I.N. p. 733
REM p. 1221
Davisson, J.W. and Finlay, A.C.; U.S. Patent 2,895,876; July 21, 1959; assigned to Chas. Pfizer & Co., Inc.
Frohardt, R.P., Haskell, T.H., Ehrlich, J. and Knudsen, M.P.; U.S. Patent 2,916,485; Dec. 8, 1959; assigned to Parke, Davis & Company

PELARGONIC ACID

Therapeutic Function: Fungicide

Chemical Name: Nonanoic acid

Common Name: –

Structural Formula: $CH_3(CH_2)_7COOH$

Chemical Abstracts Registry No.: 112-05-0

Trade Name	Manufacturer	Country	Year Introduced
Pellar	Crookes Barnes	U.S.	1960

Raw Materials

Oleic acid
Oxygen

Manufacturing Process

A body of liquid, 18 inches high, comprising a 35% (by weight) solution of technical (95%) oleic acid in n-propanol, is maintained at a temperature of 86°C in a reactor. The solution also contains dissolved therein 0.042% by weight of cobalt, in the form of cobalt naphthenate. From the bottom of the reactor very fine bubbles of air are passed into and through the solution at the rate of about 0.3 cubic feet per minute, measured at standard conditions, per square foot for 72 hours. The gases leaving the reactor are first passed through an ice water reflux condenser and then vented to the atmosphere. At the end of the 72 hour period the reaction mixture is separated into its components. It is found that 60% of the oleic acid has been consumed in the reaction. For each pound of oleic acid consumed there are obtained 0.30 pound of azelaic acid (representing an efficiency of 46%, calculated on the basis that the technical oleic acid is 100% oleic acid), 0.13 pound of pelargonic acid (representing an efficiency of 23%) and 0.21 pound of 9,10-dihydroxystearic acid (representing an efficiency of 19%).

References

Merck Index 6923
MacKenzie, J.S. and Morgan, C.S. Jr.; U.S. Patent 2,820,046; January 14, 1958; assigned to Celanese Corp. of America

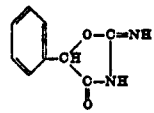
PEMOLINE

Therapeutic Function: Psychostimulant

Chemical Name: 2-imino-5-phenyl-4-oxazolidinone

Common Name: Phenoxazole; phenylisohydantoin

Structural Formula:



Chemical Abstracts Registry No.: 2152-34-3

Trade Name	Manufacturer	Country	Year Introduced
Deltamine	Aron	France	1960
Cylert	Abbott	U.K.	1975
Cylert	Abbott	U.S.	1975
Antimeran	Nichiiko	Japan	–
Betanamin	Sanwa	Japan	–
Dynalert	Restan	S. Africa	–
Hyton	Pharmacia	Sweden	–
Kethamed	Medo	U.K.	–
Nitan	Teva	Israel	–
Phenoxine	P.C.B.	Belgium	–
Pioxol	Horner	Canada	–

Trade Name	Manufacturer	Country	Year Introduced
Pondex	Chinoin	Hungary	–
Revibol	Pliva	Yugoslavia	–
Ronyl	Rona	U.K.	–
Sigmadyn	Spemsa	Italy	–
Sofro	Thilo	W. Germany	–
Stimul	Nadrol	W. Germany	–
Tradon	Beiersdorf	W. Germany	–
Vidil	Waldheim	Austria	–

Raw Materials

Mandelic acid ethyl ester
Guanidine

Manufacturing Process

It is preferably prepared by reacting mandelic acid ethyl ester with guanidine in boiling alcoholic solution whereby it is obtained as difficultly soluble precipitate with a yield of 90%.

This compound is a white, crystalline compound melting at 256°-257°C with decomposition. It is readily soluble in concentrated aqueous alkali hydroxide solutions and in concentrated aqueous mineral acids.

References

Merck Index 6931
Kleeman & Engel p. 690
PDR p. 509
DOT 9 (6) 212 (1973)
I.N. p. 736
REM p. 1137
Schmidt, L. and Scheffler, H.; U.S. Patent 2,892,753; June 30, 1959; assigned to C.H. Boehringer Sohn, Germany

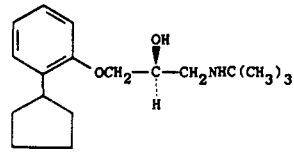
PENBUTOLOL

Therapeutic Function: Beta-Adrenergic blocker

Chemical Name: 1-(2-Cyclopentylphenoxy)-3-[(1,1-dimethylethyl)amino]-2-propanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 38363-40-5

Trade Name	Manufacturer	Country	Year Introduced
Betapressin	Hoechst	W. Germany	1980
Betapressin	Hoechst	Switz.	1982
Betapressin	Hoechst	Italy	1983

Raw Materials

2-Cyclopentylphenol
Epichlorohydrin
t-Butylamine

Manufacturing Process

21.8 g (0.1 mol) of 1,2-epoxy-3-(2'-cyclopentylphenoxy)propane, boiling at 113°C to 115°C/0.2 mm Hg (prepared from 2-cyclopentylphenol and epichlorhydrin in the presence of alkali) were dissolved in 250 ml of ethanol; to this solution, there were added dropwise, while stirring, 8.9 g (0.15 mol) of t-butylamine. The reaction mixture was stirred for 2 hours at 60°C and then the solvent and the excess t-butylamine were removed by distillation. The residue which had been purified via the aqueous hydrochloride, crystallized, after removal of the ether by evaporation, upon rubbing or inoculation and yielded, after recrystallization from n-heptane, the 1-t-butylamino-2-hydroxy-3-(2'-cyclopentylphenoxy)propane which was found to melt at 69°C to 70°C.

