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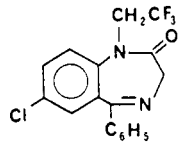
HALAZEPAM

Therapeutic Function: Tranquilizer

Chemical Name: 7-Chloro-1,3-dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-2H-1,4-benzodiazepine-2-one

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 23092-77-3

Trade Name	Manufacturer	Country	Year Introduced
Paxipam	Schering	U.S.	1981

Raw Materials

7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one
Sodium
Methanol
2,2,2-Trifluoroethyl iodide

Manufacturing Process

Prepare a solution of sodium methylate by dissolving 3.9 g of sodium metal in 500 ml of methanol. Add 39.0 g of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one. Evaporate the reaction mixture to a residue and dissolve the residue in 170 ml of dimethylformamide. Add 30 g of 2,2,2-trifluoroethyl iodide and stir at room temperature for ½ hour, then heat to 60°C to 70°C for an additional 7 hours. Add 19 g of 2,2,2-trifluoroethyl iodide and resume the heating and stirring at 60°C to 70°C for an additional 16 hours. Filter off the solids and evaporate the filtrate to a residue in vacuo. Triturate the residue with water and extract with ethyl ether. Wash the ethereal extract with water, dry over anhydrous sodium sulfate and evaporate the solvent to a residue.

Extract the residue with ethyl ether and filter. Concentrate the ethereal extract to a residue. Dissolve the residue in benzene and chromatograph on 300 g of alumina contained in a glass column 1.5 inches in diameter to give the crude product. Elute with benzene. Crystallize this product from acetone-petroleum ether to obtain the product.

References

Merck Index 4472

DFU 3 (2) 109 (1978)
PDR p. 1645
DOT 9 (6) 237 (1973), 11 (5) 191, 211 (1975) & 18 (8) 367 (1982)
I.N. p. 476
REM p. 1062
Topliss, J.G.; U.S. Patents 3,429,874; Feb. 25, 1969 and 3,641,147; Feb. 8, 1972; both assigned to Schering Corp.

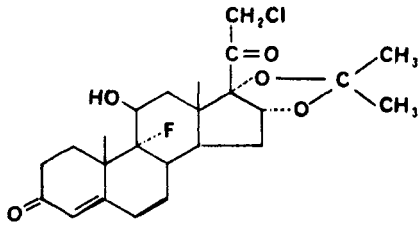
HALCINONIDE

Therapeutic Function: *Topical corticosteroid*

Chemical Name: 21-Chloro-9α-fluoro-Δ^4-pregnene-11β,16α,17α-triol-3,20-dione 16,17-acetonide

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 3093-35-4

Trade Name	Manufacturer	Country	Year Introduced
Halog	Squibb	U.S.	1974
Halciderm	Squibb	U.K.	1974
Halciderm	Squibb	Italy	1976
Halog	Von Heyden	W. Germany	1977
Halog	Squibb	France	1979
Halciderm	Squibb	U.S.	1980
Adcortin	Sankyo	Japan	1982
Beta Corton	Spirig	Switz.	–
Dihalog	Heyden	W. Germany	–
Halcimat	Heyden	W. Germany	–
Halcort	Fair	U.K.	–
Volog	Squibb	–	–

Raw Materials

16α-Hydroxy-9α-fluorohydrocortisone acetonide
Methane sulfonyl chloride
Lithium chloride

Manufacturing Process

(A) 16α-Hydroxy-9α-fluorohydrocortisone acetonide 21-mesylate: To a solution of 1.5 g of 16α-hydroxy-9α-fluorohydrocortisone acetonide in 15 ml of dry pyridine is added at 0°C, 1.5 ml of methane-sulfonyl chloride. After standing in the refrigerator for 2½ hours, excess methane-sulfonyl chloride is destroyed by the addition of a small amount of ice, after which

ice-water is added slowly to precipitate the reaction product. After ½ hour in the refrigerator the material is filtered off, washed thoroughly with water and dried in vacuo. The resulting crude material after recrystallization from acetone-hexane gives the pure 21-mesylate of the following properties: melting point about 225°C to 227°C (decomposition); $[\alpha]_D^{23}$ +112° (c, 0.5 in chloroform).

(B) 21-Chloro-9α-fluoro-Δ^4-pregnene-11β,16α,17α-triol-3,20-dione 16,17-acetonide: A solution of 200 mg of the acetonide 21-mesylate from part (A) and 900 mg of lithium chloride in 25 ml of dimethylformamide is kept at 100°C for 24 hours. The mixture is poured on ice, extracted with chloroform and the chloroform extract washed with water and dried over sodium sulfate. Evaporation of the solvent in vacuo furnishes the crystalline chloride, which after recrystallization from acetone-ethanol has a melting point about 276°C to 277°C.

References

Merck Index 4474
Kleeman & Engel p. 454
PDR p. 1745
OCDS Vol. 2 p. 187 (1980)
DOT 10 (11) 305 (1974)
I.N. p. 477
REM p. 972
Difazio, L.T. and Augustine, M.A.; U.S. Patent 3,892,857; July 1, 1975; assigned to E.R. Squibb & Sons, Inc.

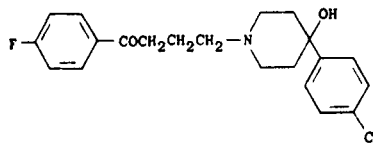
HALOPERIDOL

Therapeutic Function: Antidyskinetic; antipsychotic

Chemical Name: 4-[4-(4-Chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl-1-butanone

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 52-86-8

Trade Name	Manufacturer	Country	Year Introduced
Haldol	Janssen Le Brun	France	1960
Haldol	McNeil	U.S.	1967
Serenace	Searle	U.K.	1969
Fortunan	Steinhard	U.K.	1983
Bioperidolo	Firma	Italy	–
Brotopon	Pfizer Taito	Japan	–
Einalon S	Maruko	Japan	–
Eukystol	Merckle	W. Germany	–
Halidol	Abic	Israel	–
Halo Just	Horita	Japan	–
Haloperidol	Mohan	Japan	–
Halosten	Shionogi	Japan	–

Trade Name	Manufacturer	Country	Year Introduced
Keselan	Sumitomo	Japan	–
Linton	Yoshitomi	Japan	–
Pacedol	Protea	Australia	–
Peluces	Isei	Japan	–
Peridor	Unipharm	Israel	–
Selezyme	Sawai	Japan	–
Serenace	Dainippon	Japan	–
Serenase	Lusofarmaco	Italy	–
Serenase	Orion	Finland	–
Sigaperidol	Siegfried	Switz.	–
Vesadol	Le Brun	France	–

Raw Materials

4-(4-Chlorophenyl)piperidin-4-ol hydrochloride
1,1-Dimethoxy-1-(4-fluorophenyl)-4-chlorobutane
Hydrogen chloride
Ammonia

Manufacturing Process

A stirred slurry of 120.0 parts 4-(4-chlorophenyl)-piperidin-4-ol hydrochloride and 40.0 parts of potassium iodide in 500 parts of water is warmed to a temperature of about 35°C under a nitrogen atmosphere. Then, 70.0 parts of potassium hydroxide is added. After further heating to about 55°C, 138.0 parts of 1,1-dimethoxy-1-(4-fluorophenyl)-4-chlorobutane is added. The temperature is then raised to about 102°C and heating continued for 3.5 hours. After cooling to about 75°C, 785 parts of toluene is added to the reaction mixture and stirred for about 5 minutes. An additional 320 parts of toluene is added and the water and organic layers separated. 102 parts of methanol is used to rinse the flask and added to the organic layer to provide a solution of 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4,4-dimethoxybutyl]-piperidin-4-ol. Then, 59 parts of concentrated hydrochloric acid is added to a stirred solution of the organic layer to precipitate a solid. The solid is filtered, rinsed twice with 550 parts by volume portions of a 10:9:1 acetone-toluene-methanol mixture, twice with 400 parts by volume portions of a 10:1 acetone-methanol mixture, and air-dried. The dried solid is then dissolved in 1,950 parts of methanol with gentle heating on a steam bath. The resulting solution is filtered and 300 parts by volume of concentrated ammonium hydroxide is added. Heating is continued to reflux and maintained thereat for about 1 hour. Then, 2,520 parts of water is added and the slurry stirred at about 75°C for 1.5 hours. After cooling to about 25°C, the solid is filtered, washed twice with 600 parts by volume portions of a 3:1 mixture of water-methanol, and air-dried. The resulting product, 4-[4-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone, is obtained in 32.5% yield. This product melts at about 148.5°C to 150.5°C.

