G

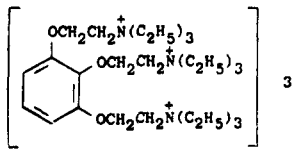
GALLAMINE TRIETHIODIDE

Therapeutic Function: Skeletal muscle relaxant

Chemical Name: 2,2',2"-[1,2,3-benzenetriyltris(oxy)] tris[N,N,N-triethylethanaminium] triiodide

Common Name: Benzcurine iodide

Structural Formula:



Chemical Abstracts Registry No.: 65-29-2

Trade Name	Manufacturer	Country	Year Introduced
Flaxedil	Davis/Geck	U.S.	1951
Flaxedil	May & Baker	U.K.	–
Flaxedil	Rhodia Iberica	Spain	–
Relaxan	Gea	Denmark	–
Sincurarina	Carlo Erba	Italy	–
Tricuran	Deutsches Hydrierwerk	E. Germany	–

Raw Materials

Pyrogallol
Diethylaminochloroethane
Sodium amide
Ethyl iodide

Manufacturing Process

12.6 grams of pyrogallol are dissolved in 100 cc of hot toluene. 14 grams of sodamide (85%) are added to the solution at about 100°C in 5 portions over a period of 15 minutes, with agitation. There are then added with agitation, over a period of 30 minutes, 100 cc of a toluene solution containing 474 grams of diethylaminochlorethane per liter of toluene.

The mixture is then heated for 1 hour, the toluene being refluxed, whereafter it is left to cool, 50 cc of water are added and, after decanting, the solution is again washed with two quantities of 50 cc of water. The toluene solution is dried over potassium carbonate and distilled in vacuo. There is thus obtained 28 grams of 1.2.3-tri-(β-diethylaminoethoxy)-benzene, boiling at 206°C under 1 mm pressure.

20 grams of 1.2.3-tri-(β-diethylaminoethoxy)-benzene is heated for 5 hours under reflux on the water bath with 30 grams of ethyl iodide. The hot mixture is dissolved in 50 cc of

water, filtered after addition of 2 grams of decolorizing black, evaporated to dryness on the water bath and recrystallized from 120 cc of alcohol. The product can be further recrystallized in mixtures of acetone and water.

The triethiodide of 1.2.3-tri-(β-diethylaminoethoxy)-benzene is thus obtained as white crystals which, after drying, have a rather indefinite melting point at about 152° to 153°C, (Maquenne block).

References

Merck Index 4214
Kleeman & Engel p. 437
I.N. p. 454
REM p. 923
Fourneau, E.; U.S. Patent 2,544,076; March 6, 1951; assigned to Societe des Usines Chimiques Rhone-Poulenc, France

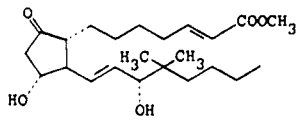
GEMEPROST

Therapeutic Function: Prostaglandin; cervical softener

Chemical Name: 11,15-Dihydroxy-16,16-dimethyl-9-oxoprosta-2,13-dien-1-oil acid methyl ester

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 64318-79-2

Trade Name	Manufacturer	Country	Year Introduced
Preglandin	Ono	Japan	1982

Raw Materials

Ethyl 9α-hydroxy-11α,15α-bis(2-tetrahydropyranyloxy)-16,16-dimethyl-prosta-trans-2,trans-13-dienoate
Potassium hydroxide
Manganese sulfate
Acetic acid

Manufacturing Process

Synthesis of 9-oxo-11α,15α-bis-(2-tetrahydropyranyloxy)-16,16-dimethyl-prosta-trans-2, trans-13-dienoic acid: 4 g of ethyl 9α-hydroxy-11α,15α-bis-(2-tetrahydropyranyloxy)-16,16-dimethyl-prosta-trans-2,trans-13-dienoate were dissolved in 130 ml of a mixture of ethanol-water (3:1), mixed with 3.9 g of potassium hydroxide and stirred at 25°C for 2 hours. The reaction mixture was acidified with aqueous solution of oxalic acid to pH 5, and diluted with 100 ml of water, extracted with ethyl acetate. The extracts were washed with water, dried over sodium sulfate and concentrated under reduced pressure to obtain 3.88 g of 9α-hydroxy-11α,15α-bis-(2-tetrahydropyranyloxy)-16,16-dimethyl-prosta-trans-2,trans-13-dienoic acid.

The obtained compound 2.46 g were dissolved in 72 ml of diethyl ether and stirred at 3°C. To which a solution of manganese sulfate (15 g), 3.1 g of chromium trioxide, 72 ml of water and 3.5 ml of sulfuric acid was added. After stirring for 3.5 hours at 3°C, extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-benzene (1:1) as eluent to give 2.35 g of the title compound.

Synthesis of 16,16-dimethyl-trans-Δ^2-PGE$_1$: 2.35 g of the bis-tetrahydropyranyl ether were dissolved in 6 ml of tetrahydrofuran and 60 ml of 65%-acetic acid aqueous solution and the solution stirred at 60°C to 70°C for 20 minutes. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-cyclohexane (2:3) as eluent to yield 270 mg of the title compound.

References

Merck Index 4245
DFU 4 (2) 911 (1979)
DOT 19 (7) 414 (1983)
I.N. p. 456
Hayashi, M., Kori, S. and Wakasata, H.; U.S. Patent 4,052,512; October 4, 1977; assigned to Ono Pharmaceutical Co. (Japan)

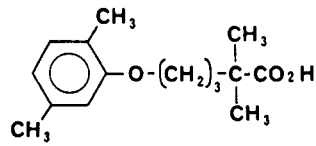
GEMFIBROZIL

Therapeutic Function: Hypocholesterolemic agent

Chemical Name: 2,2-Dimethyl-5-(2,5-xylyloxy)valeric acid

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 25812-30-0

Trade Name	Manufacturer	Country	Year Introduced
Lopid	Warner Lambert	U.S.	1982
Organolipid	Godecke	W. Germany	1982

Raw Materials

Isobutyric acid
3-(2,5-Xylyloxy)propyl bromide
n-Butyl lithium

Manufacturing Process

With stirring, 44.1 g of isobutyric acid is added to a mixture of 51.0 g of diisopropylamine, 23.2 g of a 57% sodium hydride dispersion in mineral oil, and 350 ml of tetrahydrofuran. When gas evolution subsides, the mixture is heated at reflux for 15 minutes, cooled to 0°C, and treated with 345 ml of a 1.45M solution of n-butyllithium in heptane. After 5 hr, the

mixture is warmed one-half hour at 30°C, cooled to 0°C, and treated with 122.0 g of 3-(2,5-xylyloxy)propyl bromide. After one more hour, it is stirred with 500 ml of water and the aqueous phase is separated and acidified with 150 ml of 6 N hydrochloric acid. The acidic mixture is extracted with ether and the ether extract is washed with saturated sodium chloride solution, dried over magnesium sulfate, concentrated almost to dryness, and distilled in vacuo. A distillate of 2,2-dimethyl-5-(2,5-xylyloxy)valeric acid is collected at boiling point 158°C to 159°C at 0.02 mm of Hg; melting point 61°C to 63°C following crystallization from hexane.

The same product is obtained by substituting 4.4 g of lithium hydride for the sodium hydride in the above procedure.

The same product is also obtained in the following manner. A mixture of 26.4 g of isobutyric acid, 6.0 g of magnesium oxide powder, and 250 ml of toluene is stirred and heated at reflux with continuous removal of the water formed in the reaction. When water formation ceases, the resulting mixture containing magnesium isobutyrate is concentrated to one-half its original volume, cooled in an ice bath, and treated with 31.0 g of diisopropylamine in 200 ml of dry tetrahydrofuran and then with 179 ml of 1.68 M n-butyllithium in heptane while the temperature is maintained below 10°C. After 15 more minutes, the mixture is warmed at 30°C for one-half hour, cooled to 0°C to 10°C, and treated with 75.0 g of 3-(2,5-xylyloxy)-propyl bromide. The mixture is then stirred for 18 hr at room temperature and diluted with 125 ml of 6 N hydrochloric acid and 250 ml of water. The organic phase is separated, concentrated, and the residue distilled in vacuo to give 2,2-dimethyl-5-(2,5-xylyloxy)valeric acid.

References

Merck Index 4246
DFU 1 (11) 520 (1976)
PDR p. 1364
OCDS Vol. 3 p. 45 (1984)
DOT 18 (11) 582 (1982)
I.N. p. 456
REM p. 864
Creger, P.L.; U.S. Patent 3,674,836; July 4, 1972; assigned to Parke, Davis & Co.