References

Merck Index 6935
DFU 1 (10) 494 (1976)
Kleeman & Engel p. 691
DOT 17 (12) 555 (1981) & 18 (10) 551 (1982)
I.N. p. 737
Ruschig, H., Schmitt, K., Lessenich, H. and Hartfelder, G.; U.S. Patent 3,551,493; Dec. 29, 1970; assigned to Farbwerke Hoechst A.G. (W. Germany)

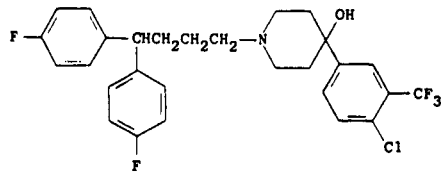
PENFLURIDOL

Therapeutic Function: Antipsychotic

Chemical Name: 1-[4,4-Bis(4-fluorophenyl)butyl]-4-[4-chloro-3-(trifluoromethyl)phenyl]-4-piperidinol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 26864-56-2

Trade Name	Manufacturer	Country	Year Introduced
Semap	Janssen Le Brun	W. Germany	1975
Semap	Janssen	France	1975

Trade Name	Manufacturer	Country	Year Introduced
Flupidol	Zambeletti	Italy	1979
Longoran	Isis	Yugoslavia	—
Micefal	Spofa	Czechoslovakia	—
Semap	Abic	Israel	—

Raw Materials

4,4-Bis(p-fluorophenyl)butyl chloride
4-(4-Chloro-α,α,α-trifluoro-m-tolyl)-4-piperidinol

Manufacturing Process

A mixture of 24 parts of 4,4-bis(p-fluorophenyl)butyl chloride, 20.9 parts of 4-(4-chloro-α,α,α-trifluoro-m-tolyl)-4-piperidinol, 13.8 parts of sodium carbonate, a few crystals of potassium iodide in 600 parts of 4-methyl-2-pentanone is stirred and refluxed for 60 hours. The reaction mixture is cooled and 150 parts of water is added. The organic layer is separated, dried, filtered and evaporated. The oily residue is crystallized from diisopropylether, yielding 4-(4-chloro-α,α,α-trifluoro-m-tolyl)-1-[4,4-bis(p-fluorophenyl)butyl] -4-piperidinol; melting point 106.5°C.

References

Merck Index 6939
Kleeman & Engel p. 691
OCDS Vol. 2 p. 334 (1980)
DOT 10 (5) 167 (1974)
I.N. p. 737
Hermans, H.K.F. and Niemegeers, C.J.E.J.; U.S. Patent 3,575,990; April 20, 1971; assigned to Janssen Pharmaceutica N.V. (Belgium)

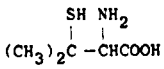
PENICILLAMINE

Therapeutic Function: Used in treatment of rheumatoid arthritis

Chemical Name: 3-Mercapto-D-valine

Common Name: Dimethylcysteine

Structural Formula:



Chemical Abstracts Registry No.: 52-67-5; 2219-30-9 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Cuprimine	MSD	U.S.	1963
Trolovol	Bayer	W. Germany	1963
Pendramine	B.D.H.	U.K.	1973
Pemine	Lilly	Italy	1975
Trolovol	Bayer	France	1979
Depen	Wallace	U.S.	1979
Artamin	Biochemie	Austria	—
Cuprenil	Polfa	Poland	—
Cupripen	Rubio	Spain	—

Trade Name	Manufacturer	Country	Year Introduced
Depamine	Berk	U.K.	–
Distamine	Dista	U.K.	–
Gerodyl	Gea	Denmark	–
Metalcapase	Knoll	W. Germany	–
Reumacillin	Medica	Finland	–
Rhumantin	Gea	Denmark	–
Sufortanon	Lacer	Spain	–

Raw Materials

Potassium benzyl penicillin
Mercuric chloride
Hydrogen sulfide
Sodium hydroxide
Phenylhydrazine

Manufacturing Process

(a) Preparation of mercuric chloride complex of penicillamine: To a solution of 372 g (1 mol) of potassium benzyl-penicillin in 940 ml of distilled water at room temperature is added a solution of 40 g (1 mol) of sodium hydroxide in 180 ml of distilled water over a period of one-half hour. The solution is then stirred for two hours at room temperature. While maintaining room temperature, 67 ml of concentrated hydrochloric acid is added at a slow rate. This solution is then added, over a period of time of one-half hour, to a solution of 271 g (1 mol) of $HgCl_2$ in 3.52 liters of distilled water in the presence of 50 g of Hyflo and 5 ml of octyl alcohol. After one hour of agitation, the resulting mixture is treated with 185 ml of concentrated hydrochloric acid and filtered.

(b) Removal of benzylpenilloaldehyde: To the filtrate obtained in step (a), warmed to 50°C is slowly added 108 g (1 mol) of phenyl hydrazine. The mixture is cooled to room temperature and 84 ml of concentrated hydrochloric acid are added. The mixture is agitated briefly and the precipitated benzylpenilloaldehyde phenyl hydrazone is filtered off.

(c) Preparation of isopropylidene penicillamine hydrochloride: To the filtrate obtained in step (b) is added at 20°C to 25°C a total of 85 g of hydrogen sulfide. The precipitated HgS is filtered off and the filtrate is concentrated under reduced pressure to a volume of 200 to 500 ml. Following a polish filtration, the product-rich concentrate is mixed with 1.5 liters of isobutyl acetate. The mixture is refluxed at about 40°C under reduced pressure in equipment fitted with a water separation device. When no further water separates, the batch is cooled to 30°C and filtered. The reactor is washed with 1 liter of acetone, which is used also to wash the cake. The cake is further washed with 200 ml of acetone. The acetone washes are added to the isobutyl acetate filtrate and the mixture is refluxed for 20 to 30 minutes. After a holding period of one hour at 5°C, the crystals of isopropylidene penicillamine hydrochloride are filtered and washed with 200 ml of acetone. On drying for twelve hours at 25°C this product, containing 1 mol of water, weighs about 178 g (73%).