References

Merck Index 4480
Kleeman & Engel p. 454
PDR p. 1089
OCDS Vol. 1 p. 306 (1977)
DOT 9 (6) 234 (1973)
I.N. p. 478
REM p. 1088
Dryden, H.L. Jr. and Erickson, R.A.; U.S. Patent 4,086,234; April 25, 1978; assigned to G.D. Searle & Co.

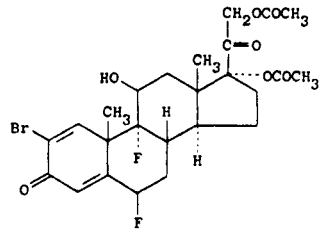
HALOPREDONE ACETATE

Therapeutic Function: Topical antiinflammatory

Chemical Name: 17,21-Bis(acetyloxy)-2-bromo-6,9-difluoro-11-hydroxypregna-1,4-diene-3,20-dione

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 57781-14-3; 57781-15-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Topicon	Pierrel	Italy	1983

Raw Materials

2-Bromo-6β-fluoro-17α,21-dihydroxy-9β,11β-oxido-pregna-1,4-diene-3,20-dione-17-21-diacetate
Hydrogen fluoride

Manufacturing Process

100 ml of a 70% hydrofluoric acid aqueous solution were cooled to -10°C in a polyethylene flask equipped with electromagnetic stirrer. 10 g of 2-bromo-6β-fluoro-17α,21-dihydroxy-9β,11β-oxido-pregna-1,4-diene-3,20-dione-17,21-diacetate were added under stirring during 15 minutes. After ½ hour the reaction mixture was precipitated in water and ammonia. The solid was collected by filtration, washed with water and dried to a constant weight, giving about 9.5 g of 2-bromo-6β,9α-difluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione-17,21-diacetate.

References

Merck Index 4481
DFU 1 (11) 526 (1976)
Kleeman & Engel p. 456
OCDS Vol. 3 p. 99 (1984)
I.N. p. 478
Riva, M. and Toscano, L.; U.S. Patent 4,272,446; June 9, 1981; assigned to Pierrel S.p.A. (Italy)

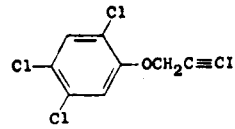
HALOPROGIN

Therapeutic Function: Antibacterial

Chemical Name: 3-iodo-2-propynyl 2,4,5-trichlorophenyl ether

Common Name: 2,4,5-trichlorophenyl γ-iodopropargyl ether

Structural Formula:



Chemical Abstracts Registry No.: 777-11-7

Trade Name	Manufacturer	Country	Year Introduced
Halotex	Westwood	U.S.	1972
Mycanden	Schering	W. Germany	1975
Mycilan	Schering	France	1978
Mycilan	Theraplix	France	–
Polik	Meiji	Japan	–

Raw Materials

2,4,5-Trichlorophenyl propargyl ether
Cuprous chloride
Iodine

Manufacturing Process

4.7 grams of 2,4,5-trichlorophenyl propargyl ether (MP 64° to 65°C) are added to an aqueous solution of cupro-ammonium complex salt which has been prepared by warming a mixture of 4.0 grams of cuprous chloride, 11.0 grams of ammonium carbonate and 20 cc of water to 50°C. The resulting admixture is shaken vigorously. The cuprous acetylide deposited is filtered, washed with water and suspended in 100 cc of water, and the suspension is mixed under agitation with a solution of 5.0 grams of iodine and 5.0 grams of potassium iodide in 15 cc of water. The mixture is stirred for a period of 1 hour. The precipitate is filtered, washed with water and extracted with ether. After the drying of the ethereal extract, the solvent is distilled off. Recrystallization of the residue from n-hexane gives about 5.6 grams of 2,4,5-trichlorophenyl iodopropargyl ether, MP 114° to 115°C.

References

Merck Index 4483
Kleeman & Engel p. 456
PDR p. 1891
DOT 8 (8) 292 (1972)
I.N. p. 478
REM p. 1228
Seki, S., Nomiya, B. and Ogawa, H.; U.S. Patent 3,322,813; May 30, 1967; assigned to Meiji Seika Kaisha, Ltd., Japan

HALOTHANE

Therapeutic Function: Inhalation anesthetic

Chemical Name: 2-bromo-2-chloro-1,1,1-trifluoroethane

Common Name: –

Structural Formula: $F_3CCHBrCl$

Chemical Abstracts Registry No.: 151-67-7

Trade Name	Manufacturer	Country	Year Introduced
Fluothane	Ayerst	U.S.	1958
Fluopan	Propan-Lipworth	S. Africa	—
Fluothane	I.C.I.	U.K.	—
Halan	Arzneimittelwerk Dresden	E. Germany	—
Halothan Hoechst	Hoechst	W. Germany	—
Halovis	Vister	Italy	—
Narcotan	Spofa	Czechoslovakia	—
Rhodialothan	Rhodia Pharma	W. Germany	—
Somnothane	Hoechst	—	—

Raw Materials

1,1,1-Trifluoro-2-chloroethane
Bromine

Manufacturing Process

According to U.S. Patent 2,849,502, the apparatus used consisted of a 2" x 24" silica tube packed with silica chips and enclosed in a vertical electric furnace. 1,1,1-trifluoro-2-chloroethane as vapor and bromine as liquid were introduced into a narrow tube passing down the inside of the reaction tube. The mixed reactants then passed up through the reaction tube which was maintained at a temperature of about 465°C. The reaction products were passed through a water-cooled condenser which condensed out most of the desired 1,1,1-trifluoro-2-bromo-2-chloroethane along with any high boiling by-products and unchanged bromine.

This condensate was washed with dilute caustic soda solution and dried over calcium chloride. The exit gases from this condenser were scrubbed with water and dilute caustic soda solution, dried and passed to a condenser cooled with a mixture of solid carbon dioxide and trichloroethylene which caused the unchanged 1,1,1-trifluoro-2-chloroethane to condense. This second condensate was then combined with the first and the mixture was fractionally distilled.

During a run of 2 hours 620 grams of 1,1,1-trifluoro-2-chloroethane and 630 grams of bromine were fed to the reactor and the product was worked up as described above. On fractional distillation there was obtained a first cut up to 50°C consisting of unchanged 1,1,1-trifluoro-2-chloroethane, then a middle cut between 50° and 52°C consisting of substantially pure 1,1,1-trifluoro-2-bromo-chloroethane and a higher boiling residue that contained a further quantity of the desired product together with some 1,1,1-trifluoro-2,2-dibromo-2-chloroethane. On redistillation of the middle fraction pure 1,1,1-trifluoro-2-bromo-2-chloroethane was obtained with BP 50° to 50.5°C.