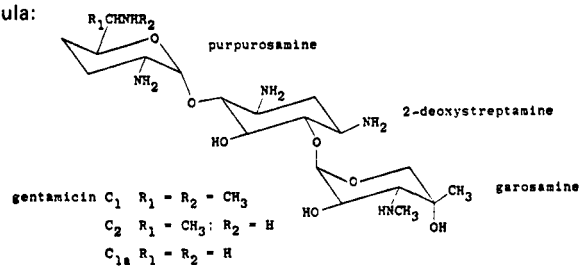
GENTAMICIN SULFATE

Therapeutic Function: Antibacterial

Chemical Name: See structural formula

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 1405-41-0; 1403-66-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Garamycin	Schering	U.S.	1966
Garramycin	Kirby-Warrick	U.K.	1966
Refobacin	Merck	W. Germany	1967
Gentalyn	Essex	Italy	1967
Gentalline	Unicet	France	1968
Genoptic	Allergan	U.S.	1979
U-Gencin	Upjohn	U.S.	1980
Bristagen	Bristol	U.S.	1980
Apogen	Beecham	U.S.	1980
Jenamicin	Hauck	U.S.	1982
Gentafair	Pharmafair	U.S.	1983
Biogen	Cusi	Spain	–
Biomargen	Biologia Marina	Spain	–
Cidomycin	Roussel	U.K.	–
Duramycin	Durachemie	W. Germany	–
Espectrosina	Centrum	Spain	–
Gensumycin	Roussel	–	–
Genta	I.E. Kimya Evi	Turkey	–
Genta-Gobens	Normon	Spain	–
Gentabac	Infan	Mexico	–
Gentacin	Schering-Shionogi	Japan	–
Gentadavur	Davur	Spain	–
Gentamedical	Medical	Spain	–
Gentamicin-Pos	Ursapharm	W. Germany	–
Gentamin	Medix	Spain	–
Gentamina	Essex	Argentina	–
Gentamival	Valles Mestre	Spain	–
Gentamorgens	Morgens	Spain	–
Gentamytrex	Mann	W. Germany	–
Gentaroger	Roger	Spain	–
Gentasillin	Nobel	Turkey	–
Gentibioptal	Farmila	Italy	–
Genticina	Antibioticos	Spain	–
Genticol	S.I.F.I.	Italy	–
Gento	Bryan	Spain	–
Gentona	Asla	Spain	–
Gent-Ophtal	Winzer	W. Germany	–
Getamisin	Deva	Turkey	–
Gevramycin	Essex Espana	Spain	–
Glevomicina	Bago	Argentina	–
G-Mycin	Neofarma	Finland	–
Miramycin	Teva	Israel	–
Ophtagram	Chauvin-Blache	France	–
Plurisemina	Northia	Argentina	–
Ribomicin	Farmigea	Italy	–
Sulgemicin	Larma	Spain	–
Sulmycin	Byk Essex	W. Germany	–

Raw Materials

Bacterium *Micromonospora purpurea*
Soybean meal

Manufacturing Process

Germination Stage: A lyophilized culture of *M. purpurea* is added to a 300 ml shake flask

containing 100 ml of the following sterile medium: 3 grams bacto-beef extract; 5 grams tryptose; 1 gram dextrose; 24 grams starch (soluble); 5 grams yeast extract; and 1,000 ml tap water. The flask and its contents are incubated for 5 days at 37°C on a rotary shaker (280 rpm, 2 inch stroke).

Inoculum Preparation Stage: Two batches of inoculum of about 50 gallons each are prepared by the following method: A 25 ml inoculum (from the germination stage) is transferred to each of four 2-liter flasks, each containing 500 ml of the sterile medium utilized for germination. The flasks and contents are incubated for 5 days at 28°C on a rotary shaker (280 rpm, 2 inch stroke).

The contents of the flasks are pooled, a 25 ml inoculum (taken from the pool) is added to each of twenty 2-liter flasks, each containing 500 ml of the following sterile medium: 30 grams soybean meal; 40 grams dextrose (cerelose); 1 gram calcium carbonate; 1,000 milliliters tap water. The flasks and their contents are incubated for 3 to 5 days at 28°C on a rotary shaker (280 rpm, 2 inch stroke). The broth is pooled and aseptically transferred into a sterile inoculum flask having a side arm (total volume, about 10 liters).

The 10 liters of inoculum is aseptically transferred to a 65-gallon fermenter containing 50 gallons of the following sterile medium: 600 grams bacto-beef extract; 1,000 grams bacto-tryptose; 200 grams dextrose (cerelose); 4,800 grams starch (soluble); 1,000 grams yeast extract; 100 ml antifoamer GE 60 (General Electric Co. brand of silicone defoamer), or other defoamer; and tap water, qs to 50 gallons.

The pH is adjusted to 6.9 to 7.0 before sterilization and aerobic fermentation is effected for 24 hours (until the packed cell volume is about 10 to 15%) under the following conditions: temperature, 37°C; sterile air input, 54 ft^3/min; pressure, 7 psi; and agitation, 180 rpm.

Fermentation Stage: One 50-gallon batch of inoculum is aseptically transferred to a 675-gallon fermenter (fermenter A) containing the following medium: 54.0 kg soybean meal; 72.0 kg cereiose; 9.0 kg calcium carbonate; 300 ml antifoamer GE 60; and 450 gallons soft water. The other 50-gallon batch of inoculum is aseptically transferred to a similar fermenter (fermenter B) containing the same medium as fermenter A with the addition of 200 mg of $CoCl_2 \cdot 6H_2O$. Fermentation is effected in each fermenter at 35°C while agitating at 120 rpm with air input at 7 psi and 15 ft^3/min. At various times, samples of the fermented broth are withdrawn and assayed for antibiotic production by the disc assay method. The following table shows the increase in yield effected by the presence of cobalt, (as described in U.S. Patent 3,136,704).

Fermentation Time (hours)	. . Yield of Gentamicin (units/ml). . Fermenter A (no cobalt)	Fermenter B (cobalt present)
24	9.3	13
40	34	133
48	49	185
60	70	332
72	77	440
96	75	420

The conversion of the broth to gentamicin sulfate is described in U.S. Patent 3,091,572.

References

Merck Index 4251
Kleeman & Engel p. 438
PDR pp. 872, 888, 1397, 1429, 1606, 1621
DOT 2 (3) 99 (1966) & 17 (3) 106 (1981)
I.N. p. 457

REM p. 1180
Luedemann, G.M. and Weinstein, M.J.; U.S. Patent 3,091,572; May 28, 1963; assigned to Schering Corporation
Charney, W.; U.S. Patent 3,136,704; June 9, 1964; assigned to Schering Corporation

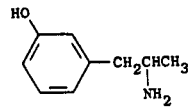
GEPEFRIN

Therapeutic Function: Antihypotensive

Chemical Name: 3-(2-Aminopropyl)phenol

Common Name: Alpha-methyltyramine

Structural Formula:



Chemical Abstracts Registry No.: 18840-47-6

Trade Name	Manufacturer	Country	Year Introduced
Pressionorm	Helopharm	W. Germany	1981

Raw Materials

D-(+)-1-(3-methoxyphenyl)-2-aminopropane
Hydrogen chloride

Manufacturing Process

Hydrolysis of D-(+)-1-(3-methoxyphenyl)-2-aminopropane: 2.42 mols (40 g) of the compound are dissolved in 6N hydrochloric acid in a bomb tube consisting of stainless steel and having a capacity of 500 ml. Hydrogen chloride gas is passed into the ice-cooled solution until this is saturated. The solution is then heated to 130°C for 2 hours in an air bath. After cooling and driving off the hydrochloric acid at a slightly elevated temperature, the hydrochloride of the 3-hydroxyphenyl derivative is present in the form of a yellowish syrup.

The free base can be liberated from the hydrochloride by extracting a butanol solution of the hydrochloride several times with sodium bicarbonate solution. After recrystallization from isopropanol/ligroin, the yield of D-(+)-1-(3-hydroxyphenyl)-2-aminopropane amounts to 33.0 g, corresponding to 90.1% of theory relative to the D-form. Melting point = 152°C to 154°C.

References

Merck Index 4262
I.N. p. 458
Helopharm W. Petrik & Co., K.G.; British Patent 1,527,479; October 4, 1978

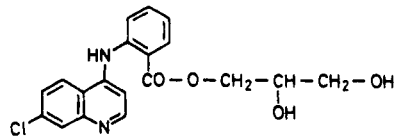
GLAFENINE

Therapeutic Function: Analgesic

Chemical Name: 2-[(7-Chloro-4-quinolinyl)amino] benzoic acid 2,3-dihydroxy-propyl ester

Common Name: Glycerylaminophenaquine

Structural Formula:



Chemical Abstracts Registry No.: 3820-67-5

Trade Name	Manufacturer	Country	Year Introduced
Glifanan	Roussel	France	1965
Glifanan	Albert Roussel	W. Germany	1968
Adalgur	Roussel	France	–
Glifan	Roussel-Maestretti	Italy	–
Glifan	Nippon Roussel-Chugai	Japan	–

Raw Materials

2,2-Dimethyl-4-hydroxymethyl-1,3-dioxolane
o-Nitrobenzoyl chloride
Hydrogen
4,7-Dichloroquinoline

Manufacturing Process

Step A: Preparation of (2,3-isopropylidenedioxy)-propyl o-nitrobenzoate–59.6 g of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane were dissolved under agitation in 60 cc of anhydrous pyridine. The solution was cooled to +5°C and 86.5 g of o-nitrobenzoyl chloride (prepared by Leckermann et al., *Ber.* vol. 80, p. 488, 1947) were slowly introduced into it. The reaction mixture was agitated for a period of two hours at room temperature and then was poured into 500 cc of ether. The mixture was filtered and the filtrate was washed successively with 0.5 N sulfuric acid solution, with aqueous sodium bicarbonate solution and finally with water until the wash waters were neutral. The washed solution was dried over sodium sulfate and filtered again. The filtrate was distilled to dryness under vacuum to obtain 116.5 g (being a yield of 92%) of (2,3-isopropylidenedioxy)-propyl o-nitrobenzoate in the form of a yellow oil which distilled at 178°C to 180°C at a pressure of 1 mm.

Step B: Preparation of (2,3-isopropylidenedioxy)-propyl anthranilate–80 g of (2,3-isopropylidenedioxy)-propyl o-nitrobenzoate, obtained as described in Step A, were subjected to hydrogenation for a period of one hour in 800 cc of absolute alcohol in the presence of 2 g of palladized carbon black as catalyst. The reaction mixture was filtered and the filtrate was evaporated under vacuum to obtain 70.5 g (being a yield of 98.5%) of (2,3-isopropylidenedioxy)-propyl anthranilate in the form of a yellow oil which distilled at 159°C to 160°C under 0.5 mm of pressure.

Step C: Preparation of the α-monoglyceride of 4-(2'-carboxyphenylamino)-7-chloro-quinoline–A mixture of 48 g of (2,3-isopropylidenedioxy)-propyl anthranilate, 36 g of 4,7-dichloro-quinoline, 36 cc of concentrated hydrochloric acid and 300 cc of water was agitated while heating to reflux for a period of two hours. The reaction mixture was filtered and the filtrate was allowed to stand at a temperature of 0°C for a period of three hours. The hydrochloride salt was then vacuum filtered and the salt was taken up in 600 cc 50% methanol at reflux. The solution was made alkaline by the addition of 120 cc of ammonia solution and iced for a period of one hour. The crystalline precipitate obtained was vacuum filtered, washed with water and dried to obtain 38.5 g (being a yield of 56%) of the α-monoglyceride of 4-(2'-carboxyphenylamino-7-chloro-quinoline having a melting point of 165°C.

The product occurred in the form of pale yellow prisms and was insoluble in water, ether, benzene, diluted alcohols, olive oil and chloroform, slightly soluble in absolute alcohol, dioxane, tetrahydrofuran and acetone, and soluble in dilute aqueous acids and alkalis.

References

Merck Index 4293
Kleeman & Engel p. 441
OCDS Vol. 1 p. 342 (1977)
DOT 2 (4) 139 (1966)
I.N. p. 460
Allais, A. and Meier, J.; U.S. Patent 3,232,944; February 1, 1966; assigned to Roussel-Uclaf S.A. (France)

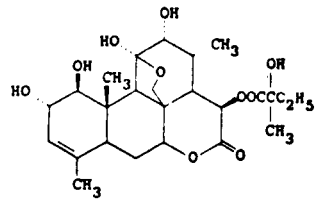
GLAUCARUBIN

Therapeutic Function: Amebicide

Chemical Name: 11,20-Epoxy-1,2,11,12-tetrahydroxy-15-(2-hydroxy-2-methyl-1-oxobutoxy)picras-3-ene-16-one

Common Name: α-Kirondrin

Structural Formula:



Chemical Abstracts Registry No.: 1448-23-3

Trade Name	Manufacturer	Country	Year Introduced
Glarubin	Massengill	U.S.	1959

Raw Materials

Aceituno meal
Water

Manufacturing Process

The preparation of pure glaucarubin from Aceituno meal is conveniently carried out by extracting the Aceituno meal with water, using about 100 gallons of the water per hundred pounds of meal. If the meal is in the form of a relatively solid cake, it should be soaked in the water for a time to cause disintegration. The temperature of the water is then raised to about 70°C for the actual extraction, and the mixture is moderately agitated, while maintaining a temperature of about 70°C for a period of about three hours, until extraction is substantially complete. If desired, the extraction may be conducted at lower temperatures down to about room temperature although at such lower temperatures, the extraction is much slower and less efficient at temperatures substantially higher than 70°C, there may be partial destruction or decomposition of the product being recovered.

The slurry or extraction mixture is filtered while hot, and the resulting filter cake is washed

with about five to ten gallons of hot water; the primary filtrate and wash water are combined and held for further processing. In order to insure complete extraction of the desired material, the filter cake is again extracted with about 100 gallons of water at 70°C. Although not essential, it is desirable to add to the second extraction a small quantity of acetic acid. The acetic acid appears to aid in obtaining a complete and thorough extraction. After extraction for about three hours with agitation at a temperature of about 70°C, the slurry is again filtered and the cake washed as before with about five to ten gallons of hot water. The resulting filtrate and wash are then combined with the primary filtrate and wash.

The combined filtrates or total aqueous extracts are cooled to about room temperature and filtered to remove any residual solids from solution. The clarified aqueous extract is then concentrated to about 70 gallons at a temperature below about 50°C, thus reducing the volume to about one-third the original volume. The resulting concentrate is cooled to room temperature or below and filtered to remove any tar or gum that may have separated. The presence of tar or gum at this stage of the process will vary depending upon the starting material and the manner in which the primary extraction has been carried out. It has been found, however, that unless any tar or gum present in the initial extract is removed by the procedure described, it will seriously interfere with the further concentration and crystallization steps hereinafter described.

After removal of such tar or gum, the concentrate is further evaporated at a temperature below about 50°C to about one-fourth the volume, i.e., 70 gallons is concentrated to about 15 to 20 gallons. This concentrate is cooled to a temperature of about 0°C to 5°C and allowed to stand for an extended period, such as overnight, whereupon there is a separation of crude crystalline glaucarubin therefrom. The crude crystals thus formed are removed by filtration and the mother liquors again concentrated to about one-half volume and cooled to permit separation of a second batch of crude glaucarubin crystals. The two batches of crude glaucarubin crystals are combined and dried preparatory to further purification.

The crude glaucarubin crystals obtained as above described from 100 pounds of Aceituno meal are slurried with about seven-and-one-half gallons of anhydrous methanol and refluxed until the crystals dissolve. The hot solution is then filtered and the resulting filter cake washed with methanol. The filter cake is then again extracted with an additional seven-and-one-half gallon quantity of anhydrous methanol in the manner described, and filtered. The methanol filtrates and washes are combined and concentrated at atmospheric pressure until crystals begin to appear, i.e., generally after concentration to about one-fifteenth volume. The solution is then cooled to about 0°C to 5°C and allowed to stand for crystallization to go substantially to completion. The resulting crystals are filtered off and the mother liquors are further concentrated and cooled to collect a second crop of crystals. The two crops of crystals are then combined and may be further purified by redissolving in methanol, filtering through activated charcoal, and recrystallizing after concentration of the methanol filtrate.

The purified crystalline glaucarubin thus obtained is colorless and odorless and is estimated to have a purity of about 96% to 97%. It has the formula $C_{25}H_{36}O_{10}$ and melts at 262°C to 263°C with decomposition (capillary tube).

References

Merck Index 4295
I.N. p. 460
Shafer, H.M.; U.S. Patent 2,864,745; December 16, 1958; assigned to Merck & Co., Inc.

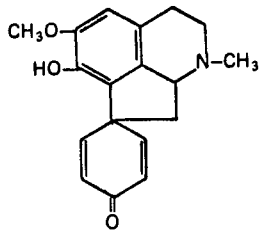
GLAZIOVINE

Therapeutic Function: Tranquilizer

Chemical Name: (±)-[Hydroxy-6-methoxy-5-methyl-11H-cyclopenta[i,j]-isoquinoline]-7-spiro-1'(2,5-cyclohexadiene-4-one)

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 17127-48-9

Trade Name	Manufacturer	Country	Year Introduced
Suavedol	Simes	Italy	1976

Raw Materials

p-Benzyloxyphenylacetic acid
3-Methoxy-4-hydroxyphenethylamine
Phosphorus oxychloride
Sodium borohydride
Hydrogen
Formaldehyde
Sodium nitrite
Sulfuric acid
Nitric acid

Manufacturing Process

The thermal condensation of p-benzyloxyphenylacetic acid and of 3-methoxy-4-hydroxyphenethylamine occurs and gives, with a yield of 86% to 92%, the N-(3-methoxy-4-hydroxyphenethyl-p-benzyloxyphenylacetamide; from this latter, by cyclization according to Bischler-Napieralski with phosphorus oxychloride in acetonitrile, followed by reduction with sodium borohydride, there is obtained with a yield of 75% to 80% the 1-(p-benzyloxybenzyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline, which is methylated with formaldehyde and formic acid giving 1(p-benzyloxybenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline with a yield of 90%.