(d) Preparation of penicillamine hydrochloride: The 178 g of isopropylidene penicillamine hydrochloride obtained in step (c) is dissolved in 350 ml of distilled water. The solution is heated at 90°C to 95°C for one to one and one-half hours, removing acetone by distillation through an efficient column. There is then added 2.6 liters of isobutyl acetate. The mixture is refluxed at a temperature of about 40°C under reduced pressure in equipment fitted with a water separation device. When no further water separates, the pressure is adjusted so that the mixture distills at a vapor temperature of 83°C to 88°C. A total of 650 ml of distillate is collected. The batch is allowed to cool to 50°C and then filtered. The crystals are washed with isobutyl acetate and then dried at 35°C for 24 hours. The virtually anhydrous penicillamine hydrochloride obtained weighs about 128 g (69% from potassium benzyl-penicillin).

References

Merck Index 6940
Kleeman & Engel p. 693

PDR pp. 1153, 1872
DOT 9 (7) 302 (1973)
I.N. p. 738
REM p. 1225
Restivo, A.R., Dondzila, F.A. and Murphy, H. Jr.; U.S. Patent 3,281,461; October 25, 1966; assigned to E.R. Squibb & Sons, Inc.
Sota, K., Ogawa, T. and Sawada, J.; U.S. Patent 4,150,240; April 15, 1979; assigned to Taisho Pharmaceutical Co., Ltd. (Japan)

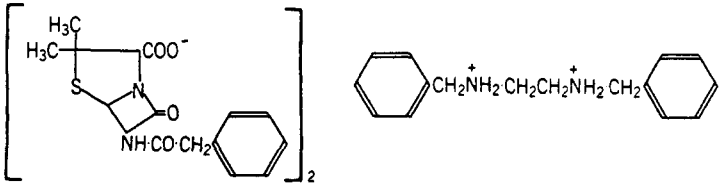
PENICILLIN G BENZATHINE

Therapeutic Function: *Antibacterial*

Chemical Name: Penicillin G compound with N,N'-dibenzylethylenediamine

Common Name: Benzethacil

Structural Formula:



Chemical Abstracts Registry No.: 1538-09-6

Trade Name	Manufacturer	Country	Year Introduced
Bicillin	Wyeth	U.S.	1951
Permapen	Pfizer	U.S.	1953
Neolin	Lilly	U.S.	1953
Extencilline	Specia	France	1954
Benzetacil-Simple	Antibioticos	Spain	—
Brevicilina-Simple	Wassermann	Spain	—
Brunocillin	Mepha	Switz.	—
Cepacilina	Cepa	Spain	—
Depotpen	Dauelsberg	W. Germany	—
Diaminocillina	Farmalabor	Italy	—
Durabiotic	Teva	Israel	—
Longacillin	Besy	Brazil	—
LPG	C.S.L.	Australia	—
Megacillin	Merck-Frosst	Canada	—
Pen-Di-Ben	Bago	Argentina	—
Pendysin	Jenapharm	E. Germany	—
Penidural	Wyeth	U.K.	—
Peniroger Retard	Roger	Spain	—
Pipercilina	Iskia	Spain	—
Retarpen	Biochemie	Austria	—
Tardocillin	Bayer	W. Germany	—
Tardopenil	Farmabion	Spain	—

Raw Materials

Ethylenediamine
Benzaldehyde
Sodium penicillin G

Manufacturing Process

Ethylenediamine (15 g, 0.25 mol) was added dropwise to 100 ml 98-100% formic acid in a two-necked 500 ml flask, fitted with an addition tube and reflux condenser with drying tube, cooled in an ice-bath. After complete addition of the base, 53 g of benzaldehyde (0.5 mol) was added in one lot. The ice-bath was removed and the flask was heated to the refluxing temperature. The initial rate of carbon dioxide evolution was too rapid to measure. After twenty minutes, the rate was circa 100 ml per minute and decreased rapidly to 8 ml per minute in one hour. Heating at reflux was continued for 35 hours.

Following the refluxing most of the excess formic acid was removed under reduced pressure. Hydrochloric acid (200 ml 6N) was added to the viscous amber residue and heated under reflux. After 15 minutes, bumping necessitated cooling and filtering to remove crystalline dihydrochloride, which after washing with isopropanol was dried, MP circa 300°C. The mother liquors were refluxed one hour and cooled, obtaining an additional amount of product, MP circa 300°C. The filtrate was concentrated in vacuo to 100 ml, cooled and made alkaline with 40% NaOH. The supernatant oil was extracted with ether, dried, and fractionated from a stillpot packed with glass wool and heated in a sand-bath at 320°C. The first fraction at 106°C at 0.6-0.7 mm was N-benzylethylenediamine (dipicrate, MP 222°C). The N,N'-dibenzylethylenediamine was collected at 177°C to 206°C at 0.6-1.0 mm as a colorless liquid.

To a solution of 60 g of sodium penicillin G in 800 cc of distilled water cooled to 0°C to 4°C in an ice-bath, a solution of 35 g of N,N'-dibenzylethylenediamine diacetate in 200 cc of distilled water is added dropwise with stirring. The thick slurry is filtered with suction, washed twice with 100 cc of cold water, dried by suction and spread out in a thin layer for completion of drying. The product weighed 80 g.

The air-dried powder has a broad melting point, sintering at 100°C, melting above 110°C to a cloudy liquid becoming clear at 135°C.

References

Merck Index 6948
Kleeman & Engel p. 85
PDR pp. 1406, 1941, 1989
I.N. p. 126
REM p. 1197
Szabo, J.L. and Bruce, W.F.; U.S. Patent 2,627,491; February 3, 1953; assigned to Wyeth, Inc.