References

Merck Index 4486
Kleeman & Engel p. 457
PDR p. 620
I.N. p. 479
REM p. 1042
Suckling, C.W. and Raventos, J.; U.S. Patent 2,849,502; August 26, 1958; assigned to Imperial Chemical Industries Limited, England
Suckling, C.W. and Raventos, J.; U.S. Patent 2,921,098; January 12, 1960; assigned to Imperial Chemical Industries, Limited, England
Scherer, O. and Kuhn, H.; U.S. Patent 2,959,624; November 8, 1960; assigned to Farbwerke Hoechst AG vormals Meister Lucius & Bruning, Germany
McGinty, R.L.; U.S. Patent 3,082,263; March 19, 1963; assigned to Imperial Chemical Industries Limited, England

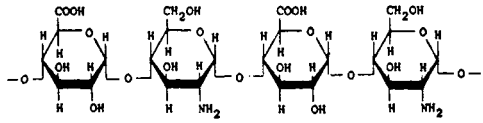
HEPARIN

Therapeutic Function: Anticoagulant

Chemical Name: See structural formula

Common Name: –

Structural Formula:



desulfated heparin

Chemical Abstracts Registry No.: 9005-49-6

Trade Name	Manufacturer	Country	Year Introduced
Heparin	Upjohn	U.S.	1942
Heprinar	Armour	U.S.	1976
Chemyparin	S.I.T.	Italy	–
Clearane	Jamco	Italy	–
Disebrin	Tubi Lux Pharma	Italy	–
Embolex	Sandoz	U.S.	–
Endoprin	Endo	U.S.	–
Eparina	Vister	Italy	–
Eparinoral	Bruco	Italy	–
Eparinovis	Vis	Italy	–
Fioricet	Sandoz	U.S.	–
Hamocura	Nordmark	W. Germany	–
Hepacort Plus	Rona Labs	U.K.	–
Hepa Gel	Spirig	Switz.	–
Heparin-Pos	Ursapharm	W. Germany	–
Heparin Sodium	Tokyo Tanabe	Japan	–
Heparinin	Sankyo	Japan	–
Hepathromb	Arzneimittelwerk Dresden	E. Germany	–
Hep-Lock	Elkins-Sinn	U.S.	–
Hepsal	Weddel	U.K.	–
Liquaemin	Organon	U.S.	–
Minihep	Leo	U.K.	–
Percase	Solac	France	–
Praecivenin	Pfleger	W. Germany	–
Pularin	Evans	U.K.	–
Thrombareduct	Azuchemie	W. Germany	–
Thromophob	Nordmark	W. Germany	–
Thrombo-Vetren	Promonta	W. Germany	–

Raw Materials

Beef intenstine	Water
Chloroform	Toluene

Manufacturing Process

5,000 pounds of beef intestine was introduced into a stainless steel reactor, jacketed with thermostated water and steam. 200 gallons of water and 10 gallons of chloroform were added. The mixture was agitated, the temperature was raised to 90°F and the agitation

stopped. 5 gallons of toluene was added and the vessel closed. Autolysis was continued for 17 hours.

The extractant solution, consisting of 30 gallons of glacial acetic acid, 35 gallons of 30% aqueous ammonia, 50% sodium hydroxide to adjust the pH to 9.6 at 80°F and water to make 300 gallons, was added to the tissue. With agitation, the temperature was raised to 60°C and held there for 2 hours. Then steam was applied and the temperature was raised to boiling. 200 pounds of coarse filter aid (perlite) was added and the mixture filtered through a string discharge vacuum filter. The cake was washed with 200 gallons of hot water on the filter.

The filtrate was allowed to stand overnight and the fat skimmed off the top. After cooling to 100°F, the filtrate was transferred to a tank with thermostated water and the temperature set at 95° to 100°F. 24 gallons of pancreatic extract, prepared as described above, was added in 4-gallon increments every 12 hours for 3 days. The batch was brought to a boil and cooled to room temperature.

The batch was then filtered into a vessel and assayed for heparin content. 40,000,000 units were found in 1,000 gallons of filtrate. 20 kg of n-octylamine was added and 105 pounds of glacial acetic acid was added to bring the pH to 6.5. 20 gallons of methyl isobutyl ketone was added and the whole mixture was vigorously agitated for 1 hour. The mixture was then allowed to stand overnight. The clear, aqueous phase was drained off and discarded. The grayish-brown interphase was then removed, together with a small amount of the ketone phase, and transferred into a small kettle. The interphase volume was 7 gallons.

30 gallons of methanol was added and the mixture warmed to 120°F and then the pH was adjusted to 9.0. The mixture was then allowed to settle overnight. The solids were collected with vacuum and washed with 5 gallons of methanol. The cake was then suspended in 5 gallons of water and the heparin precipitated with 10 gallons of methanol. The solids were collected under vacuum. The dry weight of the cake was 1,000 grams and the total units were 38,000,000, according to U.S. Patent 2,884,358.

References

Merck Index 4543
Kleeman & Engel p. 458
PDR pp. 872, 887, 1286, 1581, 1845, 1949
I.N. p. 481
REM p. 828
Bush, J.A., Freeman, L.D. and Hagerty, E.B.; U.S. Patent 2,884,358; April 28, 1959; assigned to Southern California Gland Company
Nomine, G., Penasse, L. and Barthelemy, P.; U.S. Patent 2,989,438; June 20, 1961; assigned to UCLAF, France
Toccaceli, N.; U.S. Patent 3,016,331; January 9, 1962; assigned to Ormonoterapia Richter SpA, Italy

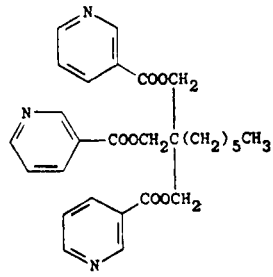
HEPRONICATE

Therapeutic Function: Peripheral vasodilator

Chemical Name: Nicotinic acid triester with 2-hexyl-2-(hydroxymethyl)-1,3-propanediol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 7237-81-2

Trade Name	Manufacturer	Country	Year Introduced
Megrin	Yoshitomi	Japan	1972

Raw Materials

2-Hexyl-2-(hydroxymethyl)-1,3-propanediol
Nicotinic acid
p-Toluene sulfonyl chloride

Manufacturing Process

In 50 ml of pyridine were dissolved 50 grams of nicotinic acid and 50 grams of p-toluenesulfonyl chloride. While stirring, the mixture gradually became hot and colorless, and finally solidified. To the mixture was added dropwise a solution of 19 grams of 2-hexyl-2-(hydroxymethyl)-1,3-propanediol in 400 ml of pyridine at a temperature below 80°C. The mixture was heated at 115° to 125°C on an oil bath for 1 hour. After cooling, the mixture was poured into 300 ml of ice water, and extracted with toluene. The toluene layer was washed in sequence with water, aqueous sodium carbonate and water, dried over potassium carbonate, and then the toluene was distilled off. The oily residue was crystallized from ethanol to give 30 grams of 2-hexyl-2-(hydroxymethyl)-1,3-propanediol trinicotinate, melting at 94° to 96°C. The yield was 59.5%.

References

Merck Index 4545
Kleeman & Engel p. 459
DOT 8 (8) 314 (1972)
I.N. p. 482
Nakanishi, M., Kobayashi, R. and Arimura, K.; U.S. Patent 3,384,642; May 21, 1968; assigned to Yoshitomi Pharmaceutical Industries, Ltd., Japan

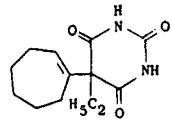
HEPTABARBITAL

Therapeutic Function: Hypnotic; sedative

Chemical Name: 5-(1-Cyclohepten-1-yl)-5-ethyl-2,4,6(1H,3H,5H)-pyrimidinetrione

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 509-86-4

Trade Name	Manufacturer	Country	Year Introduced
Medomine	Ciba Geigy	France	1948
Medomin	Geigy	U.S.	1955

Raw Materials

Cycloheptanone
Cyanoacetic acid methyl ester
Ethyl bromide
Hydrogen chloride
Sodium
Ethanol
Urea

Manufacturing Process

112 g of cycloheptanone (suberone) are mixed with 130 g of cyanoacetic acid methyl ester, 2 g of piperidine are added, and the mixture is heated on the water bath at 60°C for several hours until no more water separates from the reaction mixture. The water layer is removed, and the remainder is subjected to distillation in vacuo. The fraction distilling at 160°C to 175°C under a pressure of 20 mm is collected separately; it consists of cycloheptenyl-cyanoacetic acid methyl ester. The first fractions can be subjected to a fresh condensing reaction after addition of more piperidine.

The cycloheptenyl-cyanoacetic acid methyl ester so obtained is a colorless liquid boiling at 174°C under a pressure of 20 mm.

Into this compound, an ethyl radical is introduced at the same C-atom to which the cycloheptenyl radical is connected. This is done, for example, in the following way:

19.3 g of the above ester are added to a solution of 2.3 g of sodium in 40 cc of absolute ethyl alcohol. To this mixture, 13.0 g of ethyl bromide are gradually added while cooling, and the reaction mixture is heated under reflux on a water bath until it has become neutral. The mixture is then taken up in water, the aqueous layer is separated and the cycloheptenyl-ethyl-cyanoacetic acid methyl ester so formed distills at 169°C to 170°C under a pressure of 20 mm.

22.1 g of this latter substance are dissolved in a solution of 4.6 g of sodium in 100 cc of absolute ethyl alcohol. 12 g of urea are further added thereto, and the whole solution is heated to about 80°C for about eight hours. The alcohol is then distilled off in vacuo, the residue is dissolved in cold water, and from this solution, C-C-cycloheptenyl-ethyl barbituric acid is obtained by saponification with diluted hydrochloric acid. The crude product is recrystallized from diluted ethyl alcohol and forms colorless needles of faintly bitter taste and melting point 174°C.

The sodium salt of this acid may be prepared by dissolving 2.5 g of the acid in a solution of 0.23 g of sodium in 20 cc of ethyl alcohol, and the salt forms, after evaporating the alcohol, a colorless, water-soluble powder.

References

Merck Index 4546
Kleeman & Engel p. 459
OCDS Vol. 1 pp. 269, 272 (1977)
I.N. p. 482
Taub, W.; U.S. Patent 2,501,551; March 21, 1950

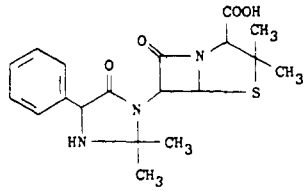
HETACILLIN POTASSIUM

Therapeutic Function: Antibacterial

Chemical Name: 6-(2,2-dimethyl-5-oxo-4-phenyl-1-imidazolidinyl)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid potassium salt

Common Name: Phenazacillin

Structural Formula:



(base)

Chemical Abstracts Registry No.: 5321-32-4; 3511-16-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Natacillin	Bristol-Banyu	Japan	1970
Versapen	Bristol	Italy	1970
Versapen	Bristol	France	1970
Versapen	Bristol	U.S.	1971
Hetabiotic	Bristol-Myers	—	—
Hetacin-K	Bristol	—	—
Penplenum	Bristol	W. Germany	—
Uropen	Bristol	—	—

Raw Materials

α-Aminobenzylpenicillin
Acetone

Manufacturing Process

To 100 grams of α-aminobenzylpenicillin slurried in 2,500 ml of acetone is added 200 ml of a 22% solution of potassium ethylhexanoate in dry n-butanol and the mixture is warmed to 45°C whereupon the acid dissolves. After the mixture is agitated for 1 hour at 40° to 45°C, the product begins to crystallize out. Agitation is continued for 4 hours at 45°C after which the product, the potassium salt of hetacillin, is collected by filtration, washed with 500 ml of dry acetone, dried for 17 hours at 40°C and found to weigh 70.0 grams.

References

Merck Index 4564
Kleeman & Engel p. 460
OCDS Vol. 1 p. 414 (1977)
DOT 3 (1) 12 (1967)
I.N. p. 483
REM p. 1200
Johnson, D.A. and Panetta, C.A.; U.S. Patent 3,198,804; August 3, 1965; assigned to Bristol-Myers Company

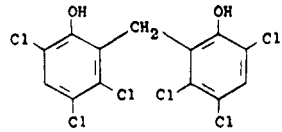
HEXACHLOROPHENE

Therapeutic Function: Topical antiinfective

Chemical Name: 2,2'-methylenebis(3,4,6-trichlorophenol)

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 70-30-4

Trade Name	Manufacturer	Country	Year Introduced
Gamophen	Ethicon	U.S.	1950
Phisohex	Winthrop	U.S.	1954
Germa-Medica	Huntington	U.S.	1979
Hexascrub	Prof. Disposables	U.S.	1980
Pre-Op	Davis & Geck	U.S.	1980
Turgex	Xttrium	U.S.	1981
Coopaphene	McDougall & Robertson	U.K.	–
Dermadex	Alconox	U.S.	–
Dermohex	Hartz	Canada	–
G-11	Givaudan	Switz.	–
Germibon	Gamir	Spain	–
Heksaden	Deva	Turkey	–
Hexal	Fischer	Israel	–
Solu-Heks	Mustafa Nevzat	Turkey	–
Soy-Dome	Dome	U.S.	–
Ster-Zac	Hough	U.K.	–
Wescohex	West	U.S.	–
Westasept	West	U.S.	–

Raw Materials

2,4,5-Trichlorophenol
Paraformaldehyde

Manufacturing Process

A mixture of 198 grams of 2,4,5-trichlorophenol and 18.8 grams of paraformaldehyde was heated to 65°C and well stirred. 65 grams of oleum 20% was added dropwise and the addition was so regulated that the temperature increased, without the application of external heat, until it reached 135°C at the end of the acid addition, which took 10 to 15 minutes. The contents of the reaction vessel were stirred for 2 minutes more and then allowed to run into a solution of 100 grams of sodium hydroxide in 1,000 cc of water.

The reaction flask was washed with a solution of 25 grams of sodium hydroxide in 250 cc of water. The combined alkaline solutions were heated to boiling for 5 minutes. A small amount (6 grams) of alkali-insoluble material remained and was filtered off. Sulfuric acid (62% H_2SO_4 content) was then added at room temperature dropwise under stirring to the filtrate until a pH of 10.3 was reached. This required about 80 grams of the acid. The monosodium salt of bis-(3,5,6-trichloro-2-hydroxyphenyl) methane precipitated out of solution and was filtered and then washed with 200 cc of water. The salt was then sus-

pended in 2,000 cc of water and sulfuric acid (62% H_2SO_4 content) was added under stirring until the contents were acid to Congo red paper. This required about 30 grams of the acid.

The resulting bis-(3,5,6-trichloro-2-hydroxyphenyl) methane was filtered, washed with water until acid-free and dried to constant weight at 100°C (170 grams, MP 154° to 158°C). Crystallization of the 170 grams of dried bis-(3,5,6-trichloro-2-hydroxyphenyl) methane from 300 grams toluene yielded a first crop amounting to 105 grams of substantially pure bis-(3,5,6-trichloro-2-hydroxyphenyl) methane, having a MP of 161° to 163°C (from U.S. Patent 2,435,593).

References

Merck Index 4574
Kleeman & Engel p. 461
PDR p. 1926
I.N. p. 484
REM p. 1161
Gump, W.S.; U.S. Patent 2,250,480; July 29, 1941; assigned to Burton T. Bush, Inc.
Luthy, M. and Gump, W.S.; U.S. Patent 2,435,593; February 10, 1948; assigned to Burton T. Bush, Inc.
Gump, W.S., Luthy, M. and Krebs, H.G.; U.S. Patent 2,812,365; November 5, 1957; assigned to The Givaudan Corporation

HEXAMETHONIUM BROMIDE

Therapeutic Function: Antihypertensive

Chemical Name: N,N,N,N′,N′,N′-Hexamethyl-1,6-hexanediaminium bromide

Common Name: —

Structural Formula: $(CH_3)_3N^+(CH_2)_6N^+(CH_3)_3 \cdot 2Br^-$

Chemical Abstracts Registry No.: 60-26-4 (Hexamethonium)

Trade Name	Manufacturer	Country	Year Introduced
Bistrium	Squibb	U.S.	1951
Hexanium	Adrian-Marinier	France	—
Methobromin	Yamanouchi	Japan	—
Vegolysen	May & Baker	—	—

Raw Materials

Hexamethylene diamine
Sodium hydroxide
Dimethyl sulfate
Hydrogen bromide

Manufacturing Process

Hexamethylene diamine (116 g), sodium carbonate (466 g), and water (800 ml) were heated to 60°C, and dimethyl sulfate (830 g) added with stirring over 1½ hours keeping the temperature below 90°C. The reaction mixture was then stirred at 90°C for 2 hours, then cooled to 20°C, acetone (1,200 ml) added and the whole cooled to 0°C.

The solid formed was removed by filtration and washed with acetone (150 ml). Filtrate and washings were diluted with water to 4 liters and heated to 60°C under reflux. To this was

added a solution prepared from embonic acid (388 g), sodium hydroxide (80 g) and water (5 liters), the whole refluxed for 10 minutes and thereafter allowed to cool overnight.

The resultant embonate (530 g) was filtered off, washed twice with a solution of acetone (75 ml) in water (425 ml), and dried at 100°C to give an amorphous yellow powder, MP 290°C to 291°C (with decomp.). 588 g of the embonate was dissolved in boiling water (4 liters).

Hydrobromic acid 50% w/w (325 g) diluted with water (2 liters) was added slowly at the boil and the precipitated embonic acid removed by filtering hot and washing twice with hot water (1 liter). The filtrate and washings were evaporated to dryness in a steam pan and the residue recrystallized from ethyl alcohol (1,200 ml), to yield the dibromide (320 g).

References

Merck Index 4582
Kleeman & Engel p. 462
I.N. p. 485
Barber, H.J.; U.S. Patent 2,641,610; June 9, 1953; assigned to May & Baker, Ltd. (U.K.)

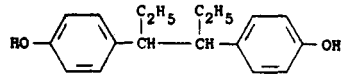
HEXESTROL

Therapeutic Function: Estrogen

Chemical Name: 4,4'-(1,2-diethyl-1,2-ethanediyl)bisphenol

Common Name: dihydrodiethylstilbestrol; hexoestrol

Structural Formula:



Chemical Abstracts Registry No.: 84-16-2

Trade Name	Manufacturer	Country	Year Introduced
Estra Plex	Rowell	U.S.	1956
Cycloestrol	Bruneau	France	–
Estrene	Lepetit	–	–
Femirogen	Fuso	Japan	–
Folliplex	Recip	Sweden	–
Hexron	Teikoku Zori	Japan	–
Hormoestrol	Siegfried	W. Germany	–
Syntex	Pharmacia	Sweden	–
Synthovo	Boots	U.K.	–

Raw Materials

p-Hydroxypropiophenone
Hydrogen chloride
Phosphorus (Red)
Sodium amalgam
Hydrogen iodide

Manufacturing Process

50 parts by weight of p-hydroxy-propiophenone are dissolved in 200 parts by weight of a 12.5% solution of caustic soda and shaken with 350 parts by weight of 3% sodium amalgam. The sodium salt of the pinacol thereby precipitating is reacted with glacial acetic acid, whereby

the free pinacol is obtained (MP 205°C to 210°C, after purification 215°C to 217°C). The yield amounts to 95% of the theoretical. The pinacol is suspended in ether and gaseous hydrogen chloride introduced, whereby water separates and the pinacolin formed is dissolved in the ether, from which it is obtained by evaporation as a viscous oil (diacetate of MP 91°C). The yield is quantitative.

40 parts by weight of pinacolin are dissolved in ethyl alcohol and gradually treated with 80 parts by weight of sodium under reflux. The solution is decomposed with water and the pinacolin alcohol formed extracted from the neutalized solution with ether. The pinacolin alcohol is a viscous oil which is characterized by a dibenzoate of MP 172°C. The yield is 95% of the theoretical.

30 parts by weight of pinacolin alcohol are dissolved in 25 parts by weight of glacial acetic acid and heated for 30 minutes to 135°C to 140°C after having added 20 parts by weight of hydriodic acid (specific gravity = 1.94) and 5 parts by weight of red phosphorus. The whole is filtered, the solution poured into water, extracted with ether and the ether solution washed with bicarbonate. The oil remaining after distilling off the ether is taken up in chloroform, whereby hexoestrol [α,β-(p,p-dihydroxy-diphenyl)-α,β-diethyl-ethane] crystallizes out. MP after recrystallization from benzene: 185°C. Yield: 20%.

References

Merck Index 4593
DFU 8 (5) 413 (1983)
Kleeman & Engel p. 466
OCDS Vol. 1 p. 102 (1977)
I.N. p. 486
Wallis, E.S. and Bernstein, S.; U.S. Patent 2,357,985; September 12, 1944; assigned to Research Corporation
Adler, E., Gie, G.J. and von Euler, H.; U.S. Patent 2,421,401; June 3, 1947; assigned to Hoffmann-La Roche, Inc.

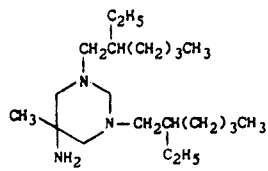
HEXETIDINE

Therapeutic Function: Antifungal

Chemical Name: 1,3-Bis(2-ethylhexyl)hexahydro-5-methyl-5-pyrimidinamine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 141-94-6

Trade Name	Manufacturer	Country	Year Introduced
Sterisil	Warner Lambert	U.S.	1956
Oraseptic	Parke Davis	Italy	1960
Hextril	Substantia	France	1961

Trade Name	Manufacturer	Country	Year Introduced
Hexoral	Goedecke	W. Germany	1967
Oraldene	Warner	France	1969
Oraldene	Warner	U.K.	1969
Bactidol	Warner-Chilcott	—	—
Bucosept	La Campana	Mexico	—
Collu-Hextril	Substantia	France	—
Drossadin	Drossapharm	Switz.	—
Glypesin	Stada	W. Germany	—
Sterisol	Warner-Chilcott	—	—

Raw Materials

Nitroethane
Formaldehyde
2-Ethylhexylamine
Hydrogen

Manufacturing Process

Nitroethane and formaldehyde are first reacted to give 2-methyl-2-nitro-1,3-propanediol. This is reacted with 2-ethylhexylamine and formaldehyde to give 5-nitro-1,3-bis(2-ethylhexyl)-5-methyl-hexahydropyrimidine.

To a hydrogenation apparatus containing 500 ml of methanol and 10 g of Raney nickel catalyst were continuously added over a period of one hour, 240 g of 5-nitro-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine. During the one-hour period, the resulting mixture was hydrogenated at approximately 1,000 pounds per square inch utilizing room temperature as the initial temperature and gradually increasing the temperature to about 70°C. At the end of the one-hour period, hydrogenation was stopped. The reaction mixture was first filtered to remove the catalyst and was then distilled at atmospheric pressure at a temperature of 70°C to remove methanol. 197.5 g of 5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine were collected.

References

Merck Index 4597
Kleeman & Engel p. 463
I.N. p. 487
Bell, W.O. and Neckar, A.E.; U.S. Patent 3,054,797; September 18, 1962; assigned to Commercial Solvents Corp.

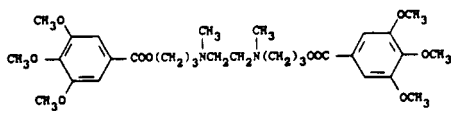
HEXOBENDINE

Therapeutic Function: Vasodilator

Chemical Name: 3,4,5-Trimethoxybenzoic acid 1,2-ethanediylbis-[(methylimino)-3,1-propanediyl] ester

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 54-03-5; 50-62-4 (Dihydrochloride)

Trade Name	Manufacturer	Country	Year Introduced
Reoxyl	Hormonchemie	W. Germany	1966
Ustimon	Merck Clevenot	France	1969
Flussicor	Farmalabor	Italy	1971
Andiamine	Polfa	Poland	—
Hityl	Biosedra	France	—
Instenon	Byk Gulden	W. Germany	—

Raw Materials

Methyl acrylate
Lithium aluminum hydride
N,N'-Dimethylethylenediamine
3,4,5-Trimethoxybenzoyl chloride

Manufacturing Process

Methyl acrylate and N,N'-dimethylethylenediamine are first reacted and that product reduced with lithium aluminum hydride to give a compound A.

To a solution of 13 parts of compound A and 12 parts by volume of absolute pyridine in 80 parts by volume of absolute dioxane there are added dropwise and under constant stirring 35 parts of 3,4,5-trimethoxybenzoyl chloride dissolved in 70 parts by volume of absolute dioxane in the course of 30 minutes. The mixture is stirred for a further 3 hours at a temperature of 100°C and the excess solvent is then evaporated in vacuo. The residue of the evaporation is treated with ethyl acetate and saturated sodium carbonate solution, whereafter the organic phase is separated, treated with water, dried with sodium sulfate and the solvent is removed in vacuo. The residue thus obtained is taken up in ether and separated from 4 parts of insoluble trimethoxybenzoic acid anhydride by filtration. After evaporation of the ether there are obtained 32.5 parts of N,N'-dimethyl-N,N'-bis-[3-(3,4,5-trimethoxybenzoxy)-propyl]-ethylene diamine, corresponding to a yield of 86% of the theoretical. MP: 75°C to 77°C.

The di-tertiary base thus obtained is dissolved in ether and the solution is saturated with hydrogen chloride gas. After isolation and reprecipitation from methanol-ether there is obtained the dihydrochloride melting at 170°C to 174°C.

References

Merck Index 4600
Kleeman & Engel p. 464
OCDS Vol. 2 p. 92 (1980)
I.N. p. 487
Kraupp, O. and Schlogl, K.; U.S. Patent 3,267,103; August 16, 1966; assigned to Oesterreichische Stickstoffwerke AG (Austria)

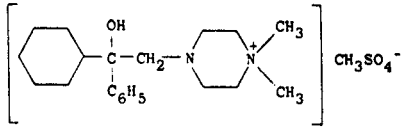
HEXOCYCLIUM METHYL SULFATE

Therapeutic Function: Antispasmodic

Chemical Name: 4-(2-cyclohexyl-2-hydroxy-2-phenylethyl)-1,1-dimethylpiperazinium methyl sulfate

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 115-63-9

Trade Name	Manufacturer	Country	Year Introduced
Tral	Abbott	U.S.	1957
Traline	Abbott	France	1959

Raw Materials

N-Phenacyl-N'-methylpiperazine
Cyclohexyl bromide
Magnesium
Dimethyl sulfate

Manufacturing Process

In a 2-liter, 3-necked, round-bottomed flask equipped with a stirrer, dropping funnel, and a condenser protected with a calcium chloride drying tube is placed 13.7 grams (0.57 mol) of magnesium turnings and the magnesium is covered with 200 cc of anhydrous ether. A crystal of iodine is added to the flask and 92.9 grams (0.57 mol) of cyclohexyl bromide dissolved in 300 cc of anhydrous ether is added dropwise with stirring while the reaction proceeds. After the addition of the cyclohexyl bromide is completed, the resulting mixture is stirred and heated on a steam bath for 3 hours. The mixture is cooled to room temperature and 49.5 grams (0.227 mol) of N-phenacyl-N'-methylpiperazine dissolved in 50 cc of anhydrous ether is added dropwise and the resulting mixture is stirred and refluxed for about 16 hours.

The reaction mixture is cooled and 50 grams of ammonium chloride dissolved in 200 cc of water is added dropwise thereto with stirring. The decomposed Grignard complex is then filtered. Benzene is added to the ether filtrate and the solvents are removed therefrom on a steam bath. The residue is fractionated and the base, N-(β-cyclohexyl-β-hydroxy-β-phenyl-ethyl)N'-methylpiperazine, is obtained as a liquid having a boiling point of 196° to 203°C at a pressure of 4.0 mm.

To 3.8 grams of the base dissolved in 35 cc of ethyl alcohol is added 1.6 grams of dimethyl sulfate. The solution is allowed to stand at room temperature for about 12 hours. The salt formed is filtered, recrystallized from ethyl alcohol, and is found to have a melting point of 203° to 204°C.

References

Merck Index 4601
Kleeman & Engel p. 465
PDR p. 553
I.N. p. 488
REM p. 918
Weston, A.W.; U.S. Patent 2,907,765; October 6, 1959; assigned to Abbott Laboratories

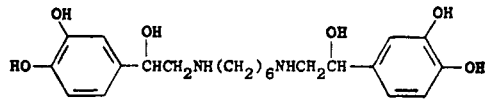
HEXOPRENALINE

Therapeutic Function: Bronchodilator

Chemical Name: 4,4'-[1,6-hexanediylbis[imino(1-hydroxy-2,1-ethanediyl)]]bis-1,2-benzenediol

Common Name: N,N'-bis[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl] hexamethylenediamine

Structural Formula:



Chemical Abstracts Registry No.: 3215-70-1

Trade Name	Manufacturer	Country	Year Introduced
Etoscol	Byk-Gulden	W. Germany	1973
Hexoprenaline	Morishita	Japan	1976
Leanol	Yoshitomi	Japan	1976
Bronalin	Byk Liprandi	Argentina	–
Gynipral	Chemie Linz	Austria	–
Ipradol	Chemie Linz	Austria	–
Prelin	Farmos	Finland	–

Raw Materials

Chloroaceto pyrocatechol
N,N'-Dibenzylhexamethylene diamine
Hydrogen

Manufacturing Process

The N,N'-dibenzyl-N,N'-bis-[2-(3',4'-dihydroxyphenyl)-2-oxoethyl] -hexamethylene-diamine-dichlorohydrate-monohydrate used as the starting material was prepared as follows: 2 mols of chloroaceto pyrocatechin were dissolved in 2,000 cc of acetone and heated to boiling with 2 mols of N,N'-dibenzylhexamethylene-diamine for 12 hours, almost the theoretical quantity of N,N'-dibenzylhexamethylene-diamine-dichlorohydrate being precipitated and removed by suction after cooling. Excess HCl was added to the filtrate, approximately 66% of the theoretically possible quantity of crude dichlorohydrate of the N,N'-dibenzyl-N,N'-bis-[2-(3',4'-dihydroxyphenyl)-2-oxoethyl] -hexamethylene-diamine being precipitated. The product was cleaned by recrystallization from water with the addition of animal charcoal. After drying the substance contained water of crystallization at ambient temperature, MP 206° to 209.5°C.

Five grams of N,N'-dibenzyl-N,N'-bis[2-(3',4'-dihydroxyphenyl)-2-oxoethyl] -hexamethylene-diamine-dichlorohydrate as a monohydrate were hydrogenated under considerable agitation by means of 2.0 grams of 10% palladium-carbon, with hydrogen in a mixture of 270 cc of methanol and 50 cc of water at 45°C and normal pressure. After about 4 hours the theoretical quantity of hydrogen (4 mols of hydrogen per 1 mol of substance) was absorbed for the splitting off of the two benzyl radicals and the reduction of the two carbonyl groups to carbinol groups, and the hydrogenation came to a stop.

After separation of the catalyst the product was concentrated until dry, the residue was triturated with acetone, the resulting crystallizate was removed by suction and washed with acetone. The yield of N,N'-bis-[2-(3',4'-dihydroxyphenyl)-2-hydroxyethyl] -hexamethylene-diamine-dichlorohydrate was 3.3 grams, i.e., 92% of the theoretical value. A quantity of 2.8 grams having a melting point of 197.5° to 198°C was obtained by precipitation from a mixture of methanol-ether.

Free N,N'-bis-[2-(3',4'-dihydroxyphenyl)-2-hydroxyethyl] -hexamethylene-diamine can be separated from these salts by the addition of the equivalent quantity of caustic alkali solution. It has a melting point of 162° to 165°C and contains half a mol of water of crystallization.

N,N'-bis-[2-(3',4'-dihydroxyphenyl)-2-hydroxyethyl] -hexamethylene-diamine-sulfate (MP

222° to 228°C) can be obtained by reacting the base with the equivalent quantity of sulfuric acid in an alcohol solution, followed by concentration and precipitation from water-alcohol solution.

References

Merck Index 4603
Kleeman & Engel p. 466
I.N. p. 488
Schmid, O., Lerchenthal, H.S.-M., Zolss, G., Gratz, R. and Wismayr, K.; U.S. Patent 3,329,709; July 4, 1967; assigned to Oesterreichische Stickstoffwerke AG, Austria

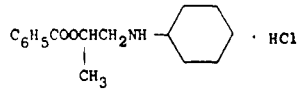
HEXYLCAINE HYDROCHLORIDE

Therapeutic Function: Local anesthetic

Chemical Name: 1-cyclohexylamino-2-propylbenzoate hydrochloride

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 532-76-3; 532-77-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Cyclaine	MSD	U.S.	1952

Raw Materials

1-Cyclohexylamino-2-propanol
Benzoyl chloride
Hydrogen chloride

Manufacturing Process

A solution of 0.1 mol of 1-cyclohexylamino-2-propanol in 30 grams of chloroform was saturated with dry hydrogen chloride gas, with cooling. A solution of 0.1 mol of benzoyl chloride in 30 grams of chloroform was added and the solution was heated in a bath at 50° to 55°C for four days under a reflux condenser protected from atmospheric moisture. Then the solvent was removed by vacuum distillation while the mixture was warmed on a water bath. Benzene was then added to the syrupy residue and the reaction product crystallized out after the benzene was removed by vacuum distillation.

The crystallized solid residue was washed with anhydrous ether to remove any unreacted benzoyl chloride. The 1-cyclohexylamino-2-propyl benzoate hydrochloride obtained was purified by two recrystallizations from absolute alcohol. It melted at 177° to 178.5°C.

References

Merck Index 4605
Kleeman & Engel p. 467
OCDS Vol. 1 p. 12 (1977)
I.N. p. 488
REM p. 1056
Cope, A.C.; U.S. Patent 2,486,374; November 1, 1949; assigned to Sharp & Dohme, Inc.

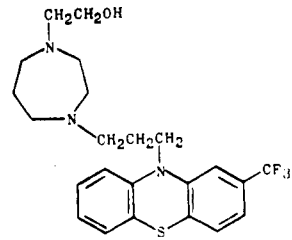
HOMOFENAZINE

Therapeutic Function: Tranquilizer

Chemical Name: Hexahydro-4-[3-[2-(trifluoromethyl)phenothiazin-10-yl] propyl] -1H-1,4-diazepine-1-ethanol

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 3833-99-6

Trade Name	Manufacturer	Country	Year Introduced
Pasaden	Homburg	Italy	1972
Oldagen	Purissimus	Argentina	–

Raw Materials

3-Trifluoromethyl-phenothiazine
3-Bromopropyl-homopiperazine
Sodium amide
2-Chloroethanol

Manufacturing Process

35 parts of 3-trifluoromethyl-phenothiazine in 200 parts of toluene were reacted with 6.1 parts soda amide and then with 28.8 parts of 3-bromopropyl-homopiperazine. After a 2 hour reaction period the reaction mixture was washed with water twice and then extracted with dilute HCl, the resulting extract alkalized with excess K_2CO_3 and the precipitated base taken up in ether. After drying the ether extract and evaporation of the ether, the residue was distilled. 20.3 parts of 3-trifluoromethyl-10-(3'-homopiperazino)-propyl-phenothiazine having a boiling point of 225° to 230°C at 1 mm Hg pressure were obtained.

20 parts of 3-trifluoromethyl-10-(3'-homopiperazino)-propyl-phenothiazine in 100 parts of butanol were refluxed for 4 hours together with 5.5 parts of 2-chloroethanol and 11 parts potassium carbonate. The reaction mixture was diluted with 200 parts of ether, then washed three times with water and dried with potassium carbonate. After evaporation of the solvent the residue was distilled under a vacuum of 1 mm Hg. 17.5 parts of 3-trifluoro methyl-10-[3'-(4"-(2"-hydroxyethyl)-homopiperazino)-propyl] -phenothiazine distilled over at 230° to 240°C. The difumarate of this base had a melting point of 148°C.

References

Merck Index 4633
Kleeman & Engel p. 468
I.N. p. 492
Schuler, W.A., Beschke, H. and von Schlichtergroll, A.; U.S. Patent 3,040,043; June 19, 1962; assigned to Deutsche Gold- und Silber-Scheideanstalt vormals Roessler, Germany

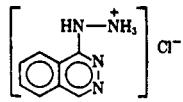
HYDRALAZINE HYDROCHLORIDE

Therapeutic Function: Antihypertensive

Chemical Name: 1(2H)-phthalazinone hydrazone hydrochloride

Common Name: 1-hydrazinophthalazine hydrochloride

Structural Formula:



Chemical Abstracts Registry No.: 304-20-1; 86-54-4 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Apresoline HCl	Ciba	U.S.	1952
Lopres	Tutag	U.S.	1971
Aiselazine	Hotta	Japan	–
Alphpress	Unipharm	Israel	–
Anaspasmin	Vitacain	Japan	–
Aprelazine	Kaigai	Japan	–
Apresazide	Ciba	U.S.	–
Aprezine	Kanto	Japan	–
Basedock D	Sawai	Japan	–
Deselazine	Kobayashi	Japan	–
Diucholin	Toyama	Japan	–
Dralzine	Lemmon	U.S.	–
Homoton	Horii	Japan	–
Hydrapres	Rubio	Spain	–
Hydrapress	Isei	Japan	–
Hydroserpine	Zenith	U.S.	–
Hypatol	Yamanouchi	Japan	–
Hyperazine	Seiko	Japan	–
Hypos	Nippon Shinyaku	Japan	–
Ipolina	Lafare	Italy	–
Lopress	Reid Provident	U.S.	–
Pressfall	Nissin	Japan	–
Prospectin	Maruishi	Japan	–
Ser-Ap-Es	Ciba	U.S.	–
Serpasil	Ciba	U.S.	–
Solesorin	Hishiyama	Japan	–
Supres	Protea	Australia	–
Tetrasoline	Maruko	Japan	–
Unipres	Reid-Rowell	U.S.	–

Raw Materials

Phthalazone
Hydrazine hydrate
Phosphorus oxychloride
Hydrogen chloride

Manufacturing Process

30 parts by weight of phthalazone are converted to 1-chlorophthalazine by the method described in *Ber. d. deutsch. chem. Ges.*, vol 26, page 521 (1893). The freshly obtained yet moist chloro compound is heated on the water bath for two hours in a mixture of 100 parts by volume of ethyl alcohol and 90 parts by volume of hydrazine hydrate. Preferably after filtering, 1-hydrazino-phthalazine crystallizes out in yellow needles on cooling.

It is filtered with suction and washed with cold ethyl alcohol. The compound is crystallized from methyl alcohol, and melts, when rapidly heated, at 172° to 173°C. On warming in alcoholic or aqueous hydrochloric acid, the hydrochloride of MP 273°C (with decomposition) is obtained.

References

Merck Index 4661
Kleeman & Engel p. 468
PDR pp. 789, 812, 830, 993, 1449, 1600, 1999
OCDS Vol. 1 p. 353 (1977)
I.N. p. 494
REM p. 847
Hartmann, M. and Druey, J.; U.S. Patent 2,484,029; October 11, 1949; assigned to Ciba Pharmaceutical Products, Inc.

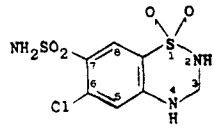
HYDROCHLOROTHIAZIDE

Therapeutic Function: Diuretic

Chemical Name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

Common Name: Chlorosulthiadil

Structural Formula:



Chemical Abstracts Registry No.: 58-93-5

Trade Name	Manufacturer	Country	Year Introduced
Hydrodiuril	MSD	U.S.	1959
Oretic	Abbott	U.S.	1959
Esidrix	Ciba	U.S.	1959
Esidrex	Ciba Geigy	France	1960
Thiuretic	Parke Davis	U.S.	1974
Lexxor	Lemmon	U.S.	1974
Aldactazide	Searle	U.S.	–
Aldoril	MSD	U.S.	–
Apresazide	Ciba	U.S.	–
Apresoline	Ciba	U.S.	–
Catiazida	Infale	Spain	–
Chemhydrazide	Chemo-Drug	Canada	–
Clothia	Iwaki	Japan	–
Chlorzide	Foy	U.S.	–
Deidran	Pharma.Farm.Spec.	Italy	–
Delco-Retic	Delco	U.S.	–
Dichlorosal	Teva	Israel	–
Dichlotride	Merck-Banyu	Japan	–
Didral	Caber	Italy	–
Dihydran	A.F.I.	Norway	–
Diidrotiazide	Omikron-Gagliardi	Italy	–
Direma	Distillers	U.K.	–

Trade Name	Manufacturer	Country	Year Introduced
Dithiazid	Arcana	Austria	–
Diuchlor H	Medic	Canada	–
Diurogen	Gentili	Italy	–
Diursana H	Santos	Spain	–
Dixidrasi	Vaillant	Italy	–
Dyazide	SKF	U.S.	–
Esoidrina	Bouty	Italy	–
Esimil	Ciba	U.S.	–
HHR	Schein	U.S.	–
Hidrosaluretil	Gayoso Wellcome	Spain	–
Hyclosid	Pharmacal	Finland	–
Hydoril	Cenci	U.S.	–
Hydrazide	Powell	Canada	–
Hydrex	Orion	Finland	–
Hydrite	Verdun	Canada	–
Hydro-D	Halsey	U.S.	–
Hydrodiuretex	Barlow Cote	Canada	–
Hydropres	MSD	U.S.	–
Hydroserpine	Schein	U.S.	–
Hydrozide	Elliott-Marion	Canada	–
Hytrid	Leiras	Finland	–
Idrodiuvis	Vis	Italy	–
Inderide	Ayerst	U.S.	–
Ivaugan	Voigt	W. Germany	–
Jen-Diril	Jenkins	U.S.	–
Lopressor	Geigy	U.S.	–
Loqua	Columbia	U.S.	–
Manuril	I.C.N.	Canada	–
Maschitt	Showa	Japan	–
Maxzide	Lederle	U.S.	–
Mikorten	Zensei	Japan	–
Moduretic	MSD	U.S.	–
Natrimax	Trianon	Canada	–
Nefrol	Riva	Canada	–
Neo-Codema	Neo	Canada	–
Neo-Flumen	Serono	Italy	–
Neo-Minzil	Valeas	Italy	–
Neo-Saluretic	Lafar	Italy	–
Newtolide	Towa	Japan	–
Novodiurex	Oti	Italy	–
Novohydrazide	Novopharm	Canada	–
Pantemon	Tatsumi	Japan	–
Ro-Hydrazide	Robinson	U.S.	–
Saldiuril	Bieffe	Italy	–
Ser-Ap-Es	Ciba	U.S.	–
Serpasil	Ciba	U.S.	–
Spironazide	Schein	U.S.	–
Tenzide	Metro Med	U.S.	–
Thiadril	Vangard	U.S.	–
Thiaretic	Blue Line	U.S.	–
Timolide	MSD	U.S.	–
Unazid	Pliva	Yugoslavia	–
Unipres	Reid-Rowell	U.S.	–
Urirex	Pharmador	S. Africa	–
Urodiazin	Apogepha	E. Germany	–
Urozide	I.C.N.	Canada	–
Zide	Reid Provident	U.S.	–

Raw Materials

5-Chloro-2,4-disulfamylaniline
Paraformaldehyde

Manufacturing Process

As described in U.S. Patent 3,163,645, a mixture of 2.9 grams of 5-chloro-2,4-disulfamyl aniline in 15 ml of anhydrous diethyleneglycol dimethyl ether, 0.5 ml of an ethyl acetate solution containing 109.5 grams of hydrogen chloride per 1,000 ml and 0.33 grams (0.011 mol) of paraformaldehyde is heated to 80° to 90°C and maintained at that temperature for 1 hour. The resulting mixture is cooled to room temperature and concentrated to one-third of its volume under reduced pressure, diluted with water, then allowed to crystallize. The product is filtered off and recrystallized from water, to yield the desired 6-chloro-7-sulfamyl-3,4-dihydro-2H-[1,2,4]-benzothiadiazine-1,1-dioxide, MP 266° to 268°C, yield 1.4 grams. By replacing paraformaldehyde by 0.84 gram of 1,1-dimethoxymethane and proceeding as above, the same compound is obtained.

As described in U.S. Patent 3,025,292, the desired product may be made by hydrogenation of chlorothiazide. Three grams of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (chlorothiazide) is suspended in 100 ml of methanol. Then 1.0 gram of a 5% ruthenium on charcoal catalyst is added, and the mixture is reduced at room temperature and at an initial hydrogen pressure of 39 psig. The theoretical amount of hydrogen to form the 3,4-dihydro derivative is absorbed after a period of about 10 hours.

The reduction mixture then is heated to boiling and filtered hot to remove the catalyst. The catalyst is washed with a little methanol and the combined filtrate is concentrated to a volume of about 25 ml by evaporation on a steam bath. Upon cooling to room temperature, white crystals separate which are filtered, washed with water, and dried in vacuo at room temperature over phosphorus pentoxide overnight. The weight of 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide obtained is 1.26 grams; MP 268.5° to 270°C. Dilution of the above filtrate with water to a volume of about 125 ml gives a second crop of product having the same melting point and weighing 1.22 grams, giving a combined yield of 83%. When the product is mixed with an authentic sample of 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide, prepared by another method, the melting point is not depressed.

References

Merck Index 4683
Kleeman & Engel p. 469
PDR pp. 546, 625, 789, 812, 896, 1014, 1137, 1184, 1201, 1211, 1449, 1606, 1674, 1713, 1999
OCDS Vol. 1 p. 358 (1977)
DOT 16 (4) 141 (1980), (8) 266 (1980), 17 (5) 213 (1981), 19 (3) 172 (1983) and 19 (9) 496 (1983)
I.N. p. 495
REM p. 939
Jones, W.H. and Novello, F.C.; U.S. Patent 3,025,292; March 13, 1962; assigned to Merck & Co., Inc.
Downing, G.V., Jr.; U.S. Patent 3,043,840; July 10, 1962; assigned to Merck & Co., Inc.
de Stevens, G. and Werner, L.H.; U.S. Patent 3,163,645; December 29, 1964; assigned to Ciba Corporation
Irons, J.S. and Cook, T.M.; U.S. Patent 3,164,588; January 5, 1965; assigned to Merck & Co., Inc.

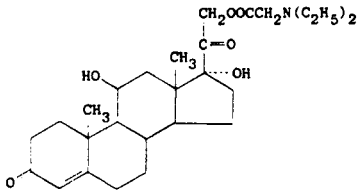
HYDROCORTAMATE HCl

Therapeutic Function: Adrenocortical steroid

Chemical Name: Cortisol 21-ester with N,N-diethylglycine

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 76-47-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Magnacort	Pfizer	U.S.	1956
Etacort	Angelini	Italy	–

Raw Materials

Hydrocortisone
Chloroacetic anhydride
Diethylamine

Manufacturing Process

1 g of hydrocortisone is introduced with stirring into 5 cc of anhydrous pyridine. After heating to 45°C and then cooling again to 0°C to 5°C there is slowly added dropwise a freshly prepared solution of 0.52 g (1 mol + 10%) of chloracetic anhydride in 4 cc of absolute ether. The reaction temperature should not exceed 10°C. During the whole time of reaction a stream of nitrogen is passed through the reaction mixture in order to achieve an exhaustive evaporation of the added ether. The batch is slowly allowed to come to room temperature, an operation requiring 4 to 5 hours, and then 0.1 cc of water is added for decomposition of the excess of anhydride. The reaction solution is introduced dropwise with stirring within 1 hour into 100 cc of water as a result of which the 21-chloracetate of hydrocortisone is deposited. After filtration with suction, washing is carried out with water, 5% hydrochloric acid, water, 2% sodium bicarbonate solution and water again. The substance is then dried in a vacuum desiccator. The white chloracetate thus obtained melts at 213°C to 214°C with decomposition. It is free from nitrogen and the yield amounts to 93.4% of the theoretical.

1 g of hydrocortisone-21-chloracetate is dissolved in 15 cc of anhydrous and peroxide-free tetrahydrofuran. The solution produced is treated with a solution of 0.42 g of diethylamine in 15 cc of tetrahydrofuran. The reaction mixture is allowed to stand for 24 hours at room temperature. The separated diethylamine hydrochloride is filtered with suction and the filtrate evaporated under vacuum in a nitrogen atmosphere at 40°C. The residue is triturated with a little absolute ether and suction filtered. It is washed on the filter with a little ether and then with hexane. The 21-diethylaminoacetate of hydrocortisone melts at 150°C to 162°C. The base can be recrystallized from ethyl acetate but its melting point remains practically unchanged at 162°C to 163°C. The yield amounts to 72.5% of the theoretical. For conversion of the base into the hydrochloride it is suspended in ether and the suspension treated with ethereal hydrochloric acid. The hydrochloride is filtered with suction and recrystallized from ethanol; MP 222°C with decomposition.

With a starting quantity of 14 g, the yield amounted to 85.4% of the theoretical.

References

Merck Index 4688

I.N. p. 497
Schering A.G.; British Patent 879,208; October 4, 1961