This intermediate is then nitrated with 65% nitric acid. The nitro compound is then hydrogenated to give a hydroxybenzylamino compound.

A solution of 94.2 g of 1-(p-hydroxybenzyl)-2-methyl-6-methoxy-7-hydroxy-8-amino-1,2,3,4-tetrahydroisoquinoline in 3 liters of 1 N sulfuric acid is supplemented, with stirring, between 0°C and 5°C, with 21 grams of sodium nitrite. The diazonium sulfate solution thus obtained is made alkaline with 2.5 liters of 2 N sodium hydroxide: the diazo-oxide which is separated at the outset as a yellow precipitate is redissolved by the excess alkali, the solution is diluted to 10 liters with deaerated water and subjected, in a nitrogen atmosphere at 15°C in a Pyrex glass apparatus, to the radiations of a 2,000 W high-pressure mercury vapor lamp until the yellow hue is discharged (about 30 to 40 minutes). The solution is brought to a pH of 8.6 with hydrochloric acid and is stirred with 1.5 liters of chloroform. The two phases are filtered, the chloroform is separated and the aqueous phase is extracted four times with 1.5 liters of chloroform. The extracts are evaporated under reduced pressure to a small volume and percolated through a chromatographic column containing 1.3 kilograms of neutral alumina (activity rating IV of the Brockmann scale). The column is then further eluted with chloroform. The eluates are evaporated under reduced pressure and the residue is recrystallized from ethyl acetate. There are thus obtained 40.2 grams (yield 45% of theory) of pure (±)-glaziovine, having a melting point of 220°C to 222°C.

References

Kleeman & Engel p. 442
DOT 13 (1) 24 (1977)
I.N. p. 460
Casagrande, C. and Canonica, L.; U.S. Patent 3,886,166; May 27, 1975; assigned to Siphar S.A. (Switz.)

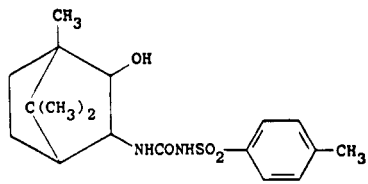
GLIBORNURIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: [1S-(endo,endo)]-N-[[(3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl)-amino]carbonyl]-4-methylbenzenesulfonamide

Common Name: 1-(p-toluenesulfonyl)-3-(2-endo-hydroxy-3-endo-D-bornyl)urea

Structural Formula:



Chemical Abstracts Registry No.: 26944-48-9

Trade Name	Manufacturer	Country	Year Introduced
Glutril	Roche	W. Germany	1972
Glutril	Roche	France	1973
Glutril	Roche	U.K.	1975
Glitrim	Roche	—	—
Gluborid	Gruenenthal	W. Germany	—
Glytril	Roche	—	—
Logiston	Laake	Finland	—

Raw Materials

3-Endo-aminoborneol HCl
o-Methyl-N-p-toluene sulfonyl urea

Manufacturing Process

2.1 grams of 3-endo-aminoborneol hydrochloride and 2.4 grams of O-methyl-N-p-toluene-sulfonyl-urea are heated at 125°C for 3 hours with 2 ml of dimethylformamide. After cooling, the reaction mixture is stirred with 100 ml of water for 10 minutes, while a pH of 3.5 is maintained by the addition of a few drops of dilute hydrochloric acid. The precipitate is removed by filtration, washed with water and suspended in 100 ml of water. The suspension is dissolved by the addition of 20 ml of 1 N caustic soda. The alkaline solution is extracted with ether, acidified with dilute hydrochloric acid and filtered. The precipitate is washed with water and recrystallized from alcohol/water to yield 1-(p-toluene-sulfonyl)-3-(2-endo-hydroxy-3-endo-bornyl)-urea having a melting point of 193° to 195°C.

References

Merck Index 4299

Kleeman & Engel p. 443
OCDS Vol. 2 p. 117 (1980)
DOT 8 (3) 88 (1972)
I.N. p. 461
Bretschneider, H., Grassmayr, K., Hohenlohe-Oehringen, K. and Grussner, A.; U.S. Patent 3,654,357; April 4, 1972; assigned to Hoffmann-La Roche Inc.

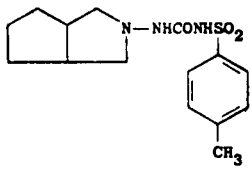
GLICLAZIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: 1-(hexahydrocyclopenta[c] pyrrol-2(1H)-yl)-3-(p-tolylsulfonyl)urea

Common Name: N-(4-methylbenzenesulfonyl)-N'-(3-azabicyclo[3.3.0] -3-octyl)urea

Structural Formula:



Chemical Abstracts Registry No.: 21187-98-4

Trade Name	Manufacturer	Country	Year Introduced
Diamicron	Servier	France	1972
Diamicron	Servier	Italy	1977
Diamicron	Servier	Switz.	1979
Diamicron	Pharmacodex	W. Germany	1980
Diamicron	Servier	U.K.	1980
Dramion	Maggioni	Italy	—

Raw Materials

4-Methylbenzenesulfonyl urethane
N-Amino-3-azabicyclo(3.3.0)octane

Manufacturing Process

To a suspension containing 4.86 parts of 4-methylbenzenesulfonyl urethane (MP 80° to 82°C) and 36 parts of anhydrous toluene there are rapidly added 2.5 parts of N-amino-3-azabicyclo(3.3.0)octane (BP/18 mm = 86°C). The reaction mixture is heated under reflux for 1 hour. The resulting clear solution crystallizes on cooling. The crystals are filtered, washed with 2 parts of toluene, then recrystallized from anhydrous ethanol. There are obtained 3.8 parts of the desired product, MP 180° to 182°C.

References

Merck Index 4300
Kleeman & Engel p. 444
DOT 8 (4) 136 (1972)
I.N. p. 461
Beregi, L., Hugon, P. and Duhault, J.; U.S. Patent 3,501,495; March 17, 1970; assigned to Science Union et Cie, Societe Francaise de Recherche Medicale, France

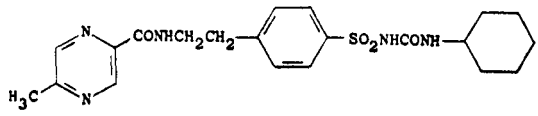
GLIPIZIDE

Therapeutic Function: Oral hypoglycemic

Chemical Name: 1-cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido)ethyl] phenyl]-sulfonyl] urea

Common Name: Glydiazinamide

Structural Formula:



Chemical Abstracts Registry No.: 29094-61-9

Trade Name	Manufacturer	Country	Year Introduced
Minidiab	Carlo Erba	Italy	1973
Glibenese	Pfizer	France	1974
Glibenese	Pfizer	U.K.	1975
Minodiab	Farmitalia	U.K.	1975
Glibenese	Pfizer	W. Germany	1977
Glucotrol	Roerig	U.S.	—
Melizid	Medica	Finland	—
Mindiab	Aesca	Austria	—
Minibetic	Ikapharm	Israel	—

Raw Materials

5-Methylpyrazine-2-carboxylic acid
p-(β-Aminoethyl)benzenesulfonamide
Thionyl chloride
Cyclohexyl isocyanate

Manufacturing Process

5-Methyl pyrazine-2-carboxylic acid is refluxed with thionyl chloride in anhydrous benzene for approximately 12 hours. Benzene and thionyl chloride excess is removed by distillation. Then some anhydrous dioxane is added and this acid chloride solution is allowed to drop into p-(β-aminoethyl)-benzenesulfonamide suspension in dioxane and anhydrous pyridine. The resulting mixture is then refluxed for 3 hours. Dioxane is removed by distillation and then the residue is washed with water and acetic acid. The raw acylated sulfonamide is then filtered and crystallized from 95% ethanol, thus obtaining a product of MP 200° to 203°C.

This product is then reacted with cyclohexyl isocyanate to give glipizide.

References

Merck Index 4302
Kleeman & Engel p. 444
PDR p. 1525
OCDS Vol. 2 p. 117 (1980)
DOT 8 (11) 435 (1972) & 9 (11) 463 (1973)
I.N. p. 462
REM p. 977
Ambrogi, V. and Logemann, W.; U.S. Patent 3,669,966; June 13, 1972; assigned to Carlo Erba SpA, Italy

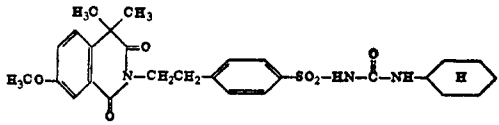
GLIQUIDONE

Therapeutic Function: Oral hypoglycemic

Chemical Name: N-[(cyclohexylamino)carbonyl]-4-[2-(3,4-dihydro-7-methoxy-4,4-dimethyl-1,3-dioxo-2(1H)-isoquinolinyl)ethyl] benzenesulfonamide

Common Name: Gliquidor

Structural Formula:



Chemical Abstracts Registry No.: 33342-05-1

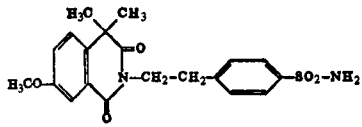
Trade Name	Manufacturer	Country	Year Introduced
Glurenorm	Thomae	W. Germany	1975
Glurenorm	Winthrop	U.K.	1979
Glurenor	Boehr. Ingel.	–	–

Raw Materials

1,2,3,4-Tetrahydro-4,4-dimethyl-7-methoxy-isochromane-1,3-dione
4-Aminosulfonyl-phenyl-(2)-ethylamine
Potassium-t-butylate
Cyclohexyl isocyanate

Manufacturing Process

A mixture consisting of 4 grams of 1,2,3,4-tetrahydro-4,4-dimethyl-7-methoxy-isochromane-dione-(1,3) (MP 95° to 97°C), 2.53 grams of 4-aminosulfonyl-phenyl-(2)-ethylamine and 150 ml of xylene was heated for 2 hours at its boiling point in an apparatus provided with a water separator. Thereafter, the reaction mixture was allowed to cool and was then vacuum-filtered, and the filter cake was recrystallized from n-propanol in the presence of activated charcoal. 2.9 grams (58% of theory) of 1,2,3,4-tetrahydro-4,4-dimethyl-2-[p-aminosulfonylphenyl-(2)-ethyl]-7-methoxy-isoquinolinedione-(1,3), MP 203° to 205°C, of the formula below were obtained.



32.2 grams of 1,2,3,4-tetrahydro-4,4-dimethyl-2-[p-aminosulfonylphenyl-(2)-ethyl]-7-methoxy-isoquinolinedione-(1,3) were dissolved in 700 ml of dimethylformamide, 9.1 grams of potassium tert-butylate were added to the solution, and, while cooling the mixture with ice, 14.9 grams of cyclohexyl isocyanate were added dropwise thereto.

Subsequently, the reaction mixture was stirred for 5 hours on an ice bath and was then allowed to stand overnight at -2°C. Thereafter, the reaction solution was admixed with water, the precipitate formed thereby was separated by vacuum-filtration, the filtrate was admixed with more water, and the aqueous solution was acidified with 2 N hydrochloric acid. A greasy substance precipitated out which crystallized after a brief period of contact with boiling methanol. 2.6 grams (85% of theory) of 1,2,3,4-tetrahydro-2-[p-(N'-cyclo-

hexyl-ureido-N-sulfonyl)-phenethyl] -4,4-dimethyl-7-methoxy-isoquinolinedione-(1,3), MP 180° to 182°C, were obtained.

References

Merck Index 4303
Kleeman & Engel p. 445
DOT 11 (7) 281 (1975) & 16 (2) 47 (1980)
I.N. p. 462
Kutter, E., Griss, G., Grell, W. and Kleemann, M.; U.S. Patent 3,708,486; January 2, 1973; assigned to Boehringer Ingelheim GmbH, Germany

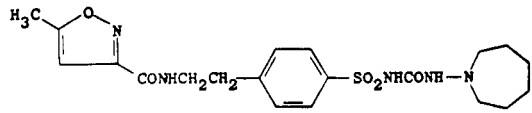
GLISOXEPID

Therapeutic Function: Oral hypoglycemic

Chemical Name: N-[2-[4-[[[[(hexahydro-1H-azepin-1-yl)amino] carbonyl] amino] sulfonyl] -phenyl] ethyl] -5-methyl-3-isoxazolecarboxamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 25046-79-1

Trade Name	Manufacturer	Country	Year Introduced
Pro-Diaban	Bayer	W. Germany	1974
Pro-Diaban	Schering	W. Germany	1974
Glysepin	Bayer	Italy	1978
Glucoben	Farmades	Italy	1979

Raw Materials

5-Methyl-isoxazole-(3)-carboxylic acid chloride
4-(β-Aminoethyl)benzene sulfonamide hydrochloride
Chloroformic acid methyl ester
N-Amino-hexamethylene imine

Manufacturing Process

There is obtained from 4-[β-[5-methyl-isoxazolyl-(3)-carboxamido] -ethyl] -benzene-sulfonamide (prepared from 5-methyl-isoxazole-(3)-carboxylic acid chloride and 4-(β-aminoethyl)-benzene-sulfonamide hydrochloride, MP 213° to 214°C in pyridine) and chloroformic acid methyl ester, in a yield of 69%, the compound N-[[-4-[β-[5-methyl-isoxazolyl-(3)-carboxamido] -ethyl]] -benzene-sulfonyl]] -methyl-urethane in the form of colorless crystals of MP 173°C.

From the sulfonyl-urethane described above and N-amino-hexamethylene-imine, there is obtained, in a yield of 70%, the compound 4-[[4-[β-[5-methyl-isoxazolyl-(3)-carboxamido] -ethyl] -benzene-sulfonyl]] -1,1-hexamethylene-semicarbazide in the form of colorless crystals of MP 189°C.

References

Merck Index 4304
Kleeman & Engel p. 445
DOT 10 (10) 257 (1974) & 16 (1) 15 (1980)
I.N. p. 462
Plumpe, H. and Puls, W.; U.S. Patent 3,668,215; June 6, 1972; assigned to Farbenfabriken Bayer AG, Germany

GLUCAGON

Therapeutic Function: Antidiabetic

Chemical Name: Polypeptide of molecular weight approximately 3,550; see Structural Formula

Common Name: Hg-Factor; HGF

Structural Formula:

Chemical Abstracts Registry No.: 9007-92-5

Trade Name	Manufacturer	Country	Year Introduced
Glucagon	Lilly	U.S.	1960
Glukagon	Lilly	W. Germany	1962
Glucagon	Novo	Italy	1964
Glucagon	Novo	France	1966
Glucagon Novo	Kodama	Japan	1977

Raw Materials

Pancreatic gland material
Acetone

Manufacturing Process

The process comprises treating pancreatic gland material having hyperglycemic activity in aqueous solution at pH 3-4 with 3-4 volumes of acetone to precipitate the hyperglycemic activity material, separating the precipitate and dializing the precipitate to remove inorganic salts and dialyzable low molecular weight impurities, and crystallizing the undialyzed hyperglycemic activity material from aqueous glycine buffer.

References

Merck Index 4307
PDR p. 1050
I.N. p. 463
REM p. 974
Eli Lilly & Co.; British Patent 762,885; December 5, 1956

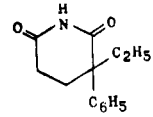
GLUTETHIMIDE

Therapeutic Function: Sedative, hypnotic

Chemical Name: 3-ethyl-3-phenyl-2,6-piperidinedione

Common Name: 3-ethyl-3-phenyl-2,6-dioxopiperidine

Structural Formula:



Chemical Abstracts Registry No.: 77-21-4

Trade Name	Manufacturer	Country	Year Introduced
Doriden	U.S.V.	U.S.	1955
Doridene	Ciba Geigy	France	1956
Alfimid	Pliva	Yugoslavia	–
Elrodorm	Deutsches Hydrierwerk	E. Germany	–
Glimid	Polfa	Poland	–
Glutethimide	Danbury	U.S.	–
Rigenox	Gedeon Richter	–	–

Raw Materials

α-Phenylbutyric acid nitrile
Methyl acrylate
Sulfuric acid
Sodium hydroxide
Acetic acid

Manufacturing Process

The 2-phenyl-2-ethyl-pentane-1,5-diacid-mononitrile-(1) of melting point 72° to 76°C, used as starting material in this process, can be produced for example from α-phenyl-butyric acid nitrile by condensation with acrylic acid methyl ester and subsequent hydrolysis of the thus-obtained 2-phenyl-2-ethyl-pentane-1,5-diacid-monomethyl ester-mononitrile-(1) of boiling point 176° to 185°C under 12 mm pressure.

140 parts by weight of 2-phenyl-2-ethyl-pentane-1,5-diacid-mononitrile-(1) are dissolved in 200 parts by volume of glacial acetic acid and, at an initial temperature of 60°C, 100 parts by volume of concentrated sulfuric acid added in portions. In this operation the temperature of the reaction mixture rises to 100°C. The whole is finally maintained for a short time on the boiling water bath, then cooled and poured on ice and neutralized with alkali to a pH of 6. Extraction with chloroform is then effected and the chloroform extract washed with dilute caustic soda solution, dried over calcium chloride, the chloroform evaporated and the residue crystallized from ethyl acetate with addition of ligroin. The obtained 3-phenyl-3-ethyl-2,6-dioxo-piperidine melts at 78° to 81°C.

References

Merck Index 4338
Kleeman & Engel p. 446
PDR pp. 830, 1606, 1812
OCDS Vol. 1 p. 257 (1977)
I.N. p. 466
REM p. 1071
Hoffmann, K. and Tagmann, E.; U.S. Patent 2,673,205; March 23, 1954; assigned to Ciba Pharmaceutical Products, Inc.

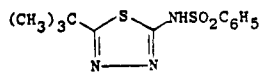
GLYBUZOLE

Therapeutic Function: Oral hypoglycemic

Chemical Name: N-(5-tert-Butyl-1,3,4-thiadiazol-2-yl)benzenesulfonamide

Common Name: Desaglybuzole

Structural Formula:



Chemical Abstracts Registry No.: 1492-02-0

Trade Name	Manufacturer	Country	Year Introduced
Gludease	Kyowa Hakko	Japan	1972

Raw Materials

2-Amino-5-t-butyl-1,3,4-thiadiazole
Benzene sulfonyl chloride

Manufacturing Process

15.7 g of 2-amino-5-tert-butyl-1,3,4-thiadiazole (0.1 mol) and 17.6 g of benzene sulfonyl chloride (0.1 mol) were dissolved in 150 ml dry pyridine and heated over steam for 4 hr. The pyridine was removed by distillation under reduced pressure and the residue treated with 50 ml 2 N HCl. The solid product, MP 162° to 163°C, was filtered off and recrystallized once from benzene and twice from 50% aqueous EtOH.

References

Merck Index 4341
Kleeman & Engel p. 447
I.N. p. 466
MacRae, F.J. and Drain, D.J.; British Patent 822,947; November 4, 1959; assigned to T.J. Smith & Nephew Limited

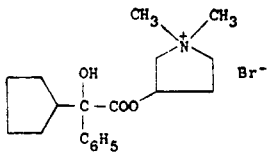
GLYCOPYRROLATE

Therapeutic Function: Antispasmodic

Chemical Name: 3-[(Cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide

Common Name: Glycopyrronium bromide

Structural Formula:



Chemical Abstracts Registry No.: 596-51-0

Trade Name	Manufacturer	Country	Year Introduced
Robinul	Robins	U.S.	1961
Robinul	Robins	U.K.	1962
Robinul	Kaken	Japan	1975
Robinul	Brenner	W. Germany	1975
Asecryl	Martinet	France	–
Gastrodyn	Medica	Finland	–
Nodapton	Geistlich	Switz.	–
Robanul	Lasa	Spain	–
Tarodyl	Lundbeck	–	–

Raw Materials

Methyl-α-cyclopentyl mandelate
1-Methyl-3-pyrrolidinol
Methyl bromide
Sodium
Hydrogen chloride

Manufacturing Process

A mixture of 42.5 grams (0.17 mol) of methyl α-cyclopentyl mandelate and 18 grams (0.175 mol) of 1-methyl-3-pyrrolidinol in 500 ml of heptane was refluxed under a Dean & Stark moisture trap, with the addition of four 0.1 gram pieces of sodium at 1-hour intervals. After 5 hours' refluxing the solution was concentrated to one-half volume, and extracted with cold 3 N HCl. The acid extract was made alkaline with aqueous sodium hydroxide and extracted with ether which was washed, dried over sodium sulfate, filtered and concentrated. The residue was fractionated at reduced pressure. Yield 33 grams (64%); BP 151° to 154°C/0.2 mm, n_D^{23} = 1.5265.

The hydrochloride salt was precipitated as an oil from an ethereal solution of the base with ethereal hydrogen chloride. It was crystallized from butanone; MP 170° to 171.5°C.

The methyl bromide quaternary was prepared by saturating a solution of the base in dry ethyl acetate with methyl bromide. After standing for 9 days the resulting crystalline solid was filtered and recrystallized from butanone and from ethyl acetate; MP 193° to 194.5°C.

References

Merck Index 4365
Kleeman & Engel p. 448
PDR pp. 830, 1466
DOT 18 (3) 128 (1982)
I.N. p. 467
REM p. 915
Lunsford, C.D.; U.S. Patent 2,956,062; October 11, 1960; assigned to A.H. Robins Co., Inc.

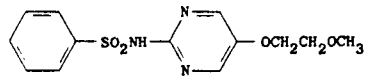
GLYMIDINE

Therapeutic Function: Antidiabetic

Chemical Name: N-[5-(2-Methoxyethoxy)-2-pyrimidinyl] benzenesulfonamide

Common Name: Glycodiazine

Structural Formula:



Chemical Abstracts Registry No.: 339-44-6

Trade Name	Manufacturer	Country	Year Introduced
Redul	Bayer/Schering	W. Germany	1964
Gondafon	Schering	U.K.	1966
Gondafon	Schering	Italy	1968
Glycanol	Bayer	Italy	—
Glyconormal	Bayer	France	—
Lycanol	Bayer	Japan	—

Raw Materials

Methoxyethoxyacetaldehyde-di-methoxyethyl acetal
Phosphorus pentachloride
Dimethylformamide
Sodium hydroxide
Guanidine nitrate
Benzene sulfonyl chloride

Manufacturing Process

210 g phosphorus pentachloride are gradually added to 252 g methoxyethoxyacetaldehyde-di-methoxyethylacetal with agitation. The mixture is externally cooled with ice to hold the reaction temperature below 25°C. Moisture is carefully excluded. After addition of the condensation agent is completed, the reaction mixture is further agitated at room temperature for 30 minutes. 225 ml dimethylformamide are then added drop by drop while the reaction temperature is held at 20°C to 25°C by external cooling of the reaction vessel with ice. When the dimethylformamide has been added, the temperature is raised to 60°C, and this temperature is maintained for 70 minutes.

The temperature is again lowered to 20°C to 25°C and maintained at this value by cooling with ice while 500 ml methanol are added drop by drop. The resulting solution is admixed drop by drop to a suspension of 240 g powdered caustic soda in 800 ml methanol at 20°C to 25°C. After mixing is completed, stirring is continued for 30 minutes at room temperature. The solution now contains inorganic salts and β-dimethylamino-α-methoxyethoxyacrolein.

200 g guanidine nitrate and thereafter 70 g sodium hydroxide are added to the solution. The methanol is evaporated with agitation. The residue is dissolved in 1.5 liters water and is repeatedly extracted with chloroform. The combined chloroform extracts are evaporated to dryness, and the residue is recrystallized from carbon tetrachloride. 80 g of 2-amino-5-methoxyethoxypyrimidine of MP 80°C to 81°C are obtained.

This material is then dissolved in pyridine. Benzenesulfonylchloride is added and the resulting mixture is heated two hours to 60°C. It is then poured into 300 ml water. The precipitate formed thereby is filtered off and dissolved in dilute ammonium hydroxide. The solution is purified with charcoal, and filtered. The filtrate is acidifed with acetic acid to give glymidine.

62 g 2-benzenesulfonamido-5-methoxyethoxypyrimidine are dissolved jointly with 8 g sodium hydroxide in 250 ml ethanol. The solution is evaporated to dryness, and the residue is suspended in 300 ml acetone. The sodium salt of 2-benzenesulfonamido-5-methoxyethoxypyrimidine may be filtered off, washed with acetone, and dried. The yield of glymidine sodium is about 60 g, the MP 220°C to 223°C.

References

Merck Index 4371
Kleeman & Engel p. 448
OCDS Vol. 1 p. 125 (1977)
DOT 1 (2) 72 (1965) & 2 (3) 104 (1966)
I.N. p. 468
Priewe, H. and Gutsche, K.; U.S. Patent 3,275,635; September 27, 1966; assigned to Schering A.G. (W. Germany)

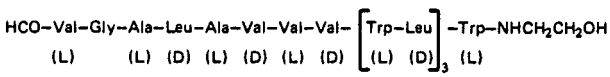
GRAMICIDIN

Therapeutic Function: Antibacterial

Chemical Name: Gramicidin D

Common Name: –

Structural Formula:



Chemical Abstracts Registry No: 113-73-5

Trade Name	Manufacturer	Country	Year Introduced
Gramoderm	Schering	U.S.	1949
Mytrex	Savage	U.S.	–
Neosporin	Burroughs-Wellcome	U.S.	–
Nyst-Olone	Schein	U.S.	–
Tri-Thalmic	Schein	U.S.	–

Raw Materials

Tyrothricin fermentation liquor
Pentane
Acetone
Ethanol
Benzene

Manufacturing Process

5 lb of acid precipitated solid (Hotchkiss, *Advances in Enzymology,* pages 157-158) from 30 gal of tyrothricin fermentation liquor containing about 40 g (2%) of tyrothricin were extracted with 12 liters of absolute ethyl alcohol and filtered. The filtrate was evaporated in vacuo to 1 liter, and the concentrate extracted twice with 1 liter of pentane. The pentane layers were discarded.

40 g of decolorizing charcoal were added to the pentane-extracted filtrate and filtered off.

To 500 ml of the charcoal-treated filtrate were added 200 ml benzene and 300 ml water, the whole shaken thoroughly, centrifuged, and the benzene layer separated. This treatment of the charcoal-treated filtrate was repeated twice, all benzene fractions were combined and evaporated in vacuo.

200 ml of absolute acetone were added to the residue and concentrated by boiling to 150 ml. The concentrate was refrigerated overnight. The crystals which had formed in the concentrate were filtered off, and the mother liquor concentrated first to 50 ml and then to 25 ml,

the two concentrates refrigerated overnight, and the formed crystals filtered off. Total yield of crystalline gramicidin was 3.85 g = 19.2% of estimated tyrothricin in the initial material.

The combined crystal crops were redissolved in 50 ml absolute acetone, and the solution refrigerated overnight. After filtering, the formed crystals were dried in vacuo. The total yield of crystalline gramicidin thus obtained was 2.5 g.

References

Merck Index 4405
PDR pp. 758, 1604, 1606
I.N. p. 470
REM p. 1203
Baron, A.L.; U.S. Patent 2,534,541; December 19, 1950; assigned to S.B. Penick & Co.

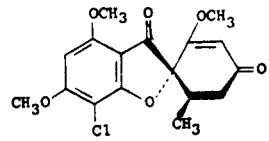
GRISEOFULVIN

Therapeutic Function: Antifungal

Chemical Name: (2S-trans)-7-chloro-2',4,6-trimethoxy-6'-methylspiro[benzofuran-2(3H),-1'-[2]cyclohexene]-3,4'-dione

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 126-07-8

Trade Name	Manufacturer	Country	Year Introduced
Grifulvin	McNeil	U.S.	1959
Fulvicin	Schering	U.S.	1959
Grisactin	Ayerst	U.S.	1959
Fulcine Forte	I.C.I.	France	1972
Gris-Peg	Dorsey	U.S.	1975
Delmofulvina	Coli	Italy	—
Fulcin	Cepharma	Italy	—
Fungivin	Nyegaard	Norway	—
Gricin	Arzneimittelwerk Dresden	E. Germany	—
Grifulin	Teva	Israel	—
Grifulvin	Yamanouchi	Japan	—
Grisefuline	Clin-Comar-Byla	France	—
Grisetin	Nippon Kayaku	Japan	—
Grisovin	Fujisawa	Japan	—
Guservin	Chugai	Japan	—
Lamoryl	Lovens	Denmark	—
Likuden	Hoechst	W. Germany	—

Raw Materials

Bacterium *Penicillium patulum*
Corn steep liquor

Manufacturing Process

Corn steep liquor nitrogen	0.40% w/v
KH_2PO_4	0.40% w/v
$CaCO_3$	0.40% w/v
KCl	0.20% w/v
Mobilpar S	0.0275% v/v
White mineral oil	0.0275% v/v
H_2SO_4	0.0125% v/v
Preinoculation volume	800 gal
Fermentation temperature	25°C
Inoculum volume	10%

The experiment was carried out on the 1,000 gallon scale. Three impellers 1'8" diameter at 220 rpm were employed. The air rates were 0 to 5 hours, 40 cfm, 5 to 10 hours, 80 cfm and after 10 hours, 125 cfm. The inoculum rate was 10% v/v. It was prepared by the standard inoculum development technique on the following medium:

Corn steep liquor nitrogen	0.30% w/v
Brown sugar	2.0% w/v
Chalk	1.0% w/v
Maize oil	1.0% v/v
Hodag MF	0.033% v/v

This was inoculated with a spore suspension of *P. patulum* (1 liter containing 3-5 x 10^7 spores/ml) and grown at 25°C in 100 gallon tank. The inoculum is transferred at 40 hours or when the mycelial volume (after spinning 10 minutes at 3,000 rpm) exceeds 25%. The fermentation is conducted as near to the ideal pH curve as possible by addition of crude glucose, according to U.S. Patent 3,069,328.

References

Merck Index 4420
Kleeman & Engel p. 449
PDR pp. 621, 931, 1307, 1620
OCDS Vol. 1 p. 314 (1977)
I.N. p. 471
REM p. 1228
Hockenhull, D.J.D.; U.S. Patent 3,069,328; December 18, 1962; assigned to Glaxo Laboratories Limited, England
Dorey, M.J., Mitchell, I.L.S., Rule, D.W. and Walker, C.; U.S. Patent 3,069,329; Dec. 18, 1962; assigned to Glaxo Laboratories Limited, England

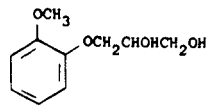
GUAIFENESIN

Therapeutic Function: Expectorant

Chemical Name: 3-(2-Methoxyphenoxy)-1,2-propanediol

Common Name: Guaiacol glyceryl ether

Structural Formula:



Chemical Abstracts Registry No.: 93-14-1

Trade Name	Manufacturer	Country	Year Introduced
GG Cen	Central	U.S.	1975
Breonesin	Breon	U.S.	1980
Cremacoat	Vicks	U.S.	1983
Ambenyl	Marion	U.S.	–
Asbron G	Sandoz	U.S.	–
Balminil	Rougier	Canada	–
Bromphen	Schein	U.S.	–
Bronchol	Streuli	Switz.	–
Broncovanil	Scharper	Italy	–
Brondecon	Parke Davis	U.S.	–
Bronkolixir	Winthrop-Breon	U.S.	–
Bronkotuss	Hyrex	U.S.	–
Congess	Fleming	U.S.	–
Cortussin	Xttrium	U.S.	–
Corutrol	Dow	U.S.	–
Coryban	Pfipharmecs	U.S.	–
Deconsal	Adams	U.S.	–
Detussin	Schein	U.S.	–
Dilaudid	Knoll	U.S.	–
Dilur-G	Savage	U.S.	–
Donatussin	Laser	U.S.	–
Dorcol	Dorsey	U.S.	–
Dura-Vent	Dura	U.S.	–
Entex	Norwich-Eaton	U.S.	–
Entuss	Hauck	U.S.	–
Fedahist	Rorer	U.S.	–
Gaiapect	Eri	Canada	–
Guajacuran	Spofa	Czechoslovakia	–
Guajasyl	Mepha	Switz.	–
Guiatuss	Schein	U.S.	–
Gvaja	Lek	Yugoslavia	–
Head & Chest	Procter & Gamble	U.S.	–
Histalet	Reid-Rowell	U.S.	–
Humibid	Adams	U.S.	–
Hustosil	Kyoto	Japan	–
Hycotuss	Du Pont	U.S.	–
Hytuss	Hyrex	U.S.	–
Lufyllin	Wallace	U.S.	–
Mucostop	Verla	W. Germany	–
Mudrane	Poythess	U.S.	–
Naldecon	Bristol	U.S.	–
Neo-Spec	Neo	Canada	–
Novahistine	Lakeside	U.S.	–
Nucofed	Beecham	U.S.	–
Quibron	Mead Johnson	U.S.	–
Reorganin	Brunnengraber	U.S.	–
Resyl	Ciba	Italy	–
Robitussin	Robins	U.S.	–
Ru-Tuss	Boots	U.S.	–
Scot-Tussin	Scot-Tussin	U.S.	–
Sinufed	Hauck	U.S.	–
Sorbutuss	Dalin	U.S.	–
Triaminic	Dorsey	U.S.	–
Tussar	U.S.V.	U.S.	–
Tussend	Merrell-Dow	U.S.	–
Zephrex	Bock	U.S.	–

Raw Materials

o-Methoxyphenol (guaiacol)
Glycidol

Manufacturing Process

A mixture of o-methoxyphenol (57 g), glycidol (32 g) and pyridine (1 g) is warmed to 95°C at which temperature a vigorous reaction takes place. The reaction mixture is cooled to prevent the temperature rising above 110°C. When the exothermic reaction has subsided the reactants are heated at 95°C for one hour longer and then distilled under low pressure. The main fraction boils in the range 176°C to 180°C/0.5 mm. It crystallizes on cooling. Recrystallization from benzene gives the pure product, MP 78.5°C to 79.0°C.

References

Merck Index 4432
Kleeman & Engel p. 449
OCDS Vol. 1 p. 118 (1977)
I.N. p. 472
REM p. 868
Bradley, W. and Forrest, J.; British Patent 628,497; August 30, 1949; assigned to British Drug Houses, Ltd.

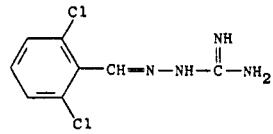
GUANABENZ

Therapeutic Function: Antihypertensive

Chemical Name: 2-[(2,6-Dichlorophenyl)methylene] hydrazinecarboximidamide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 5051-62-7

Trade Name	Manufacturer	Country	Year Introduced
Wytensin	Wyeth	U.S.	1982
Rexitene	L.P.B.	Italy	–

Raw Materials

2,6-Dichlorobenzaldehyde
Aminoguanidine bicarbonate

Manufacturing Process

A mixture of 14.0 g of 2,6-dichlorobenzaldehyde, 10.8 g of aminoguanidine bicarbonate and 100 ml of pyridine was refluxed for 3 hours. The reaction mixture was poured into water and the crystalline precipitate filtered off; MP 225°C to 227°C.

References

Merck Index 4436
DFU 1 (11) 523 (1976)
Kleeman & Engel p. 451
PDR p. 1997
OCDS Vol. 2 p. 123 (1980)
DOT 15 (11) 481 (1979)
I.N. p. 473
REM p. 846
Yates, J. and Haddock, E.; British Patent 1,019,120; February 2, 1966; assigned to Shell International Research Maatschappij N.V. (Netherlands)

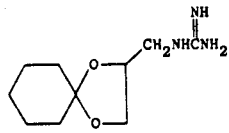
GUANADREL SULFATE

Therapeutic Function: Antihypertensive

Chemical Name: (1,4-Dioxaspiro[4.5]decan-2-ylmethyl)guanidine sulfate

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 40580-59-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Hylorel	Pennwalt	U.S.	1983
Hycoral	Pennwalt	W. Germany	1983
Anarel	Cutter	U.S.	–

Raw Materials

1,4-Dioxaspiro[4.5]decane-2-methylamine
2-Methyl-2-thiopseudourea sulfate

Manufacturing Process

A mixture of 10.5 g of 1,4-dioxaspiro[4.5]decane-2-methylamine and 8.6 g of 2-methyl-2-thiopseudourea sulfate in 40 ml of water was heated on the steam bath for 4 hours during which 2.0 g of methylmercaptan was collected in a dry ice bath connected to the reaction flask through a water cooled reflux condenser. The reaction mixture was then evaporated at 15 mm pressure to a solid residue which was then dissolved in 80 ml of 50/50 methanol-ethanol. The solution was filtered and evaporated to approximately 50 ml volume and allowed to cool and crystallize, giving a crop melting at 213.5°C to 215°C of 1,4-dioxaspiro-[4.5]decan-2-ylmethyl)-guanidine sulfate.

References

Merck Index 4438
Kleeman & Engel p. 451
PDR p. 1398

OCDS Vol. 1 p. 400 (1977)
DOT 16 (4) 140 (1980)
I.N. p. 473
REM p. 907
Hardie, W.R. and Aaron, J.E.; U.S. Patent 3,547,951; December 15, 1970

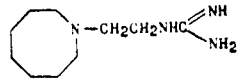
GUANETHIDINE SULFATE

Therapeutic Function: Antihypertensive

Chemical Name: [2-(hexahydro-1(2H)-azocinyl)ethyl] guanidine sulfate

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 60-02-6; 55-65-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Ismelin	Ciba	U.S.	1960
Ismelin	Ciba	W. Germany	1960
Ismelin	Ciba	U.K.	1960
Ismelin	Ciba	Italy	1961
Ismeline	Ciba Geigy	France	1963
Abapresin	Polfa	Poland	–
Antipres	Protea	Australia	–
Dopom	Galter	Italy	–
Ganda	Smith & Nephew	U.K.	–
Iporal	Euro-Labor	Portugal	–
Ipotidina	Francia	Italy	–
Izobarin	Pliva	Yugoslavia	–
Normalin	Taro	Israel	–
Pressedin	Chiesi	Italy	–
Santotensin	Egyt	Hungary	–
Visutensil	I.S.F.	Italy	–

Raw Materials

Chloroacetyl guanide
Lithium aluminum hydride
Heptamethyleneimine
Sulfuric acid

Manufacturing Process

13.6 grams of chloroacetyl guanide is added while stirring to a solution of 22.6 grams of heptamethylene imine in 200 ml of benzene. After warming for 1 hour, and then cooling, the solution is filtered and the filtrate concentrated under reduced pressure. The residue, containing the 2-(1-N,N-heptamethylene-imino)-acetic acid guanide, is suspended in tetrahydrofuran and added to a refluxing solution of 6 grams of lithium aluminum hydride in tetrahydrofuran. After completion of the reaction, the excess of lithium aluminum hydride is decomposed by adding water, then aqueous sodium hydroxide. The solid material is filtered off, the filtrate is acidified with sulfuric acid and the 2-(1-N,N-heptamethylene-imino)-ethyl-guanidine sulfate can be recovered and recrystallized from aqueous ethanol, MP 276° to 281°C (with decomposition).

References

Merck Index 4441
Kleeman & Engel p. 452
PDR p. 797
OCDS Vol. 1 p. 282 (1977) & 2, 100 (1980)
DOT 16 (4) 137 (1980)
I.N. p. 474
Mull, R.P.; U.S. Patent 2,928,829; March 15, 1960; assigned to Ciba Pharmaceutical Products, Inc.
Mull, R.P.; U.S. Patent 3,006,913; October 31, 1961; assigned to Ciba Pharmaceutical Products, Inc.
Mull, R.P.; U.S. Patent 3,055,882; September 25, 1962; assigned to Ciba Corporation

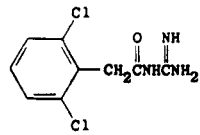
GUANFACINE

Therapeutic Function: Antihypertensive

Chemical Name: N-(Aminoiminomethyl)-2,6-dichlorobenzeneacetamide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 29110-47-2; 29110-48-3 (Hydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Estulic	Sandoz	Switz.	1980
Estulic	Sandoz	U.K.	1980
Estulic	Sandoz	W. Germany	1980
Estulic	Wander	France	1981
Estulic	Sandoz	France	1981
Hipertensal	Finadiet	Argentina	—

Raw Materials

2,6-Dichlorophenylacetic acid chloride
Guanidine
Hydrogen chloride

Manufacturing Process

2,6-Dichlorophenyl-acetyl-guanidine: A solution of 3.245 g (0.055 mol) of guanidine in isopropanol is added to a solution of 11.7 g (0.05 mol) of 2,6-dichlorophenyl-acetic acid ethyl ester (BP 142°C to 143°C/12 mm of Hg) in 20 cc of isopropanol. The reaction mixture is allowed to stand overnight and is subsequently concentrated by evaporation. After recrystallizing the residue from methanol/ether 2,6-dichlorophenyl-acetyl-guanidine is obtained in the form of white grains having a MP of 225°C to 227°C.

2,6-Dichlorophenyl-acetyl-guanidine hydrochloride: A solution of 5.6 g (0.025 mol) of 2,6-dichlorophenylacetic acid chloride (BP 137°C to 138°C/12 mm of Hg) in 10 cc of toluene is

added dropwise to a mixture of 4.5 g (0.076 mol) of guanidine and 60 cc of toluene. The reaction mixture is allowed to stand at room temperature for 20 minutes, is then heated on a steam bath for 2 hours and is subsequently cooled. The resulting precipitate is filtered off and washed twice with 25 cc amounts of water in order to separate the guanidine hydrochloride. The residue (2,6-dichlorophenyl-acetyl-guanidine) is washed with chloroform for further purification and is then dissolved in 50 cc of isopropanol. The pH-value of the solution is adjusted to 6 with ethanolic hydrochloric acid and the solution is cooled. The resulting white needles are again washed with chloroform. The resulting 2,6-dichlorophenyl-acetyl-guanidine hydrochloride has a MP of 213°C to 216°C.

References

Merck Index 4442
DFU 2 (4) 278 (1977)
OCDS Vol. 3 p. 40 (1984)
DOT 16 (12) 416 (1980)
I.N. p. 474
REM p. 846
Bream, J.B. and Picard, C.W.; U.S. Patent 3,632,645; January 4, 1972; assigned to Dr. A. Wander S.A. (Switz.)

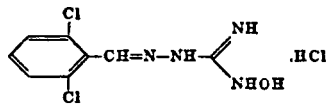
GUANOXABENZ HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 1-(2,6-Dichlorobenzylideneamino)-3-hydroxyguanidine hydrochloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 24047-25-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Benezrial	Houde	France	1978

Raw Materials

S-Methylisothiosemicarbazide hydroiodide
Hydroxylamine hydrochloride
2,6-Dichlorobenzaldehyde

Manufacturing Process

2 N sodium hydroxide solution (5 ml) is added to a stirred suspension of S-methylisothiosemicarbazide hydroiodide (2.33 g) and hydroxylamine hydrochloride (0.70 g) in water (6 ml) and stirred for 48 hours. The solution is evaporated in vacuo to provide 1-amino-3-hydroxyguanidine. One-third of the residue is dissolved in 16 ml of ethanol and 2,6-dichlorobenzaldehyde (0.6 g) is added to this solution. The reaction mixture is then stirred for 48 hours. The solution is then evaporated in vacuo and the residue dissolved in ether (30 ml) and in hydrochloric acid (30 ml). The aqueous phase is rendered alkaline with 2 N sodium carbonate solution and extracted with ether. The ether layer is dried with sodium sulfate and evaporated.

The residue is dissolved in ether and excess dry hydrogen chloride is passed into the solution.

The resultant mixture is evaporated in vacuo and the residue triturated with methylene chloride to afford a crude product. Recrystallization from ethanol-ether (1:3) provides 1-(2,6-dichlorobenzylideneamino)-3-hydroxyguanidine hydrochloride; MP 173°C to 175°C. When the above process is carried out and S-benzylisothiosemicarbazide hydroiodide is used in place of S-methylisothiosemicarbazide hydroiodide, the identical product is again obtained.

References

Merck Index 4449
Kleeman & Engel p. 453
OCDS Vol. 2 p. 123 (1980)
DOT 14 (6) 244 (1978)
I.N. p. 474
Houlihan, W.G. and Manning, R.E.; U.S. Patent 3,591,636; July 6, 1971; assigned to Sandoz-Wander, Inc.