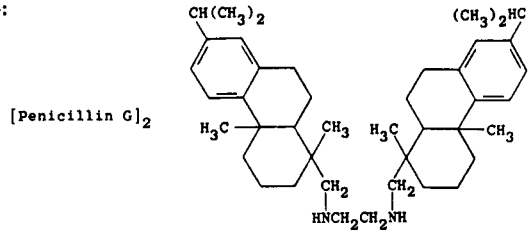
PENICILLIN G HYDRABAMINE

Therapeutic Function: Antibacterial

Chemical Name: N,N'-Bis(dehydroabietyl)ethylenediamine dipenicillin G

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 3344-16-9

Trade Name	Manufacturer	Country	Year Introduced
Compocillin	Abbott	U.S.	1954

Raw Materials

Dehydroabietylamine
Ethylene dibromide
Penicillin G

Manufacturing Process

A mixture of 142.5 g of "Rosin Amine D" containing about 70% dehydroabietylamine and 30% dihydro and tetrahydroabietylamine, 47.0 g of ethylene dibromide, and 60.6 g of triethylamine is dissolved in 350 cc of anhydrous xylene and refluxed for about 16 hours. Thereafter the triethylamine dibromide salt formed is separated from the solution by filtering the cool reaction mixture and washing with ether. The solution is then concentrated under reduced pressure to dryness to remove the ether, xylene and excess triethylamines present. The viscous oil resin is slurried twice with 250 cc portions of methanol to remove any unreacted primary amines. The oil residue after being washed with methanol is dissolved in ethyl alcohol and 75 cc of concentrated hydrochloric acid is added dropwise to the warm alcohol solution of the base. The dihydrochloride salts of the several hydroabietyl ethylenediamines precipitates immediately from solution. The salt is then separated by filtering and is washed twice with 100 cc portions of cooled ethyl alcohol. The dihydrochloride salts of the dehydroabietyl, dihydroabietyl and tetrahydroabietyl ethylenediamine mixture have a melting point of about 292°C to 295°C. On subjecting the mixture to solubility analyses it is found that the dehydroabietyl ethylenediamine is present in substantially the same proportion as is the dehydroabietylamine in the original "Rosin Amine D."

An amyl acetate-penicillin acid solution (10 liters) having a potency of 100,000 U/ml which is sufficient to supply 565 g (2 mols) of penicillin acid is added with constant agitation to 505 g of crude N,N'-bis-(dehydroabietyl)-ethylenediamine dissolved in 500 ml of amyl acetate. A slight excess of the ethylenediamine bases is added to the mixture until precipitation is completed. The reaction is preferably carried out in a cold room having a temperature of about 5°C. The precipitation salts comprise about 70% N,N'-bis-(dehydroabietyl)-ethylenediamine-dipenicillin salt and approximately 25-30% of the N,N'-bis-(dihydroabietyl)-ethylenediamine- and N,N'-bis-(tetrahydroabietyl)-ethylenediamine-dipenicillin salts are recovered by filtration and are washed with about 1/10 solution volume of amyl acetate. The crude preparation is further washed with 1/10 solution volume of diethyl ether and dried. The melting point of the product is about 153°C when taken on a microblock.

The total yield of the crude precipitation obtained in the above manner comprising about 1 kg is then dissolved in chloroform so as to form a 15% solution of a crude penicillin salt. To the filtered chloroform solution is added ethyl acetate slowly and with agitation until the solution becomes turbid as crystallization begins. Thereafter crystallization is allowed to proceed undisturbed for about 30-60 minutes in a cold room having a temperature of about 5°C. Sufficient ethyl acetate is slowly added to provide a final concentration of about 50% ethyl

acetate and the mixture is allowed to stand in the cold room for one hour to complete crystallization. The precipitate is filtered and washed with about 750 ml of ethyl acetate and thereafter washed with the same volume of ether. The crystals are dried in vacuo and a yield of about 900 g of N,N'-bis-(dehydroabietyl)-ethylenediamine-dipenicillin G is obtained. The penicillin product melts with decomposition at a temperature of 170°C to 172°C on a Kofler hot stage. *Solubility analysis of the product shows the product to be 95.3% pure.*

References

Merck Index 6951
I.N. p. 739
De Rose, A.F.; U.S. Patent 2,812,326; November 5, 1957; assigned to Abbott Laboratories

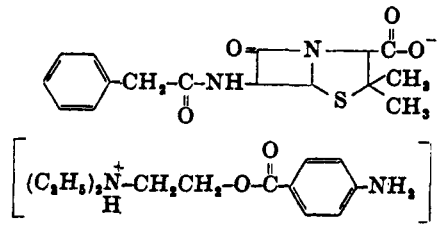
PENICILLIN G PROCAINE

Therapeutic Function: Antibacterial

Chemical Name: Penicillin G compound with 2-(diethylamino)ethyl p-aminobenzoate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 54-35-3

Trade Name	Manufacturer	Country	Year Introduced
Duracillin	Lilly	U.S.	1948
Flo-Cillin	Bristol	U.S.	1949
Ledercillin	Lederle	U.S.	1949
Wycillin	Wyeth	U.S.	1949
Diurnal Penicillin	Upjohn	U.S.	1950
Abbocillin	Abbott	U.S.	1951
Ampin-Penicillin	Badische Arzneim.	W. Germany	–
Aquacaine	C.S.L.	Australia	–
Aquasuspen	SK Kauelsberg	W. Germany	–
Aqucilina	Antibioticos	Spain	–
Cilicaine	Sigma	Australia	–
Distaquaine	Distillers	U.K.	–
Excolicin	Jenapharm	E. Germany	–
Farmaproina	Cepa	Spain	–
Francacilline	Franca	Canada	–
Hypercillin	Cutter	U.S.	–
Hypropen	Biochemie	Austria	–
Intrasept	Streuli	Switz.	–
Klaricina	Clariana	Spain	–
Novocillin	Solac	France	–
Penifasa	Lifasa	Spain	–

Trade Name	Manufacturer	Country	Year Introduced
Peniroger Procain	Roger	Spain	–
Premocillin	Premo	U.S.	–
Procapen	Orion	Finland	–
Prokapen	Weifa	Norway	–
Retardillin	Egyt	Hungary	–
Sanciline Procaina	Santos	Spain	–
Therapen I.M.	Therapex	Canada	–

Raw Materials

Penicillin G
Procaine

Manufacturing Process

There was added to 250 ml of a concentrated butyl acetate extract containing 74,000 units of the acid form of penicillin per ml, 50 ml of a butyl acetate solution containing 0.238 g per ml of procaine base. The solution was agitated for one hour. The precipitate which formed was very gummy and not in the form of discrete crystals. This precipitate was crystallized by scratching the side of the vessel and agitating further. After this treatment 18.25 g of crystalline procaine penicillin was obtained which assayed 1010 units per mg representing a yield of 99.6% of the activity contained in the concentrated extract.

References

Merck Index 6953
PDR pp. 1408, 1742, 1941, 1989
I.N. p. 739
REM p. 1198
Bardolph, M.P.; U.S. Patent 2,739,962; March 27, 1956; assigned to Commercial Solvents Corp.

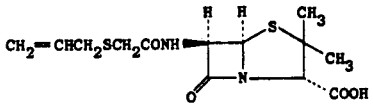
PENICILLIN O

Therapeutic Function: Antibacterial

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

Common Name: Allylmercaptomethylpenicillin

Structural Formula:



Chemical Abstracts Registry No.: 87-09-2

Trade Name	Manufacturer	Country	Year Introduced
Cero-O-Cillin	Upjohn	U.S.	1950

Raw Materials

Bacterium *Penicillium*

Lactose
Corn steep liquor
N-(2-Hydroxyethyl)allylmercaptoacetamide

Manufacturing Process

A culture medium is prepared in the following proportions:

Lactose	125 g
Corn steep solids	150 g
Calcium carbonate	25 g
N-(2-Hydroxyethyl)-allylmercaptoacetamide	0.140 g
Water	5,000 cc

The culture medium is distributed in 200 cc portions in 1 liter Erlenmeyer flasks, sterilized, inoculated with a spore suspension of *Penicillium* mold strain Q-176, and stoppered with cotton plugs. The flasks are maintained at a temperature of about 23°C to 26°C and shaken constantly for five days. The flask contents are then filtered to remove the mold mycelium, the filtrate cooled to about 0°C, acidified to about pH 2.2 with o-phosphoric acid and shaken with an equal volume of amyl acetate. The amy acetate layer is separated and extracted with three 100 cc portions of cold water to which cold N/10 sodium bicarbonate solution is added during the course of each extraction until a pH of about 7.1 to 7.3 is attained in the aqueous phase. The aqueous extracts are combined, cooled to about 0°C, acidified to about pH 2.2 with o-phosphoric acid and extracted with three 100 cc portions of ether. The ether extracts are combined, and are passed through a chromatographic type silica adsorption column about 30 mm in diameter and 300 mm long, and containing a pH 6.2 phosphate buffer. The silica column is developed by percolation with six 100 cc portions of ether containing successively increasing amounts of methanol in the order of ½, 1, 1½, 2, 2½, and 3 percent.

The developed silica column is divided into about 12 equal sections and each section is eluted with three 30 cc portions of M/15 phosphate buffer of pH 7.0. The eluates are assayed bacteriologically to determine their penicillin content. Most of the antibiotic activity originates in a single bank in the silica column and results from the presence of allylmercaptomethylpenicillin. The eluates obtained from this band are combined, cooled to about 0°C, acidified to about pH 2.2 and extracted with three 50 cc portions of chloroform. The combined chloroform extracts are then passed through a silica adsorption column containing a pH 6.2 phosphate buffer. This silica gel column is developed by percolation with three 100 cc portions of chloroform containing successively increasing amounts of methanol in the order of 1, 2 and 3 percent. The developed silica column is then divided into 12 equal sections and each section is eluted with three 30 cc portions of M/15 phosphate buffer of pH 7.0. Again, most of the total antibiotic activity originates in a single band in the silica column. The eluates obtained by extraction of the silica column sections which comprise this band are combined, cooled to about 0°C, acidified to about pH 2.2 and extracted with three 100 cc portions of ether. The ether extracts are combined and extracted with about 75 cc of a cool dilute aqueous solution of sodium hydroxide to which N/10 sodium hydroxide solution is added during the course of the extraction so that a final pH of about 7.0 is obtained in the aqueous phase. From this aqueous solution the sodium salt of allylmercaptomethylpenicillin is separated, for example, by freezing and evaporation in vacuo from the frozen state.

References

Merck Index 6955
I.N. p. 58
Behrens, O.K., Jones, R.G., Soper, Q.F. and Corse, J.W.; U.S. Patent 2,623,876; December 30, 1952; assigned to Eli Lilly & Co.

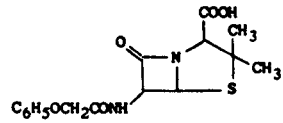
PENICILLIN V

Therapeutic Function: Antibacterial

Chemical Name: 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid

Common Name: 6-phenoxyacetamidopenicillanic acid; phenoxymethylpenicillin

Structural Formula:



Chemical Abstracts Registry No.: 87-08-1

Trade Name	Manufacturer	Country	Year Introduced
Oracilline	Theraplix	France	1954
V-Cillin	Lilly	U.S.	1955
Pen-Vee	Wyeth	U.S.	1955
Calcipen	Farmabion	Spain	—
Fenocin	Dumex	Denmark	—
Fenospen	Farmalabor	Italy	—
Ibaden	Lek	Yugoslavia	—
Intalpen	Inter-Alia	U.K.	—
Ospen	Biochemie	Austria	—
Penorline	Allard	France	—
Rivopen V	Rivopharm	Switz.	—
V-Tablopen	Arzneimittelwerk Dresden	E. Germany	—
Weifapenin	Weifa	Norway	—

Raw Materials

Phenoxyacetyl chloride
6-Aminopenicillanic acid

Manufacturing Process

The following description is taken from U.S. Patent 2,941,995. A solution of phenoxyacetyl chloride (360 mg) in dry acetone (5 ml) was added dropwise during 10 minutes to a stirred solution of 6-aminopenicillanic acid (450 mg, approximately 75% pure) in 3% aqueous bicarbonate (18 ml) and acetone (12 ml). When addition was complete the mixture was stirred at room temperature for 30 minutes and then extracted with ether (30 ml in 3 portions), only the aqueous phase being retained. This aqueous solution was covered with butanol (5 ml) and adjusted to pH 2 by the addition of N hydrochloric acid. After separating the layers, the aqueous phase was extracted with two 2.5 ml portions of butanol, adjusting to pH 2 each time. The combined butanol solutions (which at this stage contained the free penicillanic acid) were washed with water (3 x 2 ml) and then shaken with water (10 ml) to which sufficient 3% sodium bicarbonate solution was added to bring the aqueous phase to pH 7. The butanol solution was further extracted with two 5 ml portions of water to each of which was added enough bicarbonate solution to produce an aqueous phase of pH 7. The combined aqueous solutions were washed with ether (20 ml) and then evaporated at low temperature and pressure to leave the crude sodium salt of phenoxymethyl penicillin which, after drying in a vacuum desiccator, was obtained as a slightly hygroscopic powder (591 mg).

References

Merck Index 6957
Kleeman & Engel p. 716
PDR pp. 673, 694, 1071, 1381, 1606, 1723, 1770, 1968

I.N. p. 760
REM p. 1199
Behrens, O.K., Jones, R.G., Soper, Q.F. and Corse, J.W.; U.S. Patent 2,562,410; July 31, 1951; assigned to Eli Lilly and Company
Sheehan, J.C.; U.S. Patent 3,159,617; December 1, 1964; assigned to Arthur D. Little, Inc.
Doyle, F.P., Nayler, J.H.C. and Rolinson, G.N.; U.S. Patent 2,941,995; June 21, 1960; assigned to Beecham Research Laboratories Limited, England

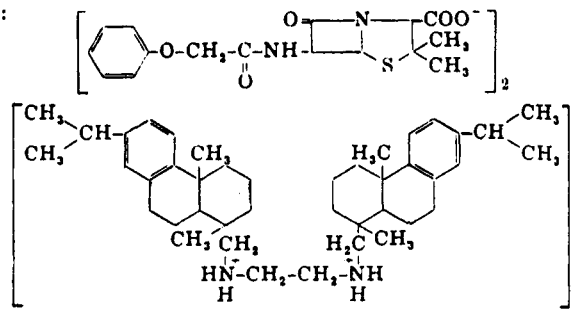
PENICILLIN V HYDRABAMINE

Therapeutic Function: Antibacterial

Chemical Name: N,N'-Bis(dehydroabietyl)ethylendiamine bis(phenoxymethylpenicillin)

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 6591-72-6

Trade Name	Manufacturer	Country	Year Introduced
Compocillin-V	Abbott	U.S.	1954
Flavopen	G.P.	Australia	–

Raw Materials

Phenoxymethylpenicillin (Penicillin V)
Dehydroabietylethylenediamine

Manufacturing Process

The crude dihydrochlorides of dehydroabietylethylenediamine bases (985 g) are extracted with a solution of about 3 liters of chloroform and 3 liters of water which is adjusted to about pH 10 and a second extraction is performed using a solution of about 2 liters of chloroform and the mixture readjusted to about pH 10 with 6N NaOH if necessary. The chloroform layer containing the mixed free bases is separated from the aqueous layer containing NaCl and is washed with about 1/10 its volume of water to remove any NaCl in the wet chloroform solution. The chloroform solution containing a mixture of the free bases having a volume of about 5 liters is dried with anhydrous Na_2SO_4 and then filtered to obtain a clear solution containing about 0.85 kg of the mixed free bases.

Approximately 1,000 g of phenoxymethylpenicillin acid (Penicillin V) is dissolved directly in about 5 liters of ethyl acetate to a concentration of 20% w/v. The resulting solution is fil-

tered to remove any insoluble salts. The penicillin V acid (1,000 g) may also be obtained by extracting an aqueous solution of 1,110 g of the potassium salt of phenoxymethylpenicillin at a temperature of about 5°C, this solution being adjusted to pH 2-3 by the addition of 6 N sulfuric acid, twice with a total of 5 liters of ethyl acetate so that the final washed combined volume will have a concentration of about 20% w/v. The abovementioned ethyl acetate solution having a volume of about 5 liters is then dried with anhydrous Na_2SO_4 and filtered to obtain a clear ethyl acetate solution of phenoxymethylpenicillin acid.

In place of the hydrochlorides of the abovedescribed bases any other acid salt thereof can be used, including both inorganic and organic salts such as phosphoric, sulfuric, and acetic acids. Also, in place of the mentioned penicillin, any of the other common salts of penicillin can be used as a source of penicillin acid.

The chloroform solution of the free bases prepared in the above manner is then slowly added to the ethyl acetate solution of the penicillin V acid prepared in the above manner. A clear solution forms which rapidly becomes turbid as the bases react with the penicillin acid and crystallization commences. The reaction mixture is allowed to stand overnight in a cool room having a temperature of about 5°C after thoroughly agitating the mixture. Thereafter, the crystalline N,N'-bis-(dehydroabietyl)-ethylenediamine-dipenicillin V is filtered to separate therefrom the cooled mother liquor which contains the unprecipitated N,N'-bis-(dihydroabietyl)-ethylenediamine-dipenicillin salt and N,N'-bis-(tetrahydroabietyl)-ethylenediamine-dipenicillin salt and other impurities. The precipitate is washed thoroughly with about 4 liters of a mixture of chloroform and ethyl acetate (1:1) which is divided into three separate portions. After the final washing, the crystals are substantially colorless. The crystalline penicillin salt is thoroughly dried under vacuum at a temperature of about 50°C. The N,N'-bis-(dehydroabietyl)-ethylenediamine-dipenicillin V salt is obtained having purity as determined by solubility analysis in excess of about 90% and melts with decomposition at 163°C to 165°C on a Kofler hot stage.

References

Merck Index 6959
I.N. p. 494
De Rose, A.F.; U.S. Patent 2,812,326; November 5, 1957; assigned to Abbott Laboratories

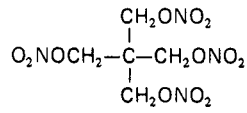
PENTAERYTHRITOL TETRANITRATE

Therapeutic Function: Coronary vasodilator

Chemical Name: 2,2-bis[(nitroxy)methyl]-1,3-propanediol dinitrate

Common Name: PETN, Pentanitrolum

Structural Formula:



Chemical Abstracts Registry No.: 78-11-5

Trade Name	Manufacturer	Country	Year Introduced
Pentanitrine	Promedica	France	1948
Peritrate	Warner Lambert	U.S.	1952
Pentritol	Armour	U.S.	1955
Pentafin	Tutag	U.S.	1956

Trade Name	Manufacturer	Country	Year Introduced
Vasodiatol	Rowell	U.S.	1958
Metranil	Meyer	U.S.	1960
Pentryate	Fellows Testagar	U.S.	1960
Tranite D-Lay	Westerfield	U.S.	1961
Peridex	Robins	U.S.	1962
Antime	Century	U.S.	1962
SK-Petin	SKF	U.S.	1971
Perispan	USV	U.S.	1971
Pentraspan	Glenwood	U.S.	1980
Pentraspan	Vitarine	U.S.	1983
Cardiacap	Consol. Chem	U.K.	—
Dilcoran	Godecke	W. Germany	—
Duotrate	Marion	U.S.	—
Hasethrol	Shionogi	Japan	—
Hypothurol	Nissin	Japan	—
Lentrat	Medinova	Switz.	—
Neo-Corodil	Ethica	Canada	—
Neo-Corovas	Amfre-Grant	U.S.	—
Nitrodex	Dexo	France	—
Nitropent	A.C.O.	Sweden	—
Pectolex	Shionogi	Japan	—
Penritol	Langley	Australia	—
Pentalong	Isis-Chemie	E. Germany	—
Peritrine	Norgine	Belgium	—
Perynitrate	Barlow Cote	Canada	—

Raw Materials

Pentaerythritol
Nitric acid

Manufacturing Process

Cooling water was turned on and 420 parts nitric acid of 94% strength was introduced into the nitrator. The amount of acid was such that the ratio of nitric acid to pentaerythritol was 4.29. The agitator was started and the agitator speed adjusted to 120 rpm. 92 parts pentaerythritol, which had been screened previously through a 14-mesh screen was used in each charge. About 45 parts pentaerythritol was added to the nitrator at such a rate that the temperature in the nitrator gradually rose to 110°F. This required about 12 minutes. Time was allowed for the temperature rise to cease before each succeeding increment of material was added.

After reaching 110°F the charge was maintained at about said temperature from 12 to 14 minutes during which time approximately 30 parts pentaerythritol was added to the nitrator. During the following 14 minutes, approximately, the remainder of the 92 parts pentaerythritol was added in like manner to the charge and the temperature gradually reduced. The pentaerythritol was introduced into the acid in finely divided and well-dispersed particles and not in large unitary quantities. The entire 92 parts of pentaerythritol tetranitrate was introduced in 35 to 40 minutes. The pentaerythritol thus obtained was separated from the spent acid by filtering or drowning in water. To recover the spent acid the charge was passed onto a nutsch and filtered. The crude product was washed with water, then with a weak water-soluble alkali solution, such as sodium carbonate for example, and subsequently with water in order to remove the acid.

After the removal of acid, the nitrate was dried by suction on the nutsch for about 15 minutes. The dried material was refined by means of acetone treatment or other suitable refining means. About 210 parts refined pentaerythritol tetranitrate per charge was obtained.

References

Merck Index 6977
DFU 4 (5) 351 (1979)
Kleeman & Engel p. 695
PDR pp. 1382, 1606
I.N. p. 741
REM p. 854
Acken, M.F. and Vyverberg, J.C. Jr.; U.S. Patent 2,370,437; February 27, 1945; assigned to E.I. du Pont de Nemours & Co.

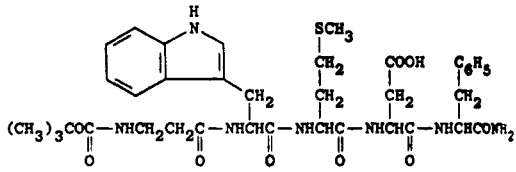
PENTAGASTRIN

Therapeutic Function: Gastrosecretory hormone

Chemical Name: N-carboxy-β-alanyl-L-tryptophyl-L-methionyl-L-aspartylphenyl-L-alanin-amide N-tert-butyl ester

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 5534-95-2

Trade Name	Manufacturer	Country	Year Introduced
Peptavlon	I.C.I.	U.K.	1967
Gastrodiagnost	Merck	W. Germany	1970
Pentagastrin	I.C.I.	Japan	1973
Peptavlon	Ayerst	U.S.	1976
Peptavlon	I.C.I.	France	1981
Acignost	VEB Berlin-Chemie	E. Germany	—

Raw Materials

L-Tryptophanyl-L-methionyl-L-aspartyl-L-phenylalanine amide trifluoroacetate
N-t-Butyloxycarbonyl-β-alanine 2,4,5-trichlorophenyl ester

Manufacturing Process

A solution of 3.55 parts of L-tryptophanyl-L-methionyl-L-aspartyl-L-phenylalanine amide trifluoroacetate in 30 parts of dimethylformamide is cooled to 0°C, and 1.01 parts of triethylamine are added. The mixture is stirred while 1.84 parts of N-tert-butyloxycarbonyl-β-alanine 2,4,5-trichlorophenyl ester are added at 0°C. The reaction mixture is kept at 0°C for 48 hours and then at 20°-23°C for 24 hours. The mixture is added to a mixture of 100 parts of ice-water, 0.37 part of concentrated hydrochloric acid (SG 1.18), 1.2 parts of acetic acid and 20 parts of ethyl acetate. The mixture is stirred for 15 minutes at 0°-10°C and is then filtered. The solid residue is washed with water and then with ethyl acetate, and is dried at 40°-50°C under reduced pressure. There is thus obtained N-tert-butyloxycarbonyl-β-alanyl-L-tryptophanyl-L-methionyl-L-aspartyl-L-phenylalanine amide, MP 213°C with decomposition.

References

Merck Index 6978
PDR p. 2004
DOT 3 (4) 150 (1967)
I.N. p. 742
REM p. 1273
Hardy, P.M., Kenner, G.W., Sheppard, R.C., MacLeod, J.K. and Morley, J.S.; British Patent 1,042,487; assigned to Imperial Chemical Industries Limited, England
Hardy, P.M., Kenner, G.W., Sheppard, R.C., Morley, J.S. and MacLeod, J.K.; U.S. Patent 3,896,103; July 22, 1975; assigned to Imperial Chemical Industries Ltd.

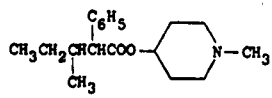
PENTAPIPERIDE METHOSULFATE

Therapeutic Function: Antispasmodic

Chemical Name: α-(1-methylpropyl)benzeneacetic acid 1-methyl-4-piperidinyl ester methosulfate

Common Name: Pentapiperium methosulfate

Structural Formula:



(base)

Chemical Abstracts Registry No.: 7681-80-3; 7009-54-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Quilene	Warner Lambert	U.S.	1969
Crylene	Auclair	France	1971
Crilin	Ayerst	Italy	1973
Perium	Rover	U.S.	–
Togestal	Biosedra	France	–

Raw Materials

Phenylacetonitrile
Sec-Butyl bromide
Thionyl chloride
Dimethyl sulfate
Sodium amide
Sodium hydroxide
1-Methyl-4-piperidinol

Manufacturing Process

Phenylacetonitrile is alkylated with secondary butyl bromide and the resultant nitrile is hydrolyzed to 3-methyl-2-phenylvaleric acid. The acid is converted to the acid chloride with thionyl chloride and the acid chloride is in turn reacted with 1-methyl-4-piperidinol. Finally dimethyl sulfate is reacted with the ester.

References

Merck Index 6988
Kleeman & Engel p. 697
OCDS Vol. 2 p. 76 (1980)
DOT 6 (2) 61 (1970)
I.N. p. 743

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

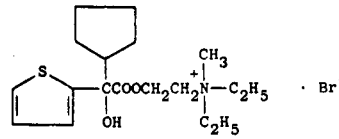
PENTHIENATE BROMIDE

Therapeutic Function: Anticholinergic

Chemical Name: 2-[(Cyclopentylhydroxy-2-thienylacetyl)oxy]-N,N-diethyl-N-methyl-ethanaminium bromide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 60-44-6

Trade Name	Manufacturer	Country	Year Introduced
Monodral	Winthrop	U.S.	1954
Monodral	Kanebo	Japan	1970

Raw Materials

2-Diethylaminoethyl chloride
Cyclopentyl(α-thienyl)hydroxyacetic acid
Methyl bromide

Manufacturing Process

An aqueous solution of 13.8 g of 2-diethylaminoethyl chloride hydrochloride was neutralized with sodium hydroxide, and the free 2-diethylaminoethyl chloride was extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, filtered, and the filtrate was added to a solution of 13.6 g of cyclopentyl-(α-thienyl)hydroxyacetic acid in 100 ml of isopropyl alcohol. The mixture was then distilled through a 25-cm Vigreaux-type column until the temperature of the vapors reached 80°C. The residual solution was refluxed overnight and then transferred to a beaker along with 350 ml of isopropyl alcohol. The crystalline hydrochloride had meanwhile separated out, and this was filtered, washed with isopropyl alcohol, ether and then dried, giving 23 g, melting point 172°C to 173.5°C. Recrystallization from 400 ml of isopropyl alcohol gave 20.3 g of 2-diethylaminoethyl cyclopentyl-(α-thienyl)hydroxyacetate hydrochloride, melting at 174°C to 175°C; deep yellow-orange color with concentrated sulfuric acid.

The hydrochloride may then be converted to the methobromide by reaction with methyl bromide.

References

Merck Index 6996
Kleeman & Engel p. 699
I.N. p. 744
Blicke, F.F.; U.S. Patent 2,541,634; February 13, 1951; assigned to Regents of the University of Michigan