R

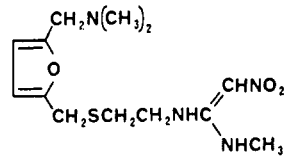
RANITIDINE

Therapeutic Function: Antiulcer, antiallergic

Chemical Name: N-[2-[[[5-(Dimethylamino)methyl-2-furanyl] methyl] thio] ethyl] -N'-methyl-2-nitro-1,1-ethenediamine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 66357-35-5

Trade Name	Manufacturer	Country	Year Introduced
Zantac	Glaxo	U.K.	1981
Zantac	Glaxo	Italy	1981
Zantic	Glaxo	Switz.	1982
Zantac	Glaxo	France	1982
Sostril	Cascan	W. Germany	1982
Zantic	Glaxo	W. Germany	1982
Zantac	Glaxo	Neth.	1982
Zantac	Glaxo	Sweden	1983
Zantac	Glaxo	Canada	1983
Zantac	Glaxo	U.S.	1983
Acidex	Syncro	Argentina	–
Ranidil	Duncan	Italy	–
Taural	Roemmers	Argentina	–
Toriol	Vita	Spain	–
Ulcex	Guidotti	Italy	–
Vizerul	Montpellier	Argentina	–

Raw Materials

N-Methyl-1-(methylthio)-2-nitroetheneamine
2-[[[5-(Dimethylamino)methyl-2-furanyl] methyl] thio] ethanamine

Manufacturing Process

N-methyl-1-(methylthio)-2-nitroetheneamine (230 g) in water (400 ml) was stirred and heated at 45°C to 50°C. 2-[[[5-(Dimethylamino)methyl-2-furanyl] methyl] thio] ethanamine (321 g) was added dropwise over 4 hours and the resultant solution stirred for a further 3½ hours.

The solution was then heated at reflux for ½ hour, cooled to 70°C and 4-methylpentan-2-one (2 liters) added. The water was removed by azeotropic distillation under reduced pressure (260 torrs) and the resultant solution treated with charcoal (10 g) at 50°C. The solution was filtered and cooled to 10°C. N-[2-[[[5-dimethylamino)methyl-2-furanyl] methyl] thio] ethyl] - N'-methyl-2-nitro-1,1-ethenediamine (380 g) was filtered off and dried, melting point 69°C to 70°C.

References

Merck Index 8019
DFU 4 (9) 663 (1979)
PDR p. 919
OCDS Vol. 3 p. 131 (1984)
DOT 18 (12) 665 (1982)
I.N. p. 839
REM p. 798
Price, B.J., Clitherow, J.W. and Bradshaw, J.; U.S. Patent 4,128,658; December 5, 1978; assigned to Allen & Hanburys Ltd.

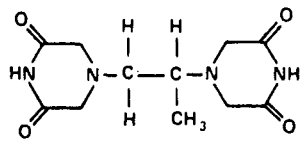
RAZOXANE

Therapeutic Function: Antitumor

Chemical Name: dl-1,2-Bis(3,5-dioxopiperazin-1-yl)propane

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 21416-87-5

Trade Name	Manufacturer	Country	Year Introduced
Razoxin	I.C.I.	U.K.	1977

Raw Materials

1,2-Diaminopropane tetraacetic acid
Formamide

Manufacturing Process

1,2-Diaminopropane tetraacetic acid (100 g) and formamide (400 ml) are heated together at reduced pressure under nitrogen at 100°C to 110°C for 1 hour, and then at 150°C to 155°C for 4 hours. The brown solution is evaporated under reduced pressure at 80°C to 90°C and the residue is taken up in methanol (120 ml) and cooled in the refrigerator overnight. Filtration, followed by washing with methanol and vacuum drying at 65°C gives dl-1,2-bis(3,5-dioxopiperazin-1-yl)propane (62 g, 70%) as a very pale cream microcrystalline solid, melting point 237°C to 239°C.

References

Merck Index 8026

DFU 2 (7) 473 (1977)
Kleeman & Engel p. 800
DOT 13 (12) 546 (1977)

Creighton, A.M.; U.S. Patents 3,941,790; March 2, 1976; and 4,275,063; June 23, 1981; both assigned to National Research Development Corp.

RELAXIN

Therapeutic Function: Ovarian hormone

Chemical Name: See under Structural Formula

Common Name: Releasin

Structural Formula: Polypeptide of approximately 6,000 molecular weight

Chemical Abstracts Registry No.: 9002-69-1

Trade Name	Manufacturer	Country	Year Introduced
Releasin	Warner Lambert	U.S.	1956
Cervilaxin	National	U.S.	1957

Raw Materials

Hog ovaries
Acetone

Manufacturing Process

500 pounds of frozen hog ovaries (relaxin content: 20,200 G.P.U./lb) are ground with 50 pounds of solid carbon dioxide (Dry Ice) in a Fitzpatrick mill using a ¼ inch screen. The resulting finely divided tissue-carbon dioxide homogenate at a temperature of -20°C is stirred into a 1.6N HCl solution prepared by mixing 15 liters of concentrated (12N) HCl with 100 liters of water. The homogenate is added to the aqueous acid over a period of approximately 1 hour so that the temperature of the mixture does not fall below -5°C. The resulting slurry is stirred for 6 hours and then allowed to stand overnight.

The following day, a quantity of 200 gallons of acetone is added to the suspension followed by stirring for 8 hours. The mixture is again allowed to stand overnight. The following day, the clear supernatant liquid is decanted from the suspension and the tissue residue is removed by filtration. The filter cake (tissue residue) is repulped with 35 gallons of a mixture of 0.3 volume 12N HCl, 9.7 volumes water and 30.0 volumes acetone and the resulting suspension is filtered. The filtrates are combined with the supernatant liquid obtained by decantation to form the acid-acetone extract with a volume of 275 gallons. The relaxin content of the extract is 9.4 G.P.U./ml or 19,600 G.P.U./lb ovaries extracted, an activity yield of about 97 percent.

References

Merck Index 8031
I.N. p. 841
Doczi, J.; U.S. Patent 3,096,246; July 2, 1963; assigned to Warner-Lambert Pharmaceutical Co.

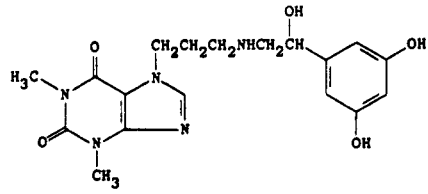
REPROTEROL

Therapeutic Function: Bronchodilator

Chemical Name: 7-[3-[[2-(3,5-Dihydroxyphenyl)-2-hydroxyethyl] amino] propyl] -3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 54063-54-6; 13055-82-8 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Bronchospasmin	Homburg	W. Germany	1977
Bronchospasmin	Farmades	Italy	1981
Bronchodil	Berlimed	U.K.	1981
Asmaterol	Lusofarmaco	Italy	–
Tiffen	Tosi	Italy	–

Raw Materials

Theophylline
3,5-Dihydroxy-ω-bromoacetophenone
Hydrogen
1-Bromo-3-chloropropane
Benzylamine

Manufacturing Process

Theophylline is reacted first with 1-bromo-3-chloropropane to give chloropropyl theophylline, then with benzylamine to give benzylaminopropyltheophylline. That is reacted with 3,5-dihydroxy-ω-bromoacetophenone to give the starting material.

500 g of 7-[3-[2-(3,5-dihydroxyphenyl)-2-oxoethyl-benzylamino] -propyl] -theophylline hydrochloride obtained as above were dissolved in 5 liters of dimethyl acetamide. There were added 25 g of a 10% palladium-carbon catalyst, the mixture heated to 70°C and hydrogenated with stirring at this temperature and 2 bar pressure until the speed of hydrogenation perceptibly slowed (about 2 hours). Subsequently, the mixture was filtered and after addition of a further 25 g of the palladium catalyst hydrogenated at 6 bar to the end (2 to 3 hours). The mixture was filtered, the greatest part of the solvent distilled off at a water jet vacuum, and the residue treated with 8 liters of ethanol. The solution was cooled for 12 hours with flowing water and the precipitated material filtered off with suction. Then it was boiled for one hour with 2 liters of methanol with stirring and the passing through of nitrogen, allowed to cool to 25°C and filtered off with suction. After drying in a vacuum at 55°C there were obtained 391 g (= 94.5% of theory) of pure 7-[3-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino] -propyl] -theophylline hydrochloride. Melting point 263°C to 265°C.

References

Merck Index 8035
Kleeman & Engel p. 800
OCDS Vol. 3 p. 231 (1984)
DOT 13 (2) 552 (1977)

I.N. p. 842
Klingler, K.H. and Bickel, E.; U.S. Patent 4,150,227; April 17, 1979; assigned to Degussa (Germany)

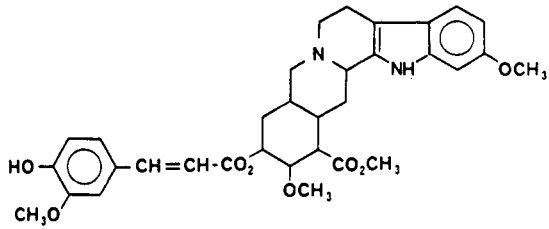
RESCIMETOL

Therapeutic Function: Antihypertensive

Chemical Name: Methylreserpate 3'-methoxy-4'-hydroxycinnamate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 73573-42-9

Trade Name	Manufacturer	Country	Year Introduced
Toscara	Nippon Chemiphar	Japan	1982

Raw Materials

Methylreserpate 3'-methoxy-4'-ethoxycarboxycinnamate
Sodium
Methanol

Manufacturing Process

28 mg of a metal sodium were dissolved in 25 ml of anhydrous methanol, and one drop of water was added thereto. 1.5 g of methylreserpate 3'-methoxy-4'-ethoxycarboxycinnamate in 25 ml of tetrahydrofuran were added thereto.

The mixture was then stirred at room temperature for 2 hours. One drop of acetic acid was added thereto, and the solvent was evaporated. The residue was extracted with chloroform, the extract was washed with saturated sodium bicarbonate solution and then with water.

The chloroform layer was dried over sodium sulfate, and the solvent was evaporated, so that there was obtained a brown amorphous matter. This was recrystallized from chloroform-hexane, and there was then obtained 1.0 g (78% of yield) of methylreserpate 3'-methoxy-4'-hydroxycinnamate which was characterized as pale yellow needles having a melting point of 259°C to 260°C.

References

Merck Index 8038
DFU 3 (3) 183 (1978) (As CD-3400) & 5 (12) 635 (1980)
DOT 18 (10) 551 (1982)
Kametani, T.; U.S. Patent 3,898,215; August 5, 1975; assigned to Nippon Chemiphar Co., Ltd.

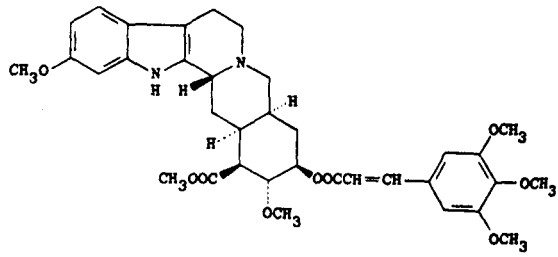
RESCINNAMINE

Therapeutic Function: Antihypertensive

Chemical Name: 11,17α-dimethoxy-18β-[[1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-oxy]-3β,20α-yohimban-16β-carboxylic acid methyl ester

Common Name: 3,4,5-trimethoxycinnamoyl methyl reserpate

Structural Formula:



Chemical Abstracts Registry No.: 24815-24-5

Trade Name	Manufacturer	Country	Year Introduced
Moderil	Pfizer	U.S.	1956
Aldatense	Searle	France	—
Anaprel	Servier	France	—
Apolon	Toyama	Japan	—
Aporecin	Kayaku	Japan	—
Aporesin	A.L.	Norway	—
Apotension	Santen	Japan	—
Apoterin	Seiko	Japan	—
Atension	Santen	Japan	—
Caniramine	Hokuriku	Japan	—
Cartric	Sanwa	Japan	—
Cinnaloid	Taito Pfizer	Japan	—
Colstamin	Kowa	Japan	—
Daisaloid	Mohan	Japan	—
Isocalsin	Kowa	Japan	—
Paresinan	Wakamoto	Japan	—
Rescamin	Pharmacia	Sweden	—
Rescimin	Torlan	Spain	—
Rescinate	Ohta	Japan	—
Rescisan	Pharmacia	Sweden	—
Rescitens	Fargal	Italy	—
Resiloid	Nippon Shoji	Japan	—
Rosex	Teikoku	Japan	—
Rozex	Teisan	Japan	—
Sciminan	Kotani	Japan	—
Seripinin	Fuji Zoki	Japan	—
Sinselpin	Kobayashi	Japan	—

Raw Materials

3,4,5-Trimethoxycinnamic acid
Methyl reserpate
Thionyl chloride
Rauwolfia plants

Manufacturing Process

4.0 grams of 3,4,5-trimethoxycinnamic acid, MP 125.5° to 127°C was refluxed for 35 minutes under anhydrous conditions with 6.0 parts by volume of redistilled thionyl chloride.

The excess thionyl chloride was removed under vacuum and by distilling from the residue two portions of dry benzene. The crystalline residue was crystallized twice from hexane-ether to yield 3,4,5-trimethoxycinnamoyl chloride which was obtained in the form of bright yellow prisms, MP 95° to 96°C.

To a solution of 0.80 part by weight of methyl reserpate in 10 parts by volume of dry distilled pyridine at 10° to 15°C were added in portions during 20 minutes with stirring and external cooling 1.1 parts by weight of 3,4,5-trimethoxycinnamoyl chloride. The reaction was carried out under nitrogen. After standing at room temperature for 65 hours the pyridine was removed under reduced pressure and at a temperature of 50° to 60°C. A brown solid froth-like material was obtained which was chromatographed on 30 parts by weight of alumina (activity II-III). The fractions eluted with benzene-acetone mixtures, on crystallization from benzene yielded 3,4,5-trimethoxycinnamate of methyl reserpate in the form of needles, which on recrystallization from methanol melted at 232° to 234°C as described in U.S. Patent 2,854,454.

The 3,4,5-trimethoxycinnamic ester of methyl reserpate is also present in Rauwolfia plants and obtainable in purified form therefrom by extraction as described in U.S. Patents 2,974,144 and 2,876,228.

References

Merck Index 8039
Kleeman & Engel p. 801
PDR p. 1422
OCDS Vol. 1 p. 319 (1977)
I.N. p. 843
REM p. 909

Ulshafer, P.R.; U.S. Patent 2,854,454; September 30, 1958
Ordway, H.W. and Guercio, P.A.; U.S. Patent 2,876,228; March 3, 1959; assigned to Chas. Pfizer & Co., Inc.
Klohs, M.W., Draper, M.D. and Keller, F.; U.S. Patent 2,974,144; March 7, 1961; assigned to Riker Laboratories, Inc.

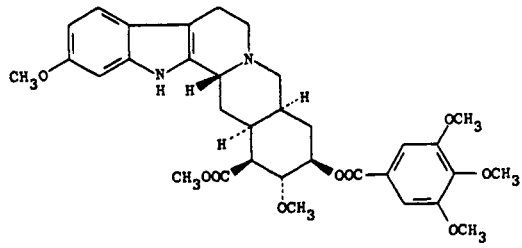
RESERPINE

Therapeutic Function: Antihypertensive

Chemical Name: 11,17α-dimethoxy-18β-[(3,4,5-trimethoxybenzoyl)oxy]-3β,20α-yohimban-16β-carboxylic acid methyl ester

Common Name: 3,4,5-trimethoxybenzoyl methyl reserpate

Structural Formula:



Chemical Abstracts Registry No.: 50-55-5

Trade Name	Manufacturer	Country	Year Introduced
Serpasil	Ciba	U.S.	1953
Sandril	Lilly	U.S.	1954
Rau-Sed	Squibb	U.S.	1954
Crystoserpine	Dorsey	U.S.	1954
Serpine	Pitman Moore	U.S.	1954
Serfin	Parke Davis	U.S.	1954
Reserpoid	Upjohn	U.S.	1954
Serpiloid	Riker	U.S.	1954
Serpanray	Panray	U.S.	1954
Vio-Serpine	Rowell	U.S.	1955
Serpena	Haag	U.S.	1955
Serpate	Vale	U.S.	1955
Rausaingle	Philips Roxane	U.S.	1955
Sertabs	Table Rock	U.S.	1955
Eskaserp	SKF	U.S.	1955
Serolfia	Mallard	U.S.	1955
Resercen	Central	U.S.	1956
Banasil	*Ulmer*	U.S.	1956
Roxinoid	MSD	U.S.	1956
Respital	*Premo*	U.S.	1956
Raurine D-Lay	Westerfield	U.S.	1961
Lemiserp	Lemmon	U.S.	1962
Abesta	A.N.A.	France	–
Broserpine	Brothers Pharm	U.S.	–
Cardioserpine	Star	Finland	–
Chloroserpine	Schein	U.S.	–
Demi-Regroton	U.S.V.	U.S.	–
Diupres	MSD	U.S.	–
Diutensin	Wallace	U.S.	–
HHR	Schein	U.S.	–
Hydro-Fluserpine	Schein	U.S.	–
Hydromox	Lederle	U.S.	–
Hydropres	MSD	U.S.	–
Hydroserpine	Schein	U.S.	–
Key-Serpine	Key	U.S.	–
Lemiserp	Lemmon	U.S.	–
Metatensin	Merrell Dow	U.S.	–
Naquival	Schering	U.S.	–
Neo-Serp	*Neo*	Canada	–
Raulen	Paul Maney	Canada	–
Rausan	*Wassermann*	*Spain*	–
Rausedan	Arzneimittelwerk Dresden	E. Germany	–
Rauvilid	Pharmacia	Sweden	–
Rauwita	Lifasa	Spain	–
Regroton	U.S.V.	U.S.	–
Renese-R	Pfipharmecs	U.S.	–
Resedril	Estedi	Spain	–
Rese-Lar	Perga	Spain	–
Reser-Ar	Luar	U.S.	–
Resercrine	Casgrain & Charbonneau	Canada	–
Reserfia	Medic	Canada	–
Reserpur	A.F.I.	Norway	–
Resine	Kirk	U.S.	–
Resomine	Bonjean	Belgium	–
Rivasin	Giulini	W. Germany	–
Salutensin	Bristol	U.S.	–
Ser-Ap-Es	Ciba	U.S.	–
Serolfia	Ascher	U.S.	–

Trade Name	Manufacturer	Country	Year Introduced
Serpalan	Lannett	U.S.	–
Serpax	Verdun	Canada	–
Serpedin	Pharmacia	Sweden	–
Serpena	Haag	U.S.	–
Serpentil	Pliva	Yugoslavia	–
Serpipur	Kwizda	Austria	–
Serpivite	Vitarine	U.S.	–
Serpoid	Canfield	U.S.	–
Serpone	Hartz	Canada	–
Serpresan	Maipe	Spain	–
Sertina	Fellows-Testagar	U.S.	–
SK-Reserpine	SKF	U.S.	–
Unipres	Reid-Rowell	U.S.	–
Vio-Serpine	Rowell	U.S.	–
V-Serp	Vangard	U.S.	–

Raw Materials

Rauwolfia plant bark
Methanol

Manufacturing Process

7,000 parts by weight of powdered bark from the root of *Rauwolfia serpentina* Benth, are percolated with about 35,000 parts by volume of methanol. After evaporating the methanol extract, 1,050 parts by weight are obtained of a dark colored powder which is treated several times with water for removal of soluble constituents. The insoluble residue remaining from this operation is subsequently masticated five times, in each case with 1,500 parts by volume of 10% aqueous acetic acid, the solution being best separated from the smeary residue by centrifuging. The brown acetic acid solution, which for further working up can be concentrated at low temperature to a small volume or be diluted with half the volume of water, possesses a pH of about 3.9. This solution is extracted by shaking with 3,500 to 4,000 parts by volume of chloroform divided into 3 to 4 portions. These chloroform extracts are washed once with potassium carbonate solution and twice with water, dried with sodium sulfate and evaporated to dryness under reduced pressure. The residue, amounting to 70 to 80 parts by weight, forms a green-brown colored powder. For further purification, this residue is dissolved in benzene and chromatographed over 1,000 to 1,200 parts by weight of neutral aluminum oxide (activity H-III according to Brockmann). On elution with benzene there are first obtained small quantities of a yellow oil and 0.9 part by weight of an inactive crystallizate of melting point 238°C to 239°C, after which the substance of sedative activity follows. As soon as the major quantity of the active substance has been eluted, further elution is carried out with a mixture of 2 parts by volume of benzene and 1 part by volume of acetone. In this manner the residue of the sedative substance is obtained and after that a further inactive crystallizate of melting point 141°C to 143°C. The eluate fractions containing the sedative substance are evaporated to dryness. By recrystallization of the residue from hot acetone or a mixture of chloroform and ether, 6.5 to 7 parts by weight of reserpine are obtained in the form of almost colorless crystals of melting point 262°C to 263°C (with decomposition).

References

Merck Index 8042
Kleeman & Engel p. 802
PDR pp. 710, 812, 993, 1011, 1168, 1185, 1231, 1409, 1449, 1606, 1634, 1723, 1820, 1876, 1999
I.N. p. 843
REM p. 908
Schwyzer, R. and Mueller, J.; U.S. Patent 2,833,771; May 6, 1958; assigned to Ciba Pharmaceutical Products, Inc.

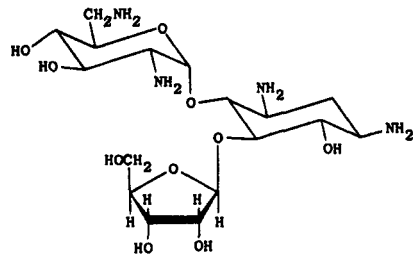
RIBOSTAMICIN

Therapeutic Function: Antibiotic

Chemical Name: O-2,6-Diamino-2,6-dideoxy-α-D-glucopyranosyl-(1→4)-O-[β-D-ribofuranosyl-(1→5)] 2-deoxy-D-streptamine

Common Name: Ribostamin

Structural Formula:



Chemical Abstracts Registry No.: 25546-65-0

Trade Name	Manufacturer	Country	Year Introduced
Vistamycin	Meiji Seika	Japan	1972
Ribomycine	Delalande	France	1977
Ribostamin	Delalande	Italy	1979
Ibistacin	I.B.I.	Italy	1979
Landamycin	Delalande	W. Germany	1980

Raw Materials

Bacterium *Streptomyces thermoflavus*
Glucose
Soybean meal

Manufacturing Process

Streptomyces thermoflavus SF-733 strain was inoculated to 15 liters of a liquid medium (pH 7.0) containing glucose 2.5%, soybean meal 3.5%, soluble vegetable protein 1.0% and NaCl 0.25% and shake-cultured in a jar-fermenter at 28°C for 3 days. 10 liters of culture filtrate (potency, 200 meg/ml) obtained by filtering culture broth at pH 4.0 was adjusted to pH 7.0 and applied to a column filled with 1 liter of Amberlite IRC 50 (NH_4^+ type, Rohm & Haas) to adsorb active ingredient on ion-exchange resin. After washing with water the column was eluted with 0.5 N ammonia water. Active fractions were concentrated in vacuo and freeze-dried. 5.9 g of crude powder thus obtained was dissolved in 10 ml of water, applied to a column filled with 400 ml of Dowex 1 X2 (OH^- type, Dow Chemicals) and developed chromatographically with water to give 250 ml of active fraction which was concentrated in vacuo, whereby 2.1 g of light yellow powder of SF-733 substance was obtained. 2.0 g of this powder was dissolved in 3 ml of water, applied to a column filled with 100 ml of Amberlite CG 50 (NH_4^+ type) washed with water and eluted with 0.2 N ammonia water. 400 ml of active fraction was collected, concentrated in vacuo and freeze-dried to give 600 mg of white powder of free base of SF-733 substance. This powder was dissolved in about 5 ml of water and concentrated to syrup and added with about 50 ml of ethanol. The mother liquor together with white precipitate thus formed was concentrated in vacuo to dryness. 650 mg of ethanol-solvate-like white powder was dissolved in 6.5 ml of methanol. The solution became cloudy immediately after dissolution and crystals were gradually separated. After tightly sealed and left alone at 30°C overnight crystals were collected by means of glass filter and washed with

about 1 ml of methanol. The crystals were held on calcium chloride as a drying agent at room temperature in vacuo and then dried on phosphorus pentoxide as a drying agent at 60°C for 19 hours in vacuo to give 440 mg of free base crystals of SF-733 substance. Yield: 73%.

References

Merck Index 8106
Kleeman & Engel p. 807
DOT 9 (3) 112 (1973)
I.N. p. 848
Shomura, T., Ezaki, N., Tsuruoka, T., Niwa, T., Akita, E. and Niida, T.; U.S. Patent 3,661,892; May 9, 1972; assigned to Meiji Seika Kaisha, Ltd. (Japan)

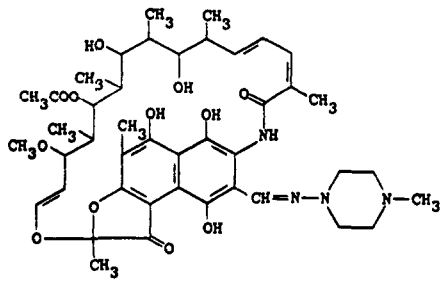
RIFAMPIN

Therapeutic Function: Antitubercular

Chemical Name: 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-methyl-1-piperazinyl)formimidoyl]-2,7-(epoxypentadeca[1,11,13]trienimino)-naphtho[2,1-b] furan-1,11(2H)-dione 21-acetate

Common Name: 3-[(4-Methyl-1-piperazinyl)iminomethyl] rifamycin SV; rifaldazine; rifamycin AMF; rifampicin

Structural Formula:



Chemical Abstracts Registry No.: 13492-46-1

Trade Name	Manufacturer	Country	Year Introduced
Rifadin	Lepetit	Italy	1968
Rifadin	Merrell	U.K.	1969
Rimactan	Ciba	W. Germany	1969
Rifadine	Lepetit	France	1969
Rimactane	Ciba Geigy	U.K.	1969
Rifadin	Daiichi	Japan	1971
Rimactan	Ciba	Japan	1971
Rimactane	Ciba	U.S.	1971
Rifadin	Dow	U.S.	1971
Archidyn	Lepetit	Italy	—
Arficin	Belupo	Yugoslavia	—
Benemicin	Polfa	Poland	—
Fenampicin	Antibioticos	Spain	—
Feronia	Lifepharma	Spain	—

Trade Name	Manufacturer	Country	Year Introduced
Riasin	Yurtoglu	Turkey	–
Rifa	Gruenenthal	W. Germany	–
Rifagen	Morgens	Spain	–
Rifam	Nobel	Turkey	–
Rifapiam	Piam	Italy	–
Rifaprodin	Prodes	Spain	–
Rifarm	Pharmacal	Finland	–
Rifobac	Llade	Spain	–
Rifonilo	Aristegui	Spain	–
Riforal	Llade	Spain	–
Rimapen	Orion	Finland	–
Ripamisin	Deva	Turkey	–
Rofact	I.C.N.	Canada	–
Santadin	Santa Farma	Turkey	–
Seamicin	Galepharma Iberica	Spain	–
Tubocin	Farmakhim	Bulgaria	–

Raw Materials

3-Formylrifamycin SV
1-Amino-4-methylpiperazine

Manufacturing Process

3-Formylrifamycin SV is treated with 1-amino-4-methylpiperazine in tetrahydrofuran to give rifampin.

References

Merck Index 8113
Kleeman & Engel p. 808
PDR pp. 810, 1236
DOT 5 (1) 24 (1969)
I.N. p 848
REM p. 1233
Maggi, N. and Sensi, P.; U.S. Patent 3,342,810; September 19, 1967; assigned to Lepetit SpA, Italy

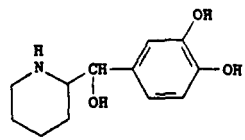
RIMITEROL

Therapeutic Function: Bronchodilator

Chemical Name: 4-(hydroxy-2-piperidinylmethyl)-1,2-benzenediol

Common Name: Erythro-3,4-dihydroxyphenyl-2-piperidinylcarbinol

Structural Formula:



Chemical Abstracts Registry No.: 32953-89-2; 31842-61-2 (Hydrogen bromide)

Trade Name	Manufacturer	Country	Year Introduced
Pulmadil	Riker	U.K.	1974
Asmaten	Riker	—	—

Raw Materials

4-Bromoveratrole
2-Cyanopyridine
Sodium hydroxide
Hydrogen
Magnesium
Hydrogen chloride
Hydrogen bromide

Manufacturing Process

To a stirred suspension of 5.0 grams (0.21 gram atom) of magnesium turnings in 15 ml of tetrahydrofuran under nitrogen is added 43.4 grams (0.2 mol) of 4-bromoveratrole to maintain constant reflux. An additional 40 ml of solvent is added and the Grignard reagent thus prepared is heated on a steam bath for one hour. This solution is then added dropwise to a solution of 20.8 grams (0.2 mol) of 2-cyanopyridine in 300 ml of ether. The mixture is stirred overnight at room temperature, decomposed by addition of 250 ml of 10% hydrochloric acid and the separated aqueous layer is made alkaline with 40% sodium hydroxide solution. This mixture is extracted with methylene chloride and the dried extract concentrated. The residue is distilled and the fraction at 190° to 235°C/12 mm is crystallized to give 3,4-dimethoxyphenyl-2-pyridyl ketone, MP 93° to 94°C.

A solution of 0.5 gram of the above ketone in 15 ml of 48% hydrobromic acid is refluxed for 1½ hours and then concentrated in vacuo. The residue is dissolved in ethanol, toluene is added, the solution concentrated and the residue stripped with toluene to yield 3,4-dihydroxyphenyl-2-pyridyl ketone hydrobromide, MP 246° to 247°C (decomposition).

A mixture of 0.5 gram of platinum oxide and a solution of 2.0 grams (0.0067 mol) of 3,4-dihydroxyphenyl-2-pyridyl ketone hydrobromide in 20 ml of water and 80 ml of ethanol is hydrogenated on the Parr apparatus using an initial hydrogen pressure of 50 psi at room temperature. The reaction mixture is filtered, the filtrate concentrated in vacuo and the residue triturated with acetone to give erythro-3,4-dihydroxyphenyl-2-piperidinylcarbinol hydrobromide, MP 210° to 211°C (decomposition).

Treatment of the above hydrobromide with aqueous sodium bicarbonate followed by extraction with ethyl acetate yields the free base of the carbinol MP 203° to 204°C which may be reacted with other acids to give other acid addition salts.

References

Merck Index 8117
Kleeman & Engel p. 809
OCDS Vol. 2 p. 278 (1980)
DOT 10 (11) 272 (1974)
I.N. p. 849
Kaiser, C. and Ross, S.T.; U.S. Patent 3,705,169; December 5, 1972; assigned to Smith Kline & French Laboratories

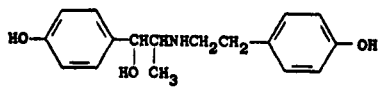
RITODRINE

Therapeutic Function: Muscle relaxant (obstetric)

Chemical Name: erythro-p-hydroxy-α-[1-[(p-hydroxyphenethyl)amino] ethyl] benzyl alcohol

Common Name: N-(p-hydroxyphenylethyl)-4-hydroxynorephedrine

Structural Formula:



Chemical Abstracts Registry No.: 26652-09-5; 23239-51-2 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Pre-Par	Duphar	Italy	1975
Yutopar	Duphar	U.K.	1976
Pre-Par	Duphar	France	1976
Pre-Par	Duphar/Thomae	W. Germany	1976
Yutopar	Merrell Dow	U.S.	1980
Yutopar	Astra	U.S.	1980
Miolene	Lusofarmaco	Japan	–
Utopar	Ferrosan	Denmark	–

Raw Materials

2-Bromo-4'-benzyloxypropiophenone
2-(4-Methoxyphenyl)ethylamine
Hydrogen bromide
Hydrogen chloride
Hydrogen

Manufacturing Process

A solution of 44 grams of 2-bromo-4'-benzyloxypropiophenone and 44 grams of 2-(4-methoxyphenyl)ethylamine in 270 ml of ethanol was refluxed for 3 hours. Then the ethanol was distilled off in vacuo and the concentrate mixed with ether. The resulting crystallizate was sucked off after which the filtrate was mixed with an excess of 2 N hydrochloric acid. As a result of this the hydrochloride of 4'-benzyloxy-2-[2-(4-methoxyphenyl)ethylamino]-propiophenone slowly crystallized. This substance was also sucked off, washed with water and alcohol, and dried in vacuo. After recrystallization from dilute alcohol the yield was 25.5 grams of a product with a melting point of 217° to 218°C.

12 grams of the product thus obtained were dissolved in a mixture of 300 ml of ethanol and 90 ml of water. After 42 ml of 1% palladium chloride solution and 3.9 grams of Norit had been added to this solution it was hydrogenated at room temperature and at a pressure of 1.1 atmospheres until approximately 760 ml of hydrogen had been taken up. Then the catalyst was removed by filtration and the solvent of the filtered solution was evaporated entirely in vacuo.

The resulting residue, which consisted of the hydrochloride of 4'-hydroxy-2-[2-(4-methoxyphenyl)ethylamino]propiophenone, was mixed with 30 ml of a 48% hydrobromic acid solution and the mixture was boiled until no methylbromide developed any more, which was the case after approximately 45 minutes. Then the reaction mixture was stored in the refrigerator, after which the hydrobromide of 4'-hydroxy-2-[2-(4-hydroxyphenyl)ethylamino]propiophenone crystallized. It was sucked off and converted into the hydrochloride by again dissolving the resulting substance in water, discoloring the solution with a little Norit and then adding an equal volume of concentrated hydrochloric acid. As a result of this the hydrochloride crystallized. The yield was 9.6 grams of a product with a melting point of 136° to 138°C. After this product had been recrystallized once again it was reduced to the amino alcohol.

For this purpose a solution of 3.2 grams of the hydrochloride in 160 ml of distilled water was provided with 0.5 gram of Norit and 8 ml of 1% palladium chloride solution and the mixture was hydrogenated at room temperature and at a pressure of 1.1 atmospheres until no hydrogen was taken up any more. The catalyst was then removed by filtration, after

which the filtrate was concentrated in vacuo. To the concentrated solution of the reduced product was then added an excess of dilute ammonia, as a result of which the base of the 1-(4-hydroxyphenyl)-2-[2-(4-hydroxyphenyl)ethylamino] propanol precipitated as a tough mass. After the mixture had been stored in the refrigerator for some time, the product was sucked off, washed with water and dried in vacuo. This base was a resinous mass with a melting point of approximately 88° to 90°C. Yield was 2.3 grams.

References

Merck Index 8121
Kleeman & Engel p. 810
PDR p. 609
OCDS Vol. 2 p. 39 (1980)
DOT 10 (1) 23 (1974)
I.N. p. 850
Claassen, V., Van Dijk, J. and Moed, H.D.; U.S. Patent 3,410,944; November 12, 1968; assigned to North American Philips Company, Inc.

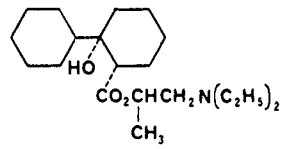
ROCIVERINE

Therapeutic Function: Antispasmodic

Chemical Name: 1-(Diethylamino)-2-propyl cis-2-hydroxy-2-cyclohexylcyclohexane-1-carboxylate

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 53716-44-2

Trade Name	Manufacturer	Country	Year Introduced
Rilaten	Guidotti	Italy	1979

Raw Materials

2-Phenyl-2-hydroxycyclohexane carboxylic acid
Hydrogen
1-Bromo-2-propanol
Diethylamine

Manufacturing Process

5.6 g of 2-phenyl-2-hydroxy-cyclohexane-carboxylic acid were dissolved in 75 cc of glacial acetic acid and reduced in the presence of 0.1 g of platinum oxide under hydrogen pressure of 22 kg/cm^2 at a temperature of 70°C to 80°C.

Hydrogen absorption being completed, the solution was filtered and evaporated to one-fifth of its volume and cooled in a refrigerator. The precipitate was filtered, washed with water, and then crystallized from ligroin, thus yielding 4 g of 2-cyclohexyl-2-hydroxy-cyclohexane-

carboxylic acid, melting point (Kofler) 122°C to 124°C. This material was esterified with 1-bromo-2-propanol by means of 85% H_2SO_4 yielding 1-bromoisopropyl-2-cyclohexyl-2-hydroxycyclohexanecarboxylate. Finally this compound was treated with diethylamine and triethylamine at 120°C to give rociverine.

References

Merck Index 8125
DFU 4 (4) 276 (1979)
I.N. p. 852
Turbanti, L; U.S. Patents 3,700,675; and 3,700,775; both dated October 24, 1972

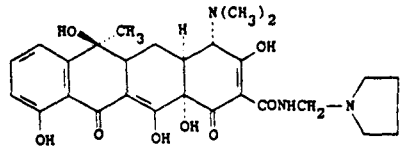
ROLITETRACYCLINE

Therapeutic Function: Antibacterial

Chemical Name: 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-N-(1-pyrrolidinyl-methyl)-2-naphthacenecarboxamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 751-97-3

Trade Name	Manufacturer	Country	Year Introduced
Syntetrin	Bristol	U.S.	1959
Velacycline	Squibb	U.S.	1960
Transcycline	Hoechst	France	1961
Anergomycil	C.N.N.	Italy	–
Bristacin	Bristol Banyu	Japan	–
Farmaciclina	Selvi	Italy	–
Hostacyclin-PRM	Hoechst	Japan	–
Kinteto	Fujita	Japan	–
Quadraciclina	Squibb	Italy	–
Reverin	Hoechst	Italy	–
Solvocillin	Fabr. Antibiot.	Rumania	–
Tetrafarmed	Neopharmed	Italy	–
Tetraldina	Italsuisse	Italy	–
Tetraverin	Polfa	Poland	–

Raw Materials

Tetracycline
Paraformaldehyde
Pyrrolidine hydrochloride

Manufacturing Process

1 g (0.00225 mol) of anhydrous tetracycline base, 0.101 g (0.0038 mol) of paraformaldehyde

and 0.302 g (0.0025 mol) pyrrolidine hydrochloride are refluxed in 25 ml absolute ethanol. After two hours an additional 0.101 g paraformaldehyde is added and refluxing is continued for two more hours. The solution is then cooled and two drops of concentrated hydrochloric acid are added. The product, N'-(1-pyrrolidyl-methyl)-tetracycline hydrochloride, forms and is isolated as a crystalline, antibacterially active solid differing in specific rotation from tetracycline hydrochloride. The product is converted to the free base by solution in water followed by the addition of one equivalent of sodium hydroxide. Thus for isolation, the alcoholic solution of N'-(1-pyrrolidyl-methyl)-tetracycline hydrochloride is diluted with 5.0 ml ether to precipitate the product, which is collected by filtration and dried in vacuo over P_2O_5. The product is a crystalline solid melting at about 158°C to 165°C with decomposition.

References

Merck Index 8127
Kleeman & Engel p. 810
OCDS Vol. 1 p. 216 (1977)
I.N. p. 853
Cheney, L.C., Risser, W.C. and Gottstein, W.J.; U.S. Patent 3,104,240; September 17, 1963; assigned to Bristol-Myers Co.

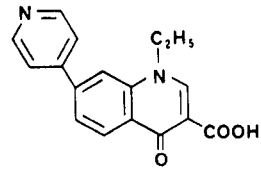
ROSOXACIN

Therapeutic Function: Antibacterial; antigonorrheal

Chemical Name: 1-Ethyl-1,4-dihydro-4-oxo-7-(4-pyridyl)-3-quinolinecarboxylic acid

Common Name: Acrosoxacin

Structural Formula:



Chemical Abstracts Registry No.: 40034-42-2

Trade Name	Manufacturer	Country	Year Introduced
Eradacin	Sterling Winthrop	U.K.	1981
Eracine	Winthrop	France	1981
Winuron	Winthrop	W. Germany	1981
Eradacil	Winthrop	Canada	1983
Winoxacin	Winthrop	Switz.	1983
Roxadyl	Winthrop	—	—

Raw Materials

4-(3-Nitrophenyl)pyridine
Ethoxymethylene malonic acid diethyl ester
Ethyl iodide
Sodium hydroxide
Iron
Acetic acid
Sodium hydride

Manufacturing Process

To a stirred suspension containing 5.1 g of 57% sodium hydride dispersed in mineral oil and

150 ml of dimethylformamide was added in portions 32.6 g of ethyl 1,4-dihydro-4-oxo-7-(4-pyridyl)-3-quinolinecarboxylate [tautomeric with ethyl 4-hydroxy-7-(4-pyridyl)-3-quinolinecarboxylate] followed by the addition of 18.7 g of ethyl iodide. The resulting reaction mixture was heated on a steam bath for three hours with stirring and then concentrated in vacuo to remove the solvent. The semisolid residue was shaken well with a mixture of chloroform and water, and a small quantity of amorphous brown solid was filtered off. The layers were separated and the chloroform layer was evaporated in vacuo to remove it.

To the oily residue containing ethyl 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridyl)-3-quinolinecarboxylate was added excess 10% aqueous sodium hydroxide solution and ethanol, and the solution was heated on a steam bath for forty-five minutes to hydrolyze the ethyl ester to the corresponding carboxylic acid. The alkaline solution was diluted to a volume of about 500 ml with water, decolorizing charcoal was added and the mixture filtered. The filtrate was neutralized with acetic acid whereupon the carboxylic acid separated as a solid. The solid was collected and dried in a rotary evaporator. The solid was boiled with ethanol, the solution chilled and the resulting solid collected. The solid was recrystallized from dimethylformamide (about 150 ml) using decolorizing charcoal. The filtrate was chilled, diluted with about one-half volume of ethanol and the separated crystalline product was collected, recrystallized again from dimethylformamide and dried in vacuo to yield 4.3 g 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridyl)-3-quinolinecarboxylic acid, melting point 272°C to 273°C raised by further recrystallization to 290°C.

4-(3-nitrophenyl)pyridine is reduced with iron in acetic acid to give 4-(3-aminophenyl)pyridine. That in turn is reacted with ethoxymethylenemalonic acid diethyl ester and then thermally rearranged to give the starting material.

References

Merck Index 8136
DFU 5 (4) 199 (1980)
Kleeman & Engel p. 811
OCDS Vol. 3 p. 185 (1984)
DOT 18 (3) 147 (1982)
I.N. p. 855

Carabateas, P.M.; U.S. Patent 3,922,278; November 25, 1975; assigned to Sterling Drug, Inc.

Lesher, G.Y. and Carabateas, P.M.; U.S. Patents 3,753,993; August 21, 1973 and 3,907,808; September 23, 1975; both assigned to Sterling Drug, Inc.

Lorenz, R.R. and Thielking, W.H.; U.S. Patent 4,107,167; August 15, 1978; assigned to Sterling Drug, Inc.