R

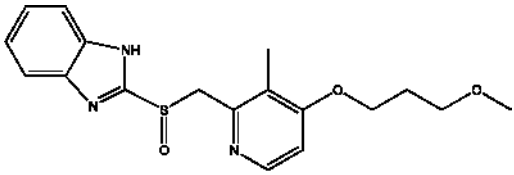
RABEPRAZOLE

Therapeutic Function: Antiulcer

Chemical Name: 1H-Benzimidazole, 2-(((4-(3-methoxypropoxy)-3-methyl-2-pyridinyl)methyl)sulfinyl)-

Common Name: Pariprazole; Rabeprazole

Structural Formula:



Chemical Abstracts Registry No.: 117976-89-3

Trade Name	Manufacturer	Country	Year Introduced
Pariet	Eisai Co.	Belgium	-
Pariet	Janssen-Cilag	-	-
Pariet	Torrent	-	-

Raw Materials

(-)-Diethyl D-tartrate
Titanium (IV) isopropoxide
2-[[[4-(3-Methoxypropoxy)-3-methyl-2-pyridinyl]methyl]thio]-1H-benzimidazole
N,N-Diisopropylethylamine
Cumene hydroperoxide (80%)

Manufacturing Process

Asymmetric synthesis of (-)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole

2.1 g (6.3 mmol) of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]thio]-1H-benzimidazole was dissolved in 50 ml of toluene. To the solution was added 40 µl (2.2 mmol) of water, 1.6 ml (9.4 mmol) of (-)-diethyl D-tartrate and 1.1 ml (3.8 mmol) of titanium (IV) isopropoxide. The mixture was stirred for 60 minutes at 50°C and then cooled to room temperature. 0.44 ml (2.6 mmol) of N,N-diisopropylethylamine and 1.1 ml (6.0 mmol) of cumene hydroperoxide (80%) were added. After stirring for 2 h at room temperature the mixture consisted of 9% sulphide, 4% sulphone and 86% sulphoxide according to achiral HPLC. To the mixture toluene (50 ml) was added and the resultant solution was extracted three times with an aqueous ammonia (12%) solution with a total volume of 150 ml. The combined aqueous layers were neutralized by the addition of concentrated acetic acid (30 ml). Thereafter, the workup procedure employed extraction, evaporation and flash chromatography yielding 1.62 g of the title compound with a purity of 99.9% (achiral analysis) and with an enantiomeric excess of 90% (chiral analysis). After treating the material with acetonitrile there was a precipitate that could be removed by filtration. Concentrating the filtrate afforded 1.36 g (60%) of the title compound as an oil with an optical purity of 91.5%.

Asymmetric synthesis of (+)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole

2.1 g (6.3 mmol) of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]thio]-1H-benzimidazole was dissolved in 50 ml of toluene. To the solution was added 40 µl (2.2 mmol) of water, 1.6 ml (9.4 mmol) of (+)-diethyl L-tartrate and 1.1 ml (3.8 mmol) of titanium (IV) isopropoxide. The mixture was stirred for 60 minutes at 50°C and then cooled to room temperature. 0.44 ml (2.6 mmol) of N,N-diisopropylethylamine and 1.1 ml (6.0 mmol) of cumene hydroperoxide (80%) were added to the solution. After stirring for 2 h at room temperature the mixture consisted of 9% sulphide, 4% sulphone and 85% sulphoxide according to HPLC. To the mixture toluene (50 ml) was added and the resultant solution was extracted three times with an aqueous ammonia (12%) solution with a total volume of 150 ml. The combined aqueous layers were neutralized by the addition of concentrated acetic acid (30 ml). Thereafter, the workup procedure employed extraction, evaporation and flash chromatography yielding 1.63 g of the title compound with a purity of 99.9% (achiral analysis) and with an enantiomeric excess (e.e.) of 91% (chiral analysis). After treating the material with acetonitrile, there was a precipitate that could be removed by filtration. Concentrating the filtrate afforded 1.1 g (49%) of the title compound as an oil with an optical purity of 96%.

References

Larson et al; US Patent No. 5,948,789; Sep. 7, 1999; Assigned to Astra Aktiebolag, Sodertalje, Sweden

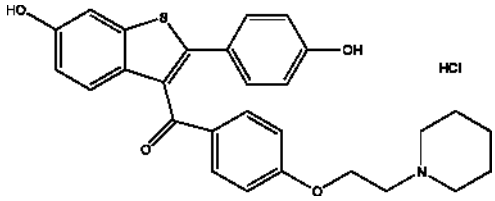
RALOXIFENE HYDROCHLORIDE

Therapeutic Function: Antiestrogen

Chemical Name: Methanone, (6-hydroxy-2-(4-hydroxyphenyl)benzo(b)thien-3-yl)(4-(2-(1-piperidinyl)ethoxy)phenyl)-, hydrochloride

Common Name: Keoxifen hydrochloride; Radoxifene hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 82640-04-8; 84449-90-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Evista	Eli Lilly	USA	-

Raw Materials

3-Methoxybenzenethiol
Polyphosphoric acid
Thionyl chloride
Methyl 4-(2-piperidinoethoxy)benzoate
α-Bromo-4-methoxyacetophenone

Manufacturing Process

4-(2-Piperidinoethoxy)benzoic acid, hydrochloride

A 183 g portion of methyl 4-(2-piperidinoethoxy)benzoate was dissolved in 600 ml of methanol, and 200 ml of 5 N sodium hydroxide was added. The mixture was stirred at ambient temperature for 48 hours, the solvent was evaporated, and the residue was dissolved in 1 liter of water. The solution was cooled to below 10°C, and was acidified with cold 6 N hydrochloric acid. The product crystallized, and was collected by filtration and washed with methanol at -40°C. The solids were recrystallized from 3400 ml of methanol to obtain 167 g of the expected product, melting point 274°-277°C.

6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene

A 100 g portion of 3-methoxybenzenethiol and 39.1 g of potassium hydroxide dissolved in 300 ml of water were added to 750 ml of denatured ethanol, and the flask was put in a cooling bath. A total of 164 g of α-bromo-4-methoxyacetophenone was then added in small portions, and the mixture was stirred for 10 minutes in the cooling bath after the addition was complete and then for 3 hours at ambient temperature. The solvent was then evaporated off in vacuum, and 200 ml of water was added. The mixture was extracted with ethyl acetate, and the organic layer was washed twice with water, twice with aqueous sodium bicarbonate solution, and twice with aqueous sodium chloride solution. The organic layer was then dried over magnesium sulfate, filtered

and evaporated under vacuum to obtain 202 g of crude α-(3-methoxyphenylthio)-4-methoxyacetophenone, which was recrystallized from methanol and washed with hexane to obtain 158 g of purified product, m.p. 53°C.

A 124 g portion of the above intermediate was added in small portions to 930 g of polyphosphoric acid at 85°C. The temperature rose to 95°C during the addition, and the mixture was stirred at 90°C for 30 minutes after the addition was complete, and was then stirred an additional 45 minutes while it cooled without external heating. One liter of crushed ice was then added to the mixture, and an external ice bath was applied to control the temperature while the ice melted and diluted the acid. 500 ml of additional water was added, and the light pink precipitate was filtered off and washed, first with water and then with methanol. The solids were dried under vacuum at 40°C to obtain 119 g of crude 6-methoxy-2-(4-methoxyphenyl)-benzo[b]thiophene. The crude product was slurried in hot methanol, filtered, and washed with cold methanol, and the solids were recrystallized from 4 liters of ethyl acetate, filtered, washed with hexane and dried to obtain 68 g of purified intermediate product, m.p. 187°-190.5°C.

90 g of pyridine hydrochloride was added to a flask equipped with a distillation head, condenser and collecting flask, and was heated with stirring until the temperature in the distillation head was 220°C. The distillation apparatus was then removed, the pot was cooled to 210°C, and 30 g of the above prepared 6-methoxy-2-(4-methoxyphenyl)-benzo[b]thiophene was added. The mixture was stirred at 210°C for 30 minutes, and was then poured into 250 ml of ice-water. The precipitate was extracted into 500 ml of ethyl acetate, and the organic layer was washed with 150 ml of saturated aqueous sodium bicarbonate and then with 150 ml of saturated aqueous sodium chloride. The organic layer was then dried over magnesium sulfate, filtered and evaporated to dryness under vacuum to obtain 25.5 g of the desired intermediate product, m.p. >260°C.

6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b] thiophene, hydrochloride

Under a nitrogen blanket, a mixture of 3 g of 4-(2-piperidinoethoxy)benzoic acid hydrochloride, 2 drops of dimethylformamide, 2.5 ml of thionyl chloride and 40 ml of chlorobenzene was heated at 70°-75°C for about one hour. The excess thionyl chloride and 15-20 ml of solvent were then distilled off. The remaining suspension was cooled to ambient temperature, and to it were added 100 ml of dichloromethane, 2.7 g of 6-methoxy-2-(4-methoxyphenyl) benzo[b]thiophene and 10 g of aluminum chloride. The solution was stirred for about one hour, 7.5 ml of ethanethiol was added, and the mixture was stirred for 45 minutes more. Then 40 ml of tetrahydrofuran was added, followed by 15 ml of 20% hydrochloric acid, with an exotherm to reflux. Fifty ml of water and 25 ml of saturated aqueous sodium chloride was added. The mixture was stirred and allowed to cool to ambient temperature. The precipitate was collected by filtration and washed successively with 30 ml of water, 40 ml of 25% aqueous tetrahydrofuran, and 35 ml of water. The solids were then dried at 40°C under vacuum to obtain 5.05 g of product, which was identified by NMR as 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]thiophene hydrochloride; melting point 217°C.

Purification of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride

200 g of crude 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride, typical of the product of Example 16 above, was added to 4400 ml of methanol and 60 ml of deionized water in a 5-liter flask. The slurry was heated to reflux, whereupon most of the crude product went into solution. The remaining solid was removed by filtration under vacuum, using a filter aid pad. A distillation head was then attached to the flask, and solvent was distilled off until the volume of the remaining solution was about 1800 ml. The heating mantle was then turned off, and the solution was cooled very slowly overnight, with constant stirring. The crystalline product was then collected by vacuum filtration, and the flask was washed out with filtrate to obtain all of the product. The crystals were washed on the filter with two 100 ml portions of cold (below 0°C) methanol, and the washed product was dried at 60°C under vacuum to obtain 140 g of dried product. The product was slurried in 3000 ml of methanol and 42 ml of water, heated to reflux and cooled very slowly. The product was filtered and dried as above to obtain 121 g of highly purified product, melting point 259°-260°C.

References

Jones C.D.; US Patent No. 4,418,068; Nov. 29, 1983; Assigned to Eli Lilly and Company, Indianapolis, IN

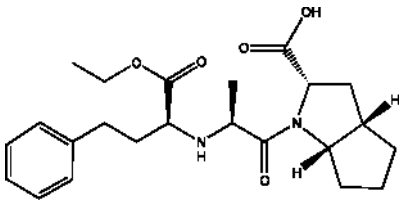
RAMIPRIL

Therapeutic Function: Antihypertensive

Chemical Name: Cyclopenta(b)pyrrole-2-carboxylic acid, octahydro-1-(2-((1-(ethoxycarbonyl)-3-phenylpropyl)amino)-1-oxopropyl), (2S-(1(R*(R*)),2-α,3a-β,6a-β))-

Common Name: Ramipril

Structural Formula:



Chemical Abstracts Registry No.: 87333-19-5

Trade Name	Manufacturer	Country	Year Introduced
Altace	Libbs	-	-
Altace	Aventis	-	-
Cardace	Hoechst	Germany	-
Cardace	Aventis Pasteur	India	-
Corpril	Ranbaxy Global Consumer Healthcare	India	-
Delix	Hoechst	Germany	-
Tritace	Hoechst Marion Roussel	Germany	-
Tritace	Aventis	-	-
Unipril	Astra Simes	-	-
Vasotop	Provet AG	-	-

Raw Materials

Platinum on carbon
Benzyl alcohol
Thionyl chloride
Dicyclohexylcarbodiimide
Cyclopentenopyrrolidine
Methyl 3-chloro-2-acetylamino-propionate
HOBt (oxybenztriazol)

Manufacturing Process

N-(1-S-Carbethoxy-3-phenyl-propyl)-S-alanyl-2-cis,endoazabicyclo-[3.3.0]-octane-3-S-carboxylicacid

1. Methyl 2-acetylamino-3-(2-oxo-cyclopentyl)-propionate

269 g of methyl 3-chloro-2-acetylamino-propionate and 257 g of cyclopentenopyrrolidine in 1.5 liters of dimethylformamide were kept at room temperature for 24 hours. The mixture was concentrated in vacuo, the residue was taken up in a little water and the aqueous mixture was adjusted to pH 2 with concentrated hydrochloric acid and extracted twice with 4 liter portions of ethyl acetate. On concentration of the organic phase, a light yellow oil remained. Yield: 290 g.

2. cis,endo-2-Azabicyclo-[3.3.0]-octane-3-carboxylic acid hydrochloride

270 g of the acetylamino derivative prepared under (1) were refluxed in 1.5 liters of 2 N hydrochloric acid for 45 minutes. The mixture was concentrated in vacuo, the residue was taken up in glacial acetic acid, 5 g of Pt/C (10% of Pt) were added and hydrogenation was carried out under 5 bar. After filtration, the mixture was concentrated and the residue was crystallized from chloroform/diisopropyl ether. Melting point 205°-209°C. Yield: 150 g.

3. Benzyl cis,endo-2-azabicyclo-[3.3.0]-octane-3-carboxylate hydrochloride

40 g of the carboxylic acid prepared under (2) were added to an ice-cold mixture of 390 g of benzyl alcohol and 65 g of thionyl chloride and the mixture was left to stand at room temperature for 24 hours. After concentration in vacuo, 47 g of the benzyl ester were crystallized from chloroform/isopropanol.Melting point: 175°C (hydrochloride).

4. Benzyl N-(2-S-carbethoxy-3-phenyl-propyl)-S-alanyl-cis,endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylate

14 g of the benzyl ester prepared according to (3) were reacted with 6.7 g of HOBt (oxybenztriazol), 13.8 g of N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanine and 10.2 g of dicyclohexylcarbodiimide in 200 ml of dimethylformamide. After the mixture had been stirred for 3 hours at room temperature, the dicyclohexylurea which had precipitated was filtered off the filtrate was concentrated, the residue was taken up in 1 liter of ethyl acetate and the mixture was extracted by shaking with 3 x 500 ml of 5% $NaHCO_3$ solution. The organic phase was concentrated and the residue was chromatographed over a column of 1 kg of silica gel using ethyl acetate/petroleum ether in the ratio 2:1. The isomer eluted first was the S,S,S-compound, and concentration of a later eluate gave the S,S,R-compound. The products were obtained as an oil. The structure of them was confirmed NMR.

5. N-(1-S-Carbethoxy-3-phenyl-propyl)-S-alanyl-cis,endo-2-azabicyclo-[3.3.0]- octane-3-S-carboxylic acid

8.0 g of the L,L,L-benzyl ester from (4) were dissolved in 100 ml of ethanol and were debenzylated hydrogenolytically under normal pressure, with addition of 0.5 g of 10% Pd/C. This reaction could also have been carried out under pressure, together with a shortening of the reaction time. After the calculated amount of hydrogen had been taken up, the catalyst was filtered off and the residue was concentrated in vacuo. The product crystallized from ether, in almost quantitative yield. Melting point: 110°-112°C (decomposition). The NMR and mass spectra obtained are in agreement with the given structure; $[\alpha]_D$ = +15.6° (c = 1, methanol).

References

Teez et al.; US Patent No. 4,727,160; Feb. 23, 1988; Assigned to Hoechst Aktiengesellschaft, Frankfurt am Main, Fed. Rep. of Germany

RANITIDINE

Therapeutic Function: Antiulcer, Antiallergic

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

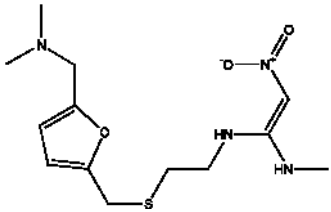
Common Name: -

Chemical Abstracts Registry No.: 66357-35-5

Raw Materials

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

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Zantac	Glaxo	UK	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	Netherlands	1982
Zantac	Glaxo	Sweden	1983
Zantac	Glaxo	Canada	1983
Zantac	Glaxo	US	1983
Acidex	Syncro	Argentina	-
Ranidil	Duncan	Italy	-
Taural	Roemmers	Argentina	-
Toriol	Vita	Spain	-
Ulcex	Guidotti	Italy	-
Vizerul	Montpellier	Argentina	-

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 3.5 hours.

The solution was then heated at reflux for 1/2 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.; US Patent 4,128,658; December 5, 1978; assigned to Allen and Hanburys Ltd.

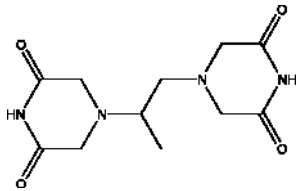
RAZOXANE

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.	UK	1977

Raw Materials

Formamide
1,2-Diaminopropane tetraacetic acid

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 and Engel p. 800
DOT 13 (12) 546 (1977)
Creighton, A.M.; US Patents 3,941,790; March 2, 1976; and 4,275,063; June 23, 1981; both assigned to National Research Development Corp.

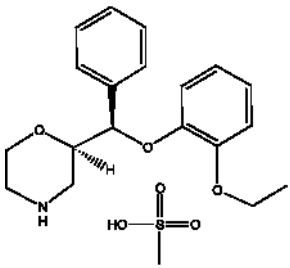
REBOXETINE MESYLATE

Therapeutic Function: Antidepressant

Chemical Name: ()-(2R*)-2-((αR*)-α-(o-ethoxyphenoxy)benzyl)morpholine, monomethanesulfonate

Common Name: Reboxetine mesilate

Structural Formula:



Chemical Abstracts Registry No.: 98769-82-5; 98769-81-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Edronax	Pharmacia and Upjohn	-	-
Lonol	Promeco	-	-
Davedax	Bracco S.p.A.	-	-
Norebox	Pharmacia and Upjohn	-	-

Raw Materials

2-[α-(2-Ethoxyphenoxy)-benzyl]-morpholin-3-one
Borane

Manufacturing Process

To 2-[α-(2-ethoxyphenoxy)benzyl]-morpholin-3-one in 60 ml of anhydrous THF there was added dropwise under stirring a solution of BH_3 in THF. The whole was heated at reflux for 3 hours and dropwise addition under cold conditions (0-(-5)°C) was then made of 3 ml of methanol and then of 3 ml of 23% HCl. The solvent was removed under reduced pressure. The residue was

diluted with H_2O, made alkaline and extracted with chloroform. The organic extracts were washed to neutrality, dried and evaporated to dryness, to obtain 2-[α-(2-ethoxyphenoxy)benzyl]-morpholine. Yield >90%; one diastereoisomer, M.P. 170-171°C.

In practice it is usually used as monomethanesulfonate salt.

References

Melloni P. et al.; US Patent No. 4,229,1980; Assigned to Farmitalia Carlo Erba, S.p.A., Milan, Italy

RELAXIN

Therapeutic Function: Ovarian hormone

Chemical Name: Polypeptide of approximately 6,000 molecular weight

Common Name: Releasin

Structural Formula: See Chemical name

Chemical Abstracts Registry No.: 9002-69-1

Trade Name	Manufacturer	Country	Year Introduced
Releasin	Warner Lambert	US	1956
Cervilaxin	National	US	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 1/4 inch screen. The resulting finely divided tissue-carbon dioxide homogenate at a temperature of -20°C is stirred into a 1.6 N HCl solution prepared by mixing 15 liters of concentrated (12 N) 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 12 N 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.; US Patent 3,096,246; July 2, 1963; assigned to Warner-Lambert Pharmaceutical Co.

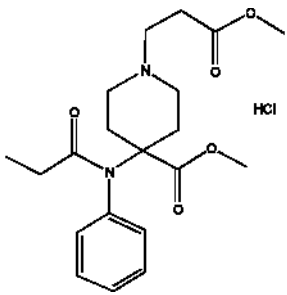
REMIFENTANIL HYDROCHLORIDE

Therapeutic Function: Analgesic, Anesthetic

Chemical Name: 1-Piperidinepropanoic acid, 4-(methoxycarbonyl)-4-((1-oxopropyl)phenylamino)-, methyl ester, monohydrochloride

Common Name: Remifentanil hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 132539-07-2; 132875-61-7 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ultiva	Glaxo Wellcome Operations Ltd.	USA	-

Raw Materials

4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-piperidine
Methyl acrylate
2-Butanone

Manufacturing Process

3-[4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester

To a solution of 4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-piperidine (200 mg, 0.68 mmol) in acetonitrile (1.1 ml) is added methyl acrylate (124 µl, 1.36 mmol) at room temperature. The solution is stirred at 50°C for 2 hours, cooled to room temperature, and concentrated to an oily residue. The residue is chromatographed on silica gel (ethyl acetate) to give 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester as an oil: 253 mg, 97%. An equimolar amount of oxalic acid is added to a solution of the free base in ethyl acetate. The precipitated salt is recrystallized by adding methanol and heating until the solid goes back into solution. Upon cooling the salt precipitates as a white solid; oxalate salt. It is recrystallized from methanol and 2-butanone; m.p. 170°-172°C.

The hydrochloride salt may be make by dissolving the free base in toluene, saturating the solution with dry hydrogen chloride and concentrating to a solid. The solid is then recrystallized from appropriate solvent.

References

Feldman et al.; US Patent No. 5,019,583; May 28, 1991; Assigned to Glaxo Inc., Research Triangle Park, N.C.

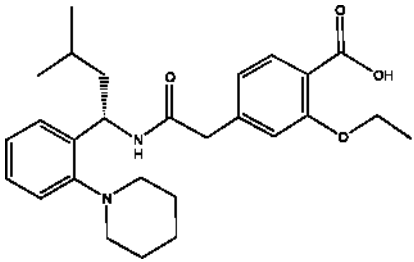
REPAGLINIDE

Therapeutic Function: Antidiabetic

Chemical Name: Benzoic acid, 2-ethoxy-4-(2-((3-methyl-1-(2-(1-piperidinyl)phenyl)butyl)amino)-2-oxoethyl)-, (S)

Common Name: Repaglinide

Structural Formula:



Chemical Abstracts Registry No.: 135062-02-1

Trade Name	Manufacturer	Country	Year Introduced
Eurepa	Torrent Pharmaceuticals Ltd.	India	-
NovoNorm	Novo Nordisk	Denmark	-
Prandin	Medley	USA	-
Repaglinide	Novo Nordisk	Denmark	-

Raw Materials

Triphenylphosphine	3-Ethoxy-4-ethoxycarbonyl-phenylacetic acid
Triethylamine	3-Methyl-1-(2-piperidino-phenyl)-1-butylamine

Manufacturing Process

Ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoate

3 g (11.9 mmols) of 3-ethoxy-4-ethoxycarbonyl-phenylacetic acid, 3.7 g (14.3 mmols) of triphenylphosphine, 3.3 ml (23.8 mmols) of triethylamine and 1.15 ml (11.9 mmols) of carbon tetrachloride were added successively to a solution of 2.9 g (11.9 mmols) of 3-methyl-1-(2-piperidino-phenyl)-1-butylamine in 29 of acetonitrile. The mixture was then stirred for 15 hours at room temperature, the solvent was removed in vacuo, and the residue was taken up in a mixture of ethyl acetate and water. The organic phase was dried over sodium sulfate, filtered and concentrated by evaporation in vacuo. The evaporation residue was purified by column chromatography on silaca gel (toluene/acetone = 10/1). Yield: 4.9 g (85% of theory). M.p. 143°-145°C (petroleum/ether). High-melting-point form (B) of 2-ethoxy-4-[N-{1-(2-piperidinophenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid.

A mixture of 4.7 g (9.7 mmols) of ethyl 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl)-aminocarbonylmethyl]-benzoate and 14.7 ml of 1 N sodium hydroxide was stirred in 47 ml of ethanol for 2 hours at 60°C, then neutralized with 14.7 ml of 1 N hydrochloric acid and cooled to 0°C. The mixture was filtered to remove the precipitated colorless crystals, and the crystals were washed with ice water and with a little ice cold ethanol and then dried at 100°C/1 Torr. Yield: 3.9 g (88% of theory). M.p. 140°-142°C. Upon further recrystallization from ethanol/water (2/1) the melting point remained constant.

Low-melting-point form (A) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid.

1 g of the high-melting-point form (B) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonyl-methyl]-benzoic acid was dissolved at room temperature in 5 ml of acetone, and 5 of petroleum ether (m.p. 60°-70°C) were added. Upon trituration, crystallization gradually set in. The same quantity of petroleum ether was added again, and after crystallization had ended, the mixture was filtered. The crystals were washed with petroleum ether, and the almost colorless crystals were dried for 2 hours at 60°C/0.1 Torr. Yield: 0.7 g. M.p. 95°-98°C (clear beginning at 135°C). The IR-spectra for this form are identical to the IR-spectra for the form (A), melting point 90°-92°C.

High-melting-point form (B) of 2-ethoxy-4-[N-{1-2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid

1 g of the low-melting-point form (A) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-amino-carbonylmethyl]-benzoic acid was dissolved in 10 ml of ethanol/water (2/1) while heating over a steam bath. The solution was then cooled to 0°C, whereupon crystallization began. The mixture was filtered, and the residue was washed with a little ice-cold ethanol and dried at 100°C/1 Torr. Yield: 0.8 g. M.p. 140°-142°C.

Foamy form (C) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid

1.5 g of the high-melting-point form (B) of 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl}-amino-carbonylmethyl]-benzoic acid was dissolved in 5 ml of methanol while heating. The solution was then cooled to 0°C with trituration. The crystals precipitated thereby were separated by filtration, washed with a little cold methanol, and dried for 2 hours at 60°C/0.1 Torr. Yield of adduct (with 1 times CH_3OH): 1.2 g. M.p. 85°-90°C. The adduct was converted into the methanol-free foamy form (C) by heating for 24 hours at 60°C/5 Torr over phosphorus pentoxide. Melting range: 75°-85°C.

References

Grell et al.; US Patent No. 5,216,167; Jun. 1, 1993; Assigned to Dr. Karl Thomae GmbH, Biberach an der Riss, Fed. Rep. of Germany
Grill et al.; US Patent No. 5,312,924; May 17, 1994; Assigned to Dr. Karl Thomae GmbH, Biberach an der Riss, Fed. Rep. of Germany

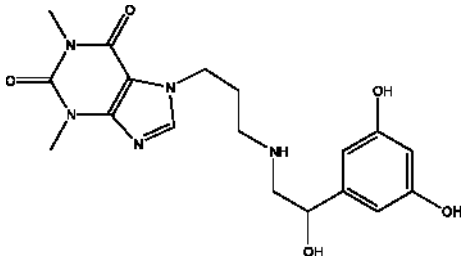
REPROTEROL

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 salt)

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

Raw Materials

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

Manufacturing Process

Theophylline is reacted first with 1-bromo-3-chloropropaneto 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 and Engel p. 800
OCDS Vol. 3 p. 231 (1984)
DOT 13 (2) 552 (1977)
I.N. p. 842
Klingler, K.H. and Bickel, E.; US Patent 4,150,227; April 17, 1979; assigned to Degussa (Germany)

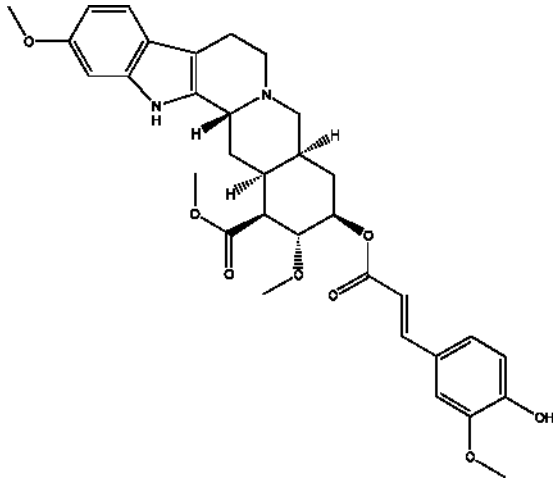
RESCIMETOL

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) and 5 (12) 635 (1980)
DOT 18 (10) 551 (1982)
Kametani, T.; US Patent 3,898,215; August 5, 1975; assigned to Nippon Chemiphar Co., Ltd.

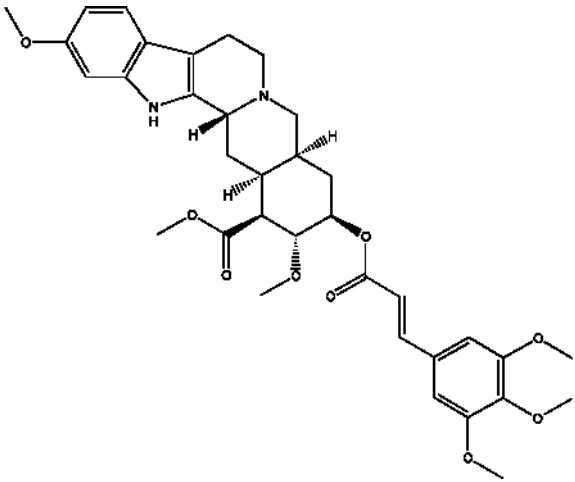
RESCINNAMINE

Therapeutic Function: Antihypertensive

Chemical Name: 11,17α-Dimethoxy-18β-[[1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-oxy]-3β,20α-yohimban-16α-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	US	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 US 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 US Patents 2,974,144 and 2,876,228.

References

Merck Index 8039
Kleeman and Engel p. 801
PDR p. 1422
OCDS Vol. 1 p. 319 (1977)
I.N. p. 843
REM p. 909
Ulshafer, P.R.; US Patent 2,854,454; September 30, 1958
Ordway, H.W. and Guercio, P.A.; US Patent 2,876,228; March 3, 1959; assigned to Chas. Pfizer and Co., Inc.
Klohs, M.W., Draper, M.D. and Keller, F.; US 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

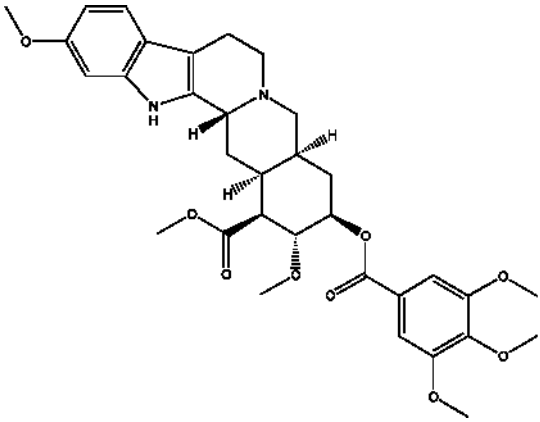
Common Name: 3,4,5-Trimethoxybenzoyl methyl reserpate

Chemical Abstracts Registry No.: 50-55-5

Raw Materials

Rauwolfia plant bark
Methanol

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Serpasil	Ciba	US	1953
Sndril	Lilly	US	1954
Rau-Sed	Squibb	US	1954
Crystoserpine	Dorsey	US	1954
Serpine	Pitman-Moore	US	1954
Serfin	Parke Davis	US	1954
Reserpoid	Upjohn	US	1954
Serpiloid	Riker	US	1954
Serpanray	Panray	US	1954
Vio-Serpine	Rowell	US	1955
Serpena	Haag	US	1955
Serpate	Vale	US	1955
Rausaingle	Philips Roxane	US	1955
Sertabs	Table Rock	US	1955
Eskaserp	SKF	US	1955
Serolfia	Mallard	US	1955
Resercen	Central	US	1956
Banasil	Ulmer	US	1956
Roxinoid	MSD	US	1956
Respital	Premo	US	1956
Raurine D-Lay	Westerfield	US	1961
Lemiserp	Lemmon	US	1962
Abesta	A.N.A.	France	-
Broserpine	Brothers Pharm	US	-
Cardioserpine	Star	Finland	-
Chloroserpine	Schein	US	-
Demi-Regroton	U.S.V.	US	-
Diupres	MSD	US	-
Diutensin	Wallace	US	-
HHR	Schein	US	-

Trade Name	Manufacturer	Country	Year Introduced
Hydro-Fluserpine	Schein	US	-
Hydromox	Lederle	US	-
Hydropres	MSD	US	-
Hydroserpine	Schein	US	-
Key-Serpine	Key	US	-
Lemiserp	Lemmon	US	-
Metatensin	Merrell Dow	US	-
Naquival	Schering	US	-
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.	US	-
Renese-R	Pfipharmecs	US	-
Resedril	Estedi	Spain	-
Rese-Lar	Perga	Spain	-
Reser-Ar	Luar	US	-
Resercrine	Casgrain and Charbonneau	Canada	-
Reserfia	Medic	Canada	-
Reserpur	A.F.I.	Norway	-
Resine	Kirk	US	-
Resomine	Bonjean	Belgium	-
Rivasin	Giulini	W. Germany	-
Slutensin	Bristol	US	-
Ser-Ap-Es	Ciba	US	-
Serolfia	Ascher	US	-
Serpalan	Lannett	US	-
Serpax	Verdun	Canada	-
Serpedin	Pharmacia	Sweden	-
Serpena	Haag	US	-
Serpentil	Pliva	Yugoslavia	-
Serpipur	Kwizda	Austria	-
Serpivite	Vitarine	US	-
Serpoid	Canfield	US	-
Serpone	Hartz	Canada	-
Serpresan	Maipe	Spain	-
Sertina	Fellows-Testagar	US	-
SK-Reserpine	SKF	US	-
Unipres	Reid-Rowell	US	-
Vio-Serpine	Rowell	US	-
V-Serp	Vangard	US	-

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 and 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.; US Patent 2,833,771; May 6, 1958; assigned to Ciba Pharmaceutical Products, Inc.

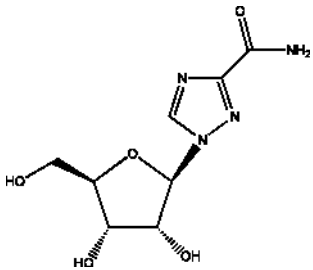
RIBAVIRIN

Therapeutic Function: Antiviral

Chemical Name: 1,2,4-Triazole-3-carboxamide, 1-β-D-ribofuranosyl-

Common Name: Ribavirin; Tribavirin

Structural Formula:



Chemical Abstracts Registry No.: 36791-04-5; 66510-90-5

Trade Name	Manufacturer	Country	Year Introduced
Copegus	Roche Laboratories	USA	-
Rebetol	Schering-Plough Labo N.V.	Belgium	-
Rebetol	Schering - Plough Corp.	USA	-
Rebetol	Fulford GALT (India) Ltd.	India	-
Ribasphere	Three Rivers Pharmaceuticals	USA	-
Ribavin	Lupin Laboratories Ltd.	India	-
Ribavirin	Dragon Hwa ChemPharm Co.	China	-
Ribavirin	Valeant Pharmaceuticals International	USA	-
Ribavirin	ICN Pharmaceuticals Inc.	USA	-
Ribavirin-Meduna	Meduna Arzneimittel	Germany	-
Virazole	ICN Switzerland AG	Switz.	-
Virazole	Valeant Pharmaceuticals International	USA	-

Raw Materials

Triethyl orthoformate
1-Cyanoformidic acid hydrazide
Triethylamine
Enzyme Nucleoside Phosphorylase (Calf Spleen)

Manufacturing Process

3-Cyano-1,2,4-triazole

A mixture of triethyl orthoformate (150 ml) and 1-cyanoformidic acid hydrazide, K. Matsuda and L. T. Morin, J. Org. Chem., 26:3783 (1961), (25.2 g, 0.30 mol) was cooled to 0°C and a solution (4.0 ml) of dioxane saturated with anhydrous hydrogen chloride was added with stirring. The mixture was stirred with cooling in an ice bath for 5 hours and stirring at 25°C was continued for 15 hours. The mixture was evaporated to dryness and ether

(500 ml) was added to the residue. The solution was filtered, washed with water, and the organic layer was dried over magnesium sulfate. The solution was filtered and the ether was removed. Crystallization of the product from ethyl acetate-benzene provided 16.0 g (56.8%) of 3-cyano-1,2,4-triazole with a melting point of 185°-187°C. All properties of the compound were identical with those of a sample prepared by the method of Cipens and Grinsteins, Latvijas PSR Zinatnu Adad. Vestis., Kim Ser., 1965 (2), 204-208. Chem Abst., 63, 13243 (1965).

1,2,4-Triazole-3-thiocarboxamide

A mixture of 3-cyano-1,2,4-triazole (4.7 g, 0.050 mol), ethanol (50 ml) and triethylamine (8.0 ml) was stirred at room temperature while hydrogen sulfide gas was bubbled into the mixture for 4 hours. The solvent was removed and water was added to the residue to provide 2.7 g of product. Recrystallization from water afforded pure 1,2,4-triazole-3-thiocarboxamide with a melting point of >350°C.

1-β-D-Ribofuransyl-1,2,4-triazole-3-carboxamide

Synthesis of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide from 1,2,4-triazole-3-carboxamide via Purified Calf Spleen Nucleoside Phosphorylase.

The samples were incubated at 25°C for 5 minutes and then frozen in dry ice/isopropanol to stop the reaction. Aliquots of the thawed samples were then spotted on silica gel together with standard solutions of 1,2,4-triazole-3-carboxamide and 1-β-D-ribofuranosyl-1,2,4-triazole- 3-carboxamide and separated in isopropanol:NH_4OH:H_2O (7:1:2). Areas of the chromatograms coinciding with 1,2,4-triazole-3-carboxamide were removed and counted to determine the percent of conversion of 1,2,4 -triazole-3-carboxamide to 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide.

1,2,4-Triazole-3-carboxamide may be also converted to 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide by reaction with the enzyme Nucleoside Phosphorylase at a pH within the range of about 7 to 8, at an enzyme concentration about 0.15 mg/ml, and a temperature approximately 25° to about 35°C. Satisfactory results have been obtained when the triazole base is present in a concentration greater than 5 x 10^{-5}M and ribose-1-phosphate is present at a concentration greater than 2 x 10^{5}M. Generally are required for the reactionabout 0.5 to about 1 hour. The source of the enzyme may be animal, tissue, or bacteria. The principal bacterial sources are E. coli and yeast, Brevebacterium, while a variety of animal sources exist, including beef spleen, rat liver, calf liver, calf thymus, beef liver, monkey brain, horse liver, calf spleen, human erythrocytes, fish skin, and fish muscle.

References

Witkowski et al.; US Patent No. 3,976,545; Aug. 24, 1976; Assigned to ICN Pharmaceuticals, Inc., Irvine, Calif.

Fujishima et al.; US Patent No. 4,614,719; Sep., 30, 1986; Assigned to Yamasa Shoyu Kabushiki Kaisha, Chiba, Japan

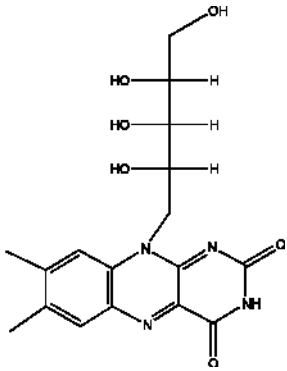
RIBOFLAVIN

Therapeutic Function: Enzyme cofactor vitamin

Chemical Name: 7,8-Dimethyl-10-(D-1-ribityl)isoalloxazine

Common Name: Lactoflavin; Lattoflavina; Ovoflavin; Riboflavin; Vitamin B_2; Vitamin G; Witamina B_2

Structural Formula:



Chemical Abstracts Registry No.: 83-88-5

Trade Name	Manufacturer	Country	Year Introduced
Riboflavin	Roche Vitamins	Germany	-
Riboflavin	Takeda Chemical Industry	Japan	-
Riboflavin	Cytoplan Ltd	-	-
Riboflavin	Hubei Guangji Pharmaceutical Co. Ltd.	China	-
Riboflavin	BASF AG	Germany	-
Riboflavin	BASF Health and Nutrition A/S	Denmark	-
Riboflavin	F.Hoffmann-La Roche AG	Germany	-
Riboflavin	Takeda Europe GmbH	Germany	-
Riboflavin	Hoffmann - La Roche Inc.	USA	-
Riboflavin	Merck and Company, Inc.	USA	-
Vitamin B_2	Pharmadass Ltd	-	-

Raw Materials

o-Amino-biphenyl
Sodium nitrite
Tetraacetyl-ribitylxylidine
Barbituric acid
Hydrogen peroxide

Manufacturing Process

A solution of o-biphenyl diazonium sulfate is prepared as follows: o-amino-biphenyl 21.1 g (0.125 mole), is dissolved by warming in a mixture of 100 ml of glacial acid and 136 ml of water. To this solution is added a mixture: 11.2 ml of concentrated sulfuric acid and 25 ml of water. The temperature is then lowered to 0° to 5°C and 8.65 g (0.125 mole) of sodium nitrite is added in small portions to the: stirred solution over a one hour period. The solution is stirred for an additional two hours at 0° to 5°C after the addition of the nitrite is complete.

A solution of ribitylxylidine is prepared as follows: a stirred suspension of 42.3 g (0.10 mole) of tetraacetylribitylxylidine and 85 ml of water is heated to 95° to 100°C. To this material is added, over a five to 10 minute period, exactly 0.40 mole of aqueous 25 to 30% sodium hydroxide solution, the temperature being held at 95° to 100°C. Shortly after the addition of the caustic solution, the mixture becomes homogeneous, the temperature rises suddenly, and a rapid evolution of steam occurs. The light, straw-colored solution is then stirred for a one hour at 95° to 100°C to insure completeness of reaction. With the resulting ribitylxylidine solution at a temperature of 90°C, 166 ml of 57.5 percent (v./v.) aqueous acetic acid is added, and the solution is then cooled to 0° to 5°C.

The solution of o-biphenyl diazonium sulfate is now added to the ribitylxylidine solution at such a rate as to maintain the temperature of the resulting mixture below 8°C. The mixture is then stirred at 0° to 5°C for 24 hours. After the stirring period is complete the crude product is isolated by filtration; the wet product is slurried in 500 ml of water, refiltered, washed with 200 ml of water, and air-dried at 50° to 60°C. The dried material is pulverized to give about 44 g of 2-(o-biphenylazo)-4,5-dimethyl-1-ribitylamino-beiizene which is obtained as a granular, orange product; m.p. 134°-139°C, dec.

To a mixture of 225 ml of ethyl acetate and 40.5 ml of glacial acetic acid is added 43.6 g (0.10 mole) of 2-(o-biphenylazo)-4,5-dimethyl-l-ribitylamino-benzene, prepared as described above, and 16.9 g (0.132 mole) of barbituric acid. The resulting mixture is refluxed with stirring for about 90 hours, at the end of which period an 0.5 ml test sample of the reaction solution, when mixed with 15 ml of 26% aqueous hydrochloric acid, gives a light straw color showing completion of the reaction. If the reaction is incomplete, the reaction mixture is refluxed for additional five hours periods until a test for completion of the reaction is obtained. The reaction mixture is cooled to 10°C for one hour and filtered. The crude product is washed successively with 50 ml of cold ethyl acetate and 50 ml of cold water, then air-dried at 70°C to give about 37 g of crude riboflavin, which is obtained as a brownish-yellow powder; yield approximately 98.5% of theory.

Crude riboflavin, prepared as described above starting with 43.6 g of 2-(o-biphehylazo)-4,5-dimethyl-1-ribityl amino-benzene, is washed with 50 ml of cold ethyl acetate, slurried with 180 ml of methanol at 65°C for thirty minutes. The methanol slurry is cooled to 10°C for thirty minutes, filtered, and the filtered material washed with 40 ml of cold methanol. The methanol washed riboflavin is then slurried with 180 ml of water at 80°C for thirty minutes, the slurry is cooled to 70°C, filtered, and the filtered material is washed with 40 ml of hot (70°C) water. The hot water-washed riboflavin is

dissolved in a mixture of 70 ml of hydrochloric acid and 23 ml of water by warming to 45°C. The aqueous hydrochloric acid solution is treated with a 1.5 ml of 30% hydrogen peroxide solution to oxidize impurities and filtered through a filter precoated with diatomaceous silica (Super-Cel). The oxidized, filtered solution is poured, with vigorous agitation, into 900 ml of water at 95° to 100°C. The resulting riboflavin slurry is cooled slowly to 10°C, filtered, and the filtered material is washed with 2 x 50 ml of water and 4 x 50 ml portions of methanol. The washed material is air-dried, at 70°C, to give about 30 g of riboflavin; yield about 80% of theory based on the 42.3 g of tetraacetylribitylxylidine used as starting material.

References

Howe Ch.A. et al.; US Patent No. 2,807,611; Sept. 24, 1957; Assignted to Merck and Co., Inc., Rahway, N.J., a corporation of New Jersey

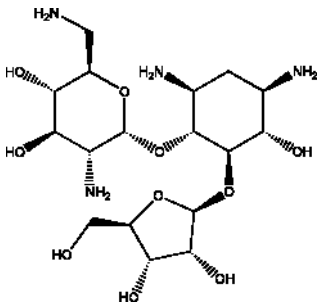
RIBOSTAMICIN

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 and 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 x 2 (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 65 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 and 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.; US Patent 3,661.892; May 9, 1972; assigned to Meiji Seika Kaisha, Ltd. (Japan)

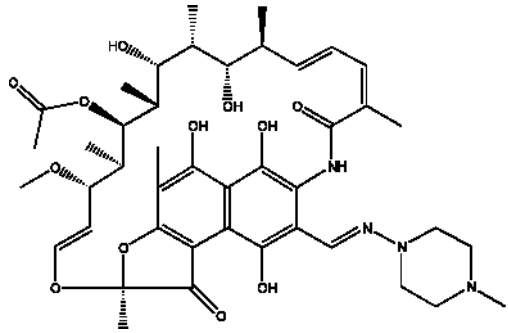
RIFAMPIN

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	UK	1969
Rimactan	Ciba	W. Germany	1969
Rifadine	Lepetit	France	1969
Rimactane	Ciba Geigy	UK	1969
Rifadin	Daiichi	Japan	1971
Rimactan	Ciba	Japan	1971
Rimactane	Ciba	US	1971
Rifadin	Dow	US	1971
Archidyn	Lepetit	Italy	-
Arficin	Belupo Ltd.	Yugoslavia	-
Benemicin	Polfa	Poland	-
Fenampicin	Antibioticos	Spain	-
Feronia	Lifepharma	Spain	-
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	-

Trade Name	Manufacturer	Country	Year Introduced
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 and Engel p. 808
PDR pp. 810, 1236
DOT 5 (1) 24 (1969)
I.N. p. 848
REM p. 1233
Maggi, N. and Sensi, P.; US Patent 3,342,810; September 19, 1967; assigned to Lepetit SpA, Italy

RIFAPENTINE

Therapeutic Function: Antibiotic, Antibacterial (leprostatic), Antibacterial (tuberculostatic)

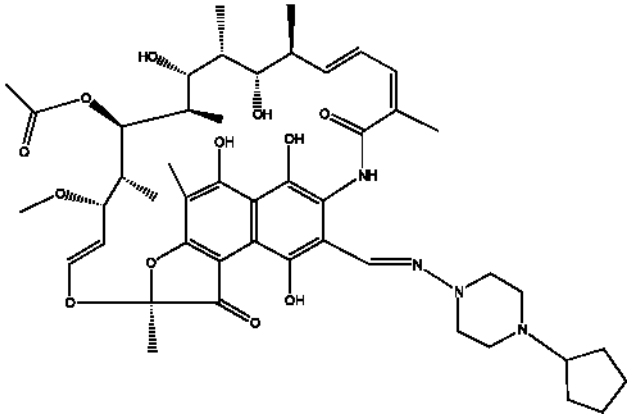
Chemical Name: Rifamycin, 3-(((4-cyclopentyl-1-piperazinyl)imino)methyl)-

Common Name: Rifapentine

Chemical Abstracts Registry No.: 61379-65-5; 71950-35-1

Trade Name	Manufacturer	Country	Year Introduced
Priftin	Aventis Pharmaceuticals	-	-
Priftin	Hoechst Marion Rou	-	-
Rifapentine	Balkanpharma-Razgrad AD	-	-
Rifapentine	Hebei Xingang Biochemistry Co., Ltd.	China	-

Structural Formula:



Raw Materials

3-Formylrifamycin SV
Cyclopentyl bromide
Manufacturing Process
N-Nitrosopiperazine
Lithium aluminum hydride
3-(4-Cyclopentyl-1-piperazinyl) iminomethylrifamycin SV

0.01 mole of 3-formylrifamycin SV is dissolved in tetrahydrofuran and to the obtained solution 0.011 mole of 1-amino-4-cyclopentylpiperazine is added to the reaction mixture at room temperature. After 30 minutes, the reaction is completed since thin layer chromatography of the mixture shows disappearance of the starting 3-formylrifamycin SV. The solvent is then evaporated off and the residue is crystallized from ethyl acetate. The title product, which melts at 179°-180°C, is obtained in a 55% yield.

The elementary analysis is in agreement with the theoretical values. The starting 1-amino-4-cyclopentylpiperazine (b.p. 80°-82°C/0.1 mm Hg) is obtained by alkylating N-nitrosopiperazine with cyclopentyl bromide in ethanol in the presence of $NaHCO_3$ and reducing the so-obtained 1-nitroso-4-cyclopentylpiperazine with $LiAlH_4$ in ethyl ether.

References

Cricchio et al.; US Patent No. 4,002,752; Jan. 11, 1977; Assigned to Gryppo Lepetit, S.p.A., Milan, Italy

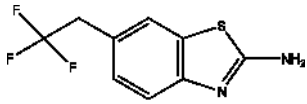
RILUZOLE

Therapeutic Function: Neuroprotective

Chemical Name: Benzothiazole, 2-amino-6-trifluoromethoxy-

Common Name: Riluzole; Rilutek

Structural Formula:



Chemical Abstracts Registry No.: 1744-22-5

Trade Name	Manufacturer	Country	Year Introduced
Rilutek	RPR	-	-
PK-26124	EMD Biosciences, Inc.	-	-

Raw Materials

Sodium nitrite
Potassium thiocyanate
Tin
4-Amino-3-nitrobenzotrifluoride
Copper thiocyanate

Manufacturing Process

To a stirred solution of 74.6 g (0.5 mol) of benzylisothiocyanate in 500 mL toluene was added dropwise 46.6 g (0.5 mol) of aniline. The solution was refluxed 18 hours. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was recrystallized from an appropriate solvent to yield N-phenyl-N'-benzylthiourea. Isothiocyanates which are not commercially available may be prepared from aliphatic or aryl primary amines by the following methods: Kurita and Iwakura, Org. Synth. 59, 195; Jochims, Chem. Ber. 101, 1746 (1968); or Castro, Pena, Santos, and Vega, J. Org. Chem. 49, 863 (1984).

To a stirred solution of 20.6 g (0.10 mol) 4-amino-3-nitrobenzotrifluoride in 30 mL conc. H_2SO_4 and 30 mL H_2O at 0°C was added dropwise 37.5 mL 20% sodium nitrite. The mixture was stirred for 90 min at 0-5°C. Potassium thiocyanate (10 g in 20 mL H_2O) was added dropwise and stirred 15 min. The reaction was poured into a vigorously stirred slurry of 18 g (0.148 mol) copper thiocyanate in 60 mL H_2O. Gas evolution began and the mixture foamed. The reaction was stirred two hours at 3°C and then heated to 70°C for 20 min. The reaction was cooled to 25°C and stirred an additional 18 hours. The solution was filtered and the water was extracted with toluene (3 x 100 mL). The toluene layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield 3-nitro-4-thiocyanatebenzotrifluoride as a purple oil. The product was purified by silica gel chromatography. The column was eluted initially with hexane followed by hexane/CH_2Cl_2 (7:3) to yield an oil which was crystallized from heptane to yield a yellow 3-nitro-4-thiocyanatebenzotrifluoride, m.p. 72-73°C.

To a vigorously stirred solution of 4.0 g (0.16 mol) 3-nitro-4-thiocyanatebenzotrifluoride in 50 mL conc. HCl was added 16.0 g (0.135 mol) granulated tin over one hour. The reaction changed from an orange to very

pale yellow to white. The reaction was stirred at 25°C for 20 hours. The reaction solution was diluted with H_2O (250 mL) and conc. NH_4OH was added dropwise. The product precipitated along with the tin salts. The solid was filtered and boiled in $CHCl_3$ (3 x 200 mL). The aqueous layer was extracted with $CHCl_3$. All the $CHCl_3$ washings were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a dark brown solid. The crude 2-amino-5-trifluoromethylbenzothiazole hydrochloride was dissolved in hot Et_2O and filtered. To the filtrate was added a solution of freshly prepared Et_2O/HCl. The product precipitate was filtered and washed with Et_2O to yield a white solid of 2-amino-5-trifluoromethylbenzothiazole hydrochloride, m.p. 255.-257°C.

References

Merck Index, Monograph number: 8389, Twelfth edition, 1996, Editor: S. Budavari; Merck and Co., Inc.

Johnson G., Pavia M. R.; US Patent No. 4,826,860; May 2, 1989; Assigned to Warner-Lambert Company (Morris Plaines, NJ)

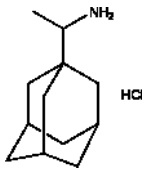
RIMANTADINE HYDROCHLORIDE

Therapeutic Function: Antiviral

Chemical Name: 1-Adamantanemethylamine, α-methyl-, hydrochloride

Common Name: Remantadine hydrochloride; Rimantadine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 1501-84-4; 13392-28-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Flumadine	Forest Pharmaceuticals, Inc.	-	-
Rimantadine hydrochloride	Tai Yuan Pharmaceutical Factory	China	-

Raw Materials

1-Adamantylmethylketone
Acetamide
Formic acid

Manufacturing Process

A mixture of 3 g of 1-adamantylmethylketone, 4 g of acetamide and 1.35 ml of 86% formic acid was boiled for 3.5 hours. Then the mixture was cooled, deluted with water and extracted with ether. The ether solution was dried over alkali, filtered and saturated with dry hydrogen chloride. The resulting precipitate was filtered off and boiled with 30 ml of concentrated hydrochloric acid for 5 hours. The reaction mixture was cooled, and the resulting precipitate was filtered off. After recrystalliszation from a mixture of absolute ethanol and ether 2.32 g of the desired product was obtained (64% to starting ketone). MP 345°-347°C.

Rimantadine may be also prepared by refluxing of the 1-adamantylmethylketone and ammonium formate in diethylene glycol or by hydrogenization of 1-adamantylmethyl ketoxime in the presence of a platinum on carbon catalyst at a room temperature and pressure.

References

Polis Y. et al.; US Patent No. 3,852,352; Dec. 3, 1974
Liu J.; US Patent No. 4,551,552; Nov. 5, 1985; Assigned to E.I. Du Pont de Nemours and Company, Wilmington, Del.

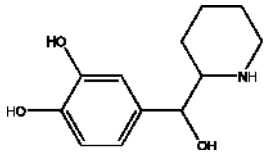
RIMITEROL

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	UK	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 1.5 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 and Engel p. 809
OCDS Vol. 2 p. 278 (1980)
DOT 10 (11) 272 (1974)
I.N. p. 849
Kaiser, C. and Ross, S.T.; US Patent 3,705,169; December 5, 1972; assigned to Smith Kline and French Laboratories

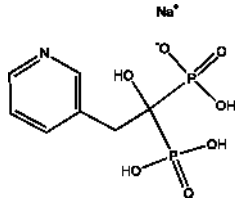
RISEDRONATE SODIUM

Therapeutic Function: Bone calcium regulator

Chemical Name: Phosphonic acid, (1-hydroxy-2-(3-pyridinyl)ethylidene)bis-, monosodium salt

Common Name: Risedronate sodium

Structural Formula:



Chemical Abstracts Registry No.: 115436-72-1; 105462-24-6 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Actonel	Aventis	-	-
Actonel	Procter and Gamble	USA	-

Raw Materials

3-Pyridine acetic acid
Phosphorus trichloride
Chlorobenzene
Celite 545

Manufacturing Process

A 3-neck round-bottom flask fitted with a reflux condenser and a magnetic stir bar is charged with 6.94 grams (0.04 mole) 3-pyridine acetic acid 9.84 grams (0.14 mole) phosphorus acid, and 150 ml of chlorobenzene. This reaction mixture is heated on a boiling water bath, and 16.5 grams (0.12 mole) phosphorus trichloride is added dropwise with stirring. This reaction mixture is heated for 2 1/2 hours during which time a viscous yellow oil forms. The reaction mixture is then cooled in an ice bath and the chlorobenzene solution is decanted off from the solidified product. The reaction flask containing this solidified product is charged with 150 ml of water and heated in a boiling water bath for several hours. The hot solution is then filtered through Celite 545 300 ml of methanol is added to the warm filtrate solution, and a precipitate develops. After cooling in ice for 1 hour, the precipitate is filtered off and then washed with methanol/water (1/1 volume/volume), methanol, and ether, and air dried. The product may be recrystallized from hot water. Yield is approximately 5.9 grams (52%). The sample is characterized by P-31 and C-13 NMR. It may be converted into the sodium salt with equivalent of NaOH.

References

Benedict et al.; US Patent No. 5,583,122; Dec. 10, 1996; Assigned to The Procter and Gamble Company, Cincinnati, Ohio

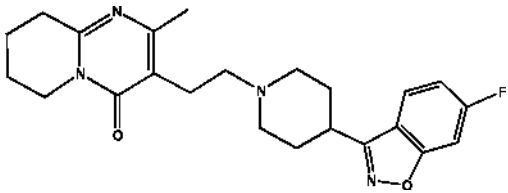
RISPERIDONE

Therapeutic Function: Antipsychotic, Neuroleptic

Chemical Name: 4H-Pyrido(1,2-a)pyrimidin-4-one, 6,7,8,9-tetrahydro-3-(2-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)ethyl)-2-methyl-

Common Name: Risperidone

Structural Formula:



Chemical Abstracts Registry No.: 106266-06-2

Trade Name	Manufacturer	Country	Year Introduced
Rasin	Pfizer	-	-
Respidon	Torrent Pharmaceuticals Ltd.	India	-
Risperdal	Janssen-Ortho Inc.	-	-
Risperidone	Janssen-Cilag	-	-
Rispolept	Janssen-Cilag SpA	-	-

Raw Materials

1,3-Difluorobenzene
1-Acetyl-4-piperidine-carbonyl chloride
Aluminum chloride
Hydroxylamine hydrochloride
Potassium iodide
3-(2-Chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride

Manufacturing Process

To a stirred mixture of 65 parts of 1,3-difluorobenzene, 130 parts of aluminium chloride and 195 parts of dichloromethane was added dropwise a solution of 95 parts of 1-acetyl-4-piperidine-carbonyl chloride in 65 parts of dichloromethane while cooling. Upon completion, stirring was continued for 3

hours at room temperature. The reaction mixture was poured into a mixture of crushed ice and hydrochloric acid. The product 1-acetyl-4-(2,4-difluorobenzoyl)piperidine as a residue. A mixture of 48 parts of 1-acetyl-4-(2,4-difluorobenzoyl)-piperidine and 180 parts of a hydrochloric acid solution 6 N was stirred and refluxed for 5 hours. The reaction mixture was evaporated and the residue was stirred in 2-propanol. The product was filtered off and dried, yielding 39 parts (83%) of (2,4-di-fluorophenyl)(4-piperidinyl)methanone hydrochloride. A mixture of 12 parts of above product, 12 parts of hydroxylamine hydrochloride and 120 parts of ethanol was stirred at room temperature and 10.5 parts of N,N-diethylethanamine were added. The whole was stirred and 25 refluxed for 3 hours. After cooling, the precipitated product was filtered off and dried, yielding 11 parts (100%) of (2,4-di-fluorophenyl)(4-piperidinyl)methanone oxime.

A mixture of 11 parts of (2,4-difluorophenyl)(4-piperidinyl)-methanone oxime, 25 parts of potassium hydroxide and 25 parts of 30 water was stirred and refluxed for 2 hours. The reaction mixture was cooled and extracted with methylbenzene. The extract was dried, filtered and evaporated. The residue was crystallized from petroleum ether, yielding 6;8 parts of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole.

A mixture of 5.3 parts of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride, 4.4 parts of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole, 8 parts of sodium carbonate, 0.1 parts of potassium iodide and 90 parts of N,N- dimethylformamide was stirred overnight at 85°-90°C. After cooling the reaction mixture was poured into water. The product was filtered off and crystallized from a mixture of N,N-dimethylformamide and 2-propanol. The product was filtered off and dried, yielding 3.8 parts (46%) of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]-pyrimidin- 4-one: melting point 170°C.

References

Kennis et al.; European Patent Office No. 0 196 132 A2, 13.03.86

RITODRINE

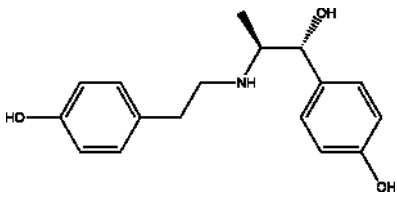
Therapeutic Function: Muscle relaxant (obstetric)

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

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

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

Structural Formula:



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

Raw Materials

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

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)ethlamino] 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 and Engei 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.; US Patent 3,410,944; November 12, 1968; assigned to North American Philips Company, Inc.

RITONAVIR

Therapeutic Function: Antiviral

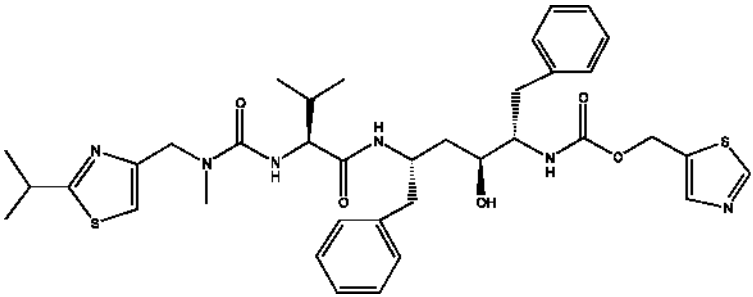
Chemical Name: 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-(2-(1-methylethyl)-4-thiazolyl)-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S-(5R*,8R*,10R*,11R*))-

Common Name: Ritonavir

Chemical Abstracts Registry No.: 155213-67-5

Trade Name	Manufacturer	Country	Year Introduced
Norvir	Abbott Laboratories	USA	-
Ritomune	Cipla Limited	India	-
Ritonavir	Abbott Laboratories	USA	-

Structural Formula:



Raw Materials

Oxalyl chloride	N-((Benzyl)oxy)carbonyl)-L-phenylalaninal
Lithium hydroxide	Phosphorous pentasulfide
Zinc	Vanadium(III) chloride
Potassium t-butoxide	Ethyl chloroacetate
Ethyl formate	α-Acetoxyisobutyryl bromide
Sodium borohydride	Thioformamide
Trifluoroacetic acid	Ethyl 2-chloro-2-formylacetate
Phenylboric acid	Barium hydroxide octahydrate
N-Methylmorpholine	Lithium aluminum hydride
Formamide	4-Nitrophenyl chloroformate
Isobutyramide	Phosphorus pentasulfide
1,3-Dichloroacetone	Methylamine
Triethylamine	4-Dimethylaminopyridine

N-Ethyl-N'-dimethylaminopropyl carbodiimide

Manufacturing Process

The synthesis of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl- 3-hydroxyhexane consists of 20 steps.

1. N-((Benzyl)oxy)carbonyl)-L-phenylalaninal. It was prepared from 50 g (0.175 mol) of N-(((benzyl)oxy)-carbonyl-L-phenylalaninol in 200 ml of dichloromethane under N_2 atmosphere at -60°C by treating with 131 ml of a 2 M solution of oxalyl chloride in dichloromethane, a solution of 24.5 ml of anhydrous dimethyl sulfoxide in 870 ml of anhydrous dichloromethane for about 2 hours. The resulting solution was stirred at -60°C for 1 h, then treated over a period of 15 min with 97 ml of triethylamine in order that the internal temperature remained below -50°C. After addition the solution was stirred at -60°C for 15 min, then, with the cooling bath in place, was treated rapidly with a solution of 163 g of citric acid in 550 ml of water. The resulting slurry was stirred vigorously for 10 min, allowed to warm, diluted to 1 liter with water, and separated. The organic layer was washed with 700 ml of water followed by a mixture of 550 ml of water and 150 ml of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo at 20°C to give the crude desired compound as a light yellow solid.

2. (2S,3R,4R,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane and (2S,3S,4S,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

A suspension of 78.5 g of VCl_3 (tetrahydrofuran)3and 16 g of zinc dust in 400 ml of dry dichloromethane was stirred under N_2 atmosphere for 1 h at 25°C. A solution of 0.175 mol of N-(((benzyl)oxy)carbonyl)-L-phenylalaninal in 200 ml of dichloromethane was then added and the resulting mixture was stirred at ambient temperature under N_2 for 16 h. The resulting mixture was added to 500 ml of 1 M aqueous HCl, diluted with 500 ml of hot chloroform, and shaked vigorously for 2 min. The layers were separated, and the organic layer was washed with 1 M aqueous HCl and separated. Filtration of the organic phase provided the crude desired product as a solid residue. The residue was slurried in 1.25 liters of acetone, treated with 5 ml of concentrated H_2SO_4, and stirred for 16 h at ambient temperature. The resulting mixture was filtered, and the residue (residue A) was washed with 50 ml of acetone. The combined filtrate was concentrated to a volume of 250 ml, diluted with 1000 ml of dichloromethane, washed three times with water and once with saturated brine, dried over $MgSO_4$ and concentrated to give a viscous oil. The oil was taken up in 1000 ml of 1 M HCl in methanol (prepared from 71 ml of acetyl chloride and 1000 ml of methanol) and stirred at ambient temperature for 2 h. The resulting precipitate was filtered, washed with methanol, and air-dried on the filter to provide 26.7 g of the desired compound as a white solid. The filtrate was concentrated and filtered to give a second crop (8.3 g) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Residue A (above, 2.65 g) was suspended in 75 ml of tetrahydrofuran (THF) and 75 ml of 1 M aqueous HCl and refluxed for 24 h. After concentration of the resulting solution in vacuo, the residue was taken up in 10% methanol in chloroform, washed two times with water, dried over Na_2SO_4 and concentrated in vacuo to provide (2S,3S,4S,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane as a white solid

3.(2S,3R,4S,5S)-3-Acetoxy-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3-bromo-1,6-diphenylhexane.

A suspension of 25 g (44 mmol) of the compound prepared in the step 2 in 500 ml of 2:1 dichloromethane/hexane was treated with 23 g of a-acetoxyisobutyryl bromide. The resulting mixture was stirred at ambient temperature until the reaction clarified, washed twice with 200 ml portions of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to give 30.8 g of the crude desired compound. A portion was purified by silica gel chromatography using 9:1 dichloromethane:ethyl acetate to provide the pure desired compound as a white solid.

4.(2S,3R,4R,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-epoxy-1,6-diphenylhexane.

A solution of 35.56 g (52.8 mmol) of the above compound (step 3) in 375 ml of dioxane was treated with 255 ml of 1 N aqueous sodium hydroxide and stirred at ambient temperature for 16 h, during which the desired compound precipitated. The resulting mixture was filtered, and the residue was washed

with water and dried to provide 22.23 g (76%) of the desired compound as a white solid.

5.(2S,3S,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A mixture of 39.2 g (71.2 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-epoxy-1,6-diphenylhexane in 600 ml of THF was treated under N_2 with 13 g (0.36 mol) of sodium borohydride. The resulting mixture was treated dropwise with 27.7 ml (0.36 mol) of trifluoroacetic acid. After being stirred for 3.5 h at ambient temperature, the resulting mixture was quenched with 1 N aqueous HCl, diluted with water, and stirred for 16 h. The resulting mixture was filtered, washed with water, and dried to provide 22.85 g (58%) of the hydroxide octahydrate in 400 ml of 1,4-dioxane and 400 ml desired compound as a white solid.

6. (2S,3S,5S)-2,5-Diamino-1,6-diphenyl-3-hydroxyhexane.

A suspension of 32 g of the crude resultant compound of step 5 and 55.5 g (176 mmol) of barium hydroxide octahydrate in 400 ml of water was refluxed for 4 h. The resulting mixture was filtered, and the residue was rinsed with dioxane. The combined filtrates were concentrated to a volume of approximately 200 ml and extracted with 4 x 400 ml portions of chloroform. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography using first 2% isopropylamine in chloroform and then 2% isopropylamine/2% methanol in chloroform to provide 10.1 g (81%) of the pure desired compound as a white solid.

7. (4S,6S,1'S)-6-(1-Amino-2-phenylethyl)-4-benzyl-2-phenyl-3-aza-2bora-1-oxacyclohexane.

A solution of 11.28 g (40 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 4.88 g (40 mmol) of phenylboric acid in 1 liter of toluene was refluxed and the water azeotropically removed with the aid of a Dean Stark trap until the distillate was clear. The solvent was then removed in vacuo to provide the crude desired compound which was used immediately without further purification.

8. Thioformamide.

To a cooled (0°C) solution of formamide (30.5 mL, 0.76 mol) in 1 L of diethyl ether was added 89 g (0.19 mol) of phosphorous pentasulfide in small portions with stirring. The reaction mixture was allowed to warm to ambient temperature, stirred for 2 h, filtered, and concentrated in vacuo to afford thioformamide as a yellow offensive smelling oil which was used without purification.

9. Ethyl 2-chloro-2-formylacetate.

To 0.5 mol of potassium t-butoxide (500 mL of a 1 M solution in THF) and 500 mL of dry THF cooled to 0°C was added dropwise a solution of ethyl chloroacetate (0.5 mol, 53.5 mL) and ethyl formate (0.5 mol, 40.4 mL), in

200 mL of THF over 3 hours. After completion of addition, the reaction mixture was stirred for 1 hour and allowed to stand overnight. The resulting solid was diluted with diethyl ether and cooled in an ice bath. Then, the pH was lowered to approximately 3 using 6 N HCl. The organic phase was separated, and the aqueous layer was washed 3 times with diethyl ether. The combined ethereal portions were dried over Na_2SO_4 and concentrated in vacuo. The crude desired compound was stored at -30°C and used without further purification.

10. Ethyl thiazole-5-carboxylate.

250 mL of dry acetone, 7.5 g (0.123 mol) of thioformamide, and 18.54 g (0.123 mol) of ethyl 2-chloro-2-formylacetate were refluxed for 2 hours. The solvent was removed in vacuo, and the residue was purified by chromatography (SiO_2, 6 cm o.d. column, 100% $CHCl_3$, R_f = 0.25) to provide 11.6 g (60%) of the desired compound as a light yellow oil.

11. 5-(Hydroxymethyl)thiazole.

To a precooled (ice bath) lithium aluminum hydride (76 mmol) in 250 mL of THF was added ethyl thiazole-5-carboxylate (11.82 g, 75.68 mmol) in 100 mL of THF dropwise over 1.5 hours to avoid excess foaming. The reaction was stirred for an additional hour, and treated cautiously with 2.9 mL of water, 2.9 mL of 15% NaOH, and 8.7 mL of water. The solid salts were filtered, and the filtrate set aside. The crude salts were refluxed in 100 mL of ethyl acetate for 30 min. The resulting mixture was filtered, and the two filtrates were combined, dried over Na_2SO_4 and concentrated in vacuo. The product was purified by silica gel chromatography eluting sequentially with 0%-2%-4% methanol in chloroform, to provide the desired compound, R_f = 0.3 (4% methanol in chloroform), which solidified upon standing in 75% yield.

11. ((5-Thiazolyl)methyl)-(4-nitrophenyl)carbonate.

A solution of 3.11 g (27 mmol) of 5-(hydroxymethyl)thiazole and excess N-methyl morpholine in 100 ml of methylene chloride was cooled to 0°C and treated with 8.2 g (41 mmol) of 4-nitrophenyl chloroformate. After being stirred for 1 h, the reaction mixture was diluted with $CHCl_3$, washed with 1 N HCl, saturated aqueous $NaHCO_3$, and saturated brine, dried over $NaSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (SiO_2, 1-2% MeOH/$CHCl_3$, R_f = 0.5 in 4% MeOH/$CHCl_3$) to yield 5.9 g (78%) of the desired compound as a yellow solid.

12.(2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexaneand (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino-1,6-diphenyl-3-hydroxyhexane.

A solution of 500 mg (1.76 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 480 mg (1.71 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 20 ml of THF was stirred at ambient temperature for 4 hours. After removal of the solvent in vacuo, the residue was purified by silica gel chromatography using first 2% then 5% methanol in chloroform to provide a mixture of the two desired compounds. Silica gel chromatography of

the mixture using a gradient of 0-1-2% methanol in 93:2 isopropylamine: chloroform provided 110 mg (16%) of (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (Rsubfsub 0.48, 96:2:2 chloroform:methanol:isopropylamine) and 185 mg (28%) of (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (R_f 0.44, 96:2:2 chloroform:methanol:isopropylamine).

13. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 40 mmol of crude (4S,6S,1'S)-6-(1-amino-2-phenylethyl)-4-benzyl-2-phenyl-3-aza-2-bora-1-oxa cyclohexane in 700 ml of anhydrous THF was cooled to -40°C and treated dropwise for 1 h with a solution of 7.83 g (27.9 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 300 ml of dry THF. The resulting solution was allowed to warm to 0°C for 3 h, then to ambient temperature for 16 h. The solvent was removed in vacuo, and the residue was taken up in 700 ml of ethyl acetate, washed with 3 x 150 ml of 1 N NaOH and one 150 ml of brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography using methanol/chloroform mixtures provided the desired compound mixed with its regioisomer. A second chromatography using 1-3% isopropylamine in chloroform provided 5.21 g of the desired compound which solidified upon standing.

14. 2-Methylpropane-thioamide.

A suspension of 100 g (1.15 mol) of isobutyramide in 4 L of diethyl ether was stirred vigorously and treated in portions with 51 g (0.115 mol) of P4S 10. The resulting mixture was stirred at ambient temperature for 2 h, filtered, and concentrated in vacuo to provide 94.2 g (80%) of the crude desired compound.

15. 4-(Chloromethyl)-2-isopropylthiazole hydrochloride.

A mixture of 94.0 g (0.91 mol) of 2-methylpropane-thioamide, 115.7 g (0.91 mol) of 1,3-dichloroacetone, and 109.7 g (0.91 mol) of $MgSO_4$ in 1.6 liters of acetone was refluxed for 3.5 h. The resulting mixture was allowed to cool, filtered, and the solvent was removed in vacuo to provide the crude desired compound as a yellow oil.

16. 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole.

A solution of 40 g of 4-(chloromethyl)-2-isopropylthiazole hydrochloride in 100 ml of water was added dropwise with stirring to 400 ml of 40% aqueous methylamine. The resulting solution was stirred for 1 h, then concentrated in vacuo. The residue was taken up in chloroform, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel chromatography using 10% methanol in chloroform provided 21.35 g (55%) of the desired compound.

17. N-(((4-Nitrophenyl)oxy)carbonyl)-L-valine methyl ester.

A solution of 66.1 g (0.328 mol) of 4-nitrophenyl chloroformate in 1.2 liters of

CH_2Cl_2 was cooled to 0°C and treated with L-valine methyl ester hydrochloride. The resulting mixture was treated slowly, with stirring, with 68.9 ml (0.626 mol) of 4-methylmorpholine. The resulting solution was allowed to slowly warm to ambient temperature and was stirred overnight. After washing with 3 portions of 10% $NaHCO_3$, the solution was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography by eluting with chloroform to provide the desired compound.

18. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine methyl ester.

A solution of 15.7 g (92 mmol) of 2-isopropyl-4-(((N-methyl)amino)-methyl)thiazole in 200 ml of THF was combined with a solution of 20.5 g (69 mmol) of N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester. The resulting solution was treated with 1.6 g of 4-dimethylaminopyridine and 12.9 ml (92 mmol) of triethylamine, heated at reflux for 2 h, allowed to cool, and concentrated in vacuo. The residue was taken up in CH_2Cl_2, washed extensively with 5% aqueous K_2CO_3, dried over Na_2SO_4, and concentrated in vacuo. The resulting product mixture was purified by silica gel chromatography using chloroform as an eluent to provide 16.3 g (54%) of the desired compound.

19. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

A solution of 1.42 g (4.3 mmol) of the resultant compound of step 18 in 17 ml of dioxane was treated with 17.3 ml of 0.50 M aqueous LiOH. The resulting solution was stirred at ambient temperature for 30 min, treated with 8.7 ml of 1 M HCl, and concentrated in vacuo. The residue was taken up in dichloromethane, washed with water, dried over Na_2SO_4, and concentrated in vacuo to provide 1.1 g (81%) of the desired compound.

20. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

A solution of 70 mg (0.223 mmol) of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine, 79 mg (0.186 mmol) of (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane, 30 mg (0.223 mmol) of 1-hydroxybenzotriazole hydrate, and 51 mg (0.266 mmol) of N-ethyl-N'-dimethylaminopropyl carbodiimide in 2 ml of THF was stirred at ambient temperature for 16 h. The resulting solution was concentrated in vacuo, and the residue was purified by silica gel chromatography using 97:3 CH_2Cl_2/CH_3OH to provide 100 mg (74%) of the desired compound (R_f 0.4, 95:5 CH_2Cl_2:CH_3OH) as a solid, melting point 61°-63°C.

The structure of the described compounds was confirmed by NMR and mass spectrum analysis.

2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-(2-(1-methylethyl)-4-thiazolyl)-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S-(5R*,8R*,10R*,11R*))- and

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane have the same structural formula.

References

Al-Razzak et al.; US Patent No. 5,484,801; Jan. 16, 1996; Assigned to Abbott Laboratories, Abbott Park, III

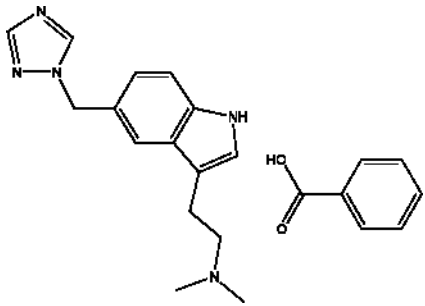
RIZATRIPTAN BENZOATE

Therapeutic Function: Serotoninergic

Chemical Name: 1H-Indole-3-ethanamine, N,N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-, monobenzoate

Common Name: Rizatriptan benzoate

Structural Formula:



Chemical Abstracts Registry No.: 145202-66-0

Trade Name	Manufacturer	Country	Year Introduced
Maxalt	Merck Sharp and Dohme	UK	-
Maxalt-MLT	Merck Sharp and Dohme	UK	-

Raw Materials

1,2,4-Triazole sodium salt
Tin(II) chloride dihydrate
Formaldehyde
Benzoic acid
Palladium on carbon
4-Hydrazine
Sodium cyanoborohydride

Manufacturing Process

1. 1-(4-Nitrophenyl)methyl-1,2,4-triazole

4-Nitrobenzylbromide (21.6 g, 0.1 mol) was added to a rapidly stirred suspension of 1,2,4-triazole sodium salt (9.1 g, 0.1 mol) in anhydrous DMF (100 ml) and the mixture stirred at room temperature for 16 h. Ethyl acetate (400 ml) was added followed by water (250 ml) and the layers separated. The organic phase was washed with water (3 x 250 ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate to give the title-product (10.6 g, 52%); m.p. 98°-100°C.

2. 1-(4-Aminophenyl)methyl-1,2,4-triazole hydrochloride

A solution of 1-(4-nitrophenyl)methyl-1,2,4-triazole (10.0 g, 49 mmol) in ethanol (50 ml), ethyl acetate (50 ml), 5 N HCl (10 ml) and water (10 ml) was hydrogenated over 10% Pd/C (1.0 g) at 40 p.s.i., in a Parr apparatus, until an uptake of 188 p.s.i., had been observed (approx 10 mins). The catalyst was removed by filtration and the solvent removed under vacuum. The residue was azeotroped with ethanol (2 times) to give the titleamine hydrochloride (10.6 g, 100%).

3. 1-(4-Hydrazinophenyl)methyl-1,2,4-triazole

A solution of sodium nitrite (3.28 g, 48 mmol) in water (20 ml) was added to a solution of the preceding amine hydrochloride (10.0 g, 48 mmol), in concentrated HCl (40 ml), at such a rate that the temperature did not exceed -10°C. After addition was complete the solution was stirred at 0°C for 0.25 h and then added portionwise to a rapidly stirred solution of $SnCl_2 \times 2H_2O$ (40 g) in concentrated HCl (40 ml). The solution was warmed to room temperature and basified with 20% aqueous NaOH solution. The solution was extracted with ethyl acetate (3 x 250 ml) and the combined extracts dried ($MgSO_4$) and filtered. The solution was evaporated to dryness to give the desired hydrazine (5.0 g, 56%) m.p. 109°-112°C.

4. 2-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine

4-Chlorobutanal dimethylacetal (3.22 g, 21.1 mmol) was added to a stirred solution of the preceding hydrazine (5.0 g, 26.4 mmol) in ethanol/water (5:1, 180 ml) and 5 N HCl (4.5 ml) and the solution refluxed for 4 h. The solvents were removed under vacuum and the residue chromatographed on silica gel, eluting with CH_2Cl_2/EtOH/NH_3 (30:8:1) to give the desired tryptamine (2.4 g, 38%).

5. N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine benzoate

A solution of formaldehyde (37% w/w solution, 0.19 g), in methanol (10 ml), was added to a mixture of the preceding tryptamine (0.36 g, 1.5 mmol), $NaCNBH_3$ (0.225 g, 3.6 mmol) and glacial acetic acid (0.45 g), in methanol (10 ml). The mixture was stirred at room temperature for 2 h before adding saturated K_2CO_3 (50 ml) and evaporating the methanol. The residue was

extracted with ethyl acetate (3 x 100 ml) and the combined extracts washed with brine (100 ml), dried (K_2CO_3), and evaporated. The crude product was chromatographed on silica gel eluting with CH_2Cl_2/EtOH/NH_3 (20:8:1) to give the free base of the title-compound (0.21 g, 52%).The benzoate salt of N,N-dimethyl-2-[5-(1,2,4-triazol-1-yl-methyl)-1H-indol-3-yl]ethylamine was prepared by addition of a solution of benzoic acid in diethyl ether to a solution of the free base in ethanol/diethyl ether (1:4). The precipitated salt was recrystallised from ethanol, mp 178°-180°C.

References

Baker et al.; US Patent No. 5,298,520; Mar. 29, 1994; Assigned to Merck Sharp and Dohme Limlted, Hertfordshire, England

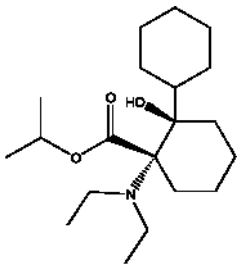
ROCIVERINE

Therapeutic Function: Spasmolytic

Chemical Name: 1-(Diethylamino)-2-propyl-cis-2-hydroxy-2-cyclohexyicyclohexane-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/cm2 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; US Patents 3,700,675; and 3,700,775; both dated October 24, 1972

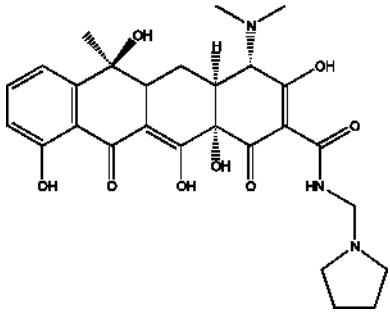
ROLITETRACYCLINE

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	US	1959
Velacycline	Squibb	US	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 and Engel p. 810
OCDS Vol. 1 p. 216 (1977)
I.N. p. 853
Cheney, L.C., Risser, W.C. and Gottstein, W.J.; US Patent 3,104,240; September 17, 1963; assigned to Bristol-Myers Co.

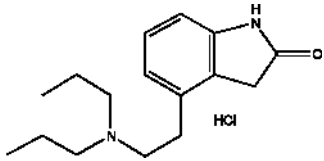
ROPINIROLE HYDROCHLORIDE

Therapeutic Function: Antianginal, Antihypertensive, Antiparkinsonian

Chemical Name: 2H-Indol-2-one, 1,3-dihydro-4-(2-(dipropylamino)ethyl)-, monohydrochloride

Common Name: Ropinirole hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 91374-20-8; 91374-21-9 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Requip	GlaxoSmithKline	USA	-
Ropinirole Hydrochloride	GlaxoSmithKline	USA	-

Raw Materials

4-(2-Di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide
5-Chloro-1-phenyl-1H-tetrazole
Phenyl tetrazole ether
Palladium on carbon

Manufacturing Process

A mixture of 3.44 g (9.63 mmoles) of 4-(2-di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide (U. S. Pat. No. 4,314,944), 22 cc of dimethylformamide, 1.79 g (9.91 mmoles) of 5-chloro-1-phenyl-1H-tetrazole, 220 cc of acetone, 10 cc of water and 2.90 g (21 mmoles) of anhydrous potassium carbonate was refluxed for about 3 hours at which time thin layer chromatographic analysis (silica gel GF, 75-23-2 ethyl acetate-methanol-conc. ammonium hydroxide) indicated that the reaction was complete.

After cooling the reaction mixture in an ice-bath, the inorganic salts were removed by filtration and washed with acetone. The combined filtrates were concentrated in vacuo. The residual syrup was diluted with saturated brine and extracted with three portions of diethyl ether. The gathered extracts were dried over anhydrous magnesium sulfate, clarified with charcoal and treated with ethereal hydrogen chloride until precipitation was complete. The solid was slurried in diethyl ether and decanted several times, filtered and air-dried to give 3.8 g (86%) of tan 4-(2-di-n-propylaminoethyl)-7-(1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-indolone hydrochloride. Recrystallization from 200 cc of hot acetonitrile gave 2.6 g (59%) of microcrystalline product, m.p. 245°C.

Evaporation of the mother liquor and recrystallization of the residue from 25 cc of hot acetonitrile gave an additional 400 mg of product, m.p. 244°-245°C.

A mixture of 2.64 g (5.78 mmoles) of the phenyl tetrazole ether, 200 cc of glacial acetic acid and 1.49 g of 10% palladium-on-carbon was hydrogenated in a Parr apparatus at 50 p.s.i. for 20 hours at 50°C. The warm reaction mixture was filtered through glass fiber filterpaper and the catalyst washed thoroughly with hot glacial acetic acid. The filtrate was concentrated in vacuo, the pale yellow waxy residue distributed in water and ethyl acetate. After acidification of the aqueous phase with 3 N hydrochloric acid, the organic phase was separated and extracted once with 1 N hydrochloric acid. The combined aqueous phases were adjusted to pH 8.5 with aqueous 10% sodium hydroxide and extracted with a mixture of ethyl acetate and diethyl ether. The combined organic extract was back-washed once with saturated brine, dried over anhydrous magnesium sulfate, clarified with charcoal, treated with ethereal hydrogen chloride and evaporated to dryness in vacuo to give 1.64 g (96%) of pale yellow crystalline solid; 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride. Recrystallization from 260 cc of hot acetonitrile which was concentrated to about 50 cc gave 1.26 g (74%) of pale yellow microcrystalline powder, melting point 240°-242°C. The hydrochloride salt (500 mg) is shaken in the presence of ether/5% sodium carbonate solution. The ether layer is separated, dried and evaporated to give the free base which is used to prepare other salt forms such as the methanesulfonate, ethanedisulfonate, sulfate or sulfamate by reacting aliquots of the base in ether with an excess of each acid.

References

Gallagher, Jr.; US Patent No. 4,452,808; Jun. 5, 1984; Assigned to Smithkline Beckman Corporation, Philadelphia, Pa.

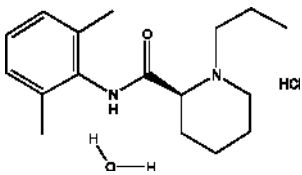
ROPIVACAINE HYDROCHLORIDE MONOHYDRATE

Therapeutic Function: Local anesthetic

Chemical Name: 2-Piperidinecarboxamide, N-(2,6-dimethylphenyl)-1-propyl-, monohydrochloride, (S)-, monohydrate

Common Name: Ropivacaine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 132112-35-7; 84057-95-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Naropin	AstraZeneca	-	-
Ropivacaine hydrochloride	AstraZeneca	Japan	-

Raw Materials

Isobutyl methyl ketone
1-Bromopropane
Sodium iodide
Pipecoloxylidide hydrochloride
Tartaric acid, dibenzoate, (-)-

Manufacturing Process

The process for preparation of ropivacaine includes three steps.

Step 1, resolution

Pipecoloxylidide hydrochloride (1.0 kg), acetone (3.75 L), and water (0.85 L) were charged. NaOH (aq) was added to pH>11. The phases, thus formed, were separated and the organic phase was diluted with water (1.4 L). L-(-)-Dibenzoyltartaric acid (0.67 kg), dissolved in acetone (3.75 L), was added. The solution was seeded. The crystal slurry was cooled to 2°C. The crystals were collected by centrifugation and were washed with acetone followed by isobutyl methyl ketone. The product was not dried. The moist crystalline product was extracted with isobutyl methyl ketone (3.60 L) and diluted NaOH (2.60 L) at pH>11. The phases were separated. The organic phase was washed with water (0.6 L) and was used directly in the next step. Yield (calculated on the dry basis) about 0.39 kg of (S)-pipecoloxylidide (about.90%).

Step 2, alkylation and salt precipitation

K_2CO_3 (0.32 kg), NaI (catalytical amount), and 1-bromopropane (0.28 kg) and about 5% of water, were added to the organic phase from the previous step. The mixture was heated to reflux to complete the reaction. The excess of bromopropane was removed by distillation. The reaction mixture was extracted with water (1.70 L). Acetone (1.70 L) was added to the organic phase followed by HCl (aq) to pH about 2. The solution was seeded. The crystal slurry was cooled to 9°C. The crystals were collected by centrifugation and were washed with acetone. The product was used directly in the next step and was not dried. Yield (calculated on the dry basis): 0.47 kg of ropivacaine hydrochloride (about 0.90%).

As an alternative, the following procedure was followed:

K_2CO_3 (0.32 kg), NaI (catalytical amount), 1-bromopropane (0.28 kg) and water (1.70 L) were added to the organic phase from the previous step. The mixture was heated to reflux to complete the reaction. The excess of bromopropane was removed by distillation. The reaction mixture was separated. Acetone (1.70 L) was added to the organic phase followed by HCl (aq) to pH about 2. The solution was seeded. The crystal slurry was cooled to

9°C. The crystals were collected by centrifugation and were washed with acetone. The product was used directly in the next step and was not dried. Yield (calc. on the dry basis): 0.47 kg of ropivacaine hydrochloride (about 0.90%).

Step 3, recrystallisation

Ropivacaine hydrochloride, from the previous step, was slurried in acetone (1.0 L) at reflux temperature. Water (0.60 L) was added. The resulting mixture was filtered and acetone (7.6 L) was added at >40°C. The solution was seeded. The slurry of crystals was cooled to 3°C. The crystals were collected by centrifugation and were washed with acetone. The crystals were dried at 30°-40°C in vacuum. Yield: about 0.42 kg of ropivacaine hydrochloride monohydrate (about 80%).

The stucture of the end product was confirmed by NMR analysis.

References

Jaksch P.; US Patent No. 5,959,112; Sep. 28, 1999; Assigned to Astra Aktiebolag, Sodertalje, Sweden

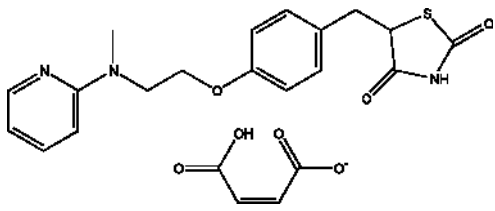
ROSIGLITAZONE MALEATE

Therapeutic Function: Hypoglycemic, Antiinflammatory, Analgesic

Chemical Name: 2,4-Thiazolidinedione, 5-((4-(2-(methyl-2-yridinylamino) ethoxy)phenyl)methyl)-, maleate (1:1)

Common Name: Rosiglitazone maleate

Structural Formula:



Chemical Abstracts Registry No.: 122320-73-4 (Base); 155141-29-0

Trade Name	Manufacturer	Country	Year Introduced
Avandia	GlaxoSmithKline	-	-
BRL 49653	GlaxoSmithKline	-	-

Raw Materials

4-Fluorobenzaldehyde
2-(N-Methyl-N-(2-pyridyl)amino)ethanol
Potassium t-butoxide
2,4-Thiazolidinedione
Maleic acid

Manufacturing Process

To 100 g of 2-(N-methyl-N-(2-pyridyl)amino)ethanol in 500 ml DMF was added 100 g of 4-fluorobenzaldehyde. The reaction mixture was stirred for 10 min at room temperature and 80 g of potassium tertiary butoxide was added to the reaction mixture. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to 5-10°C and under the cold conditions, 1.5 L of water was added and stirred for 15 min. The mixture was extracted with ethyl acetate. The combined organic layer was washed with 3 times 1 L water. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 148 g (88%) of 4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy)benzaldehyde.

4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzaldehyde was converted into highly crystalline 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione by Knoevenegal condensation with 2,4-thiazolidinedione. 800 g of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy] benzyl]thiazolidine-2,4-dione and 280 g maleic acid were dissolved in 1.3 L of acetone in 5 L three necked round bottom flask. The reaction mixture was heated to 50-55°C and the solution was filtered and slowly cooled to obtain 986 g of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione maleate, (yield 95%; M.P. 120-122°C).

References

Sharad Kumar Vyas; US Patent No. 6,515,132; Feb. 4, 2003; Assigned to Torrent Pharmactuticals, Ltd., Ahmedabad (IN)

ROSOXACIN

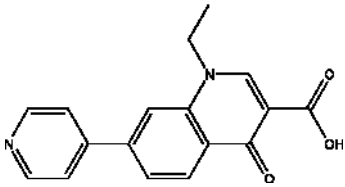
Therapeutic Function: Antibacterial, Antigonorrheal

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

Common Name: Acrosoxacin

Chemical Abstracts Registry No.: 40034-42-2

Structural Formula:



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

Raw Materials

Acetic acid
Iron
Ethyl iodide
Sodium hydroxide
4-(3-Nitrophenyl)pyridine
Ethoxymethylene malonic acid diethyl ester
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-quinolinecarboxyiate 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 ethoxymethylene malonic acid diethyl ester and then thermally rearranged to give the starting material

References

Merck Index 8136
DFU 5 (4) 199 (1980)
Kleeman and Engel p. 811
OCDS Vol. 3 p. 185 (1984)
DOT 18 (3) 147 (1982)
I.N. p. 855
Carabateas, P.M.; US Patent 3,922,278; November 25, 1975; assigned to Sterling Drug, Inc.
Lesher, G.Y. and Carabateas, P.M.; US 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.; US Patent 4,107,167; August 15, 1978; assigned to Sterling Drug, Inc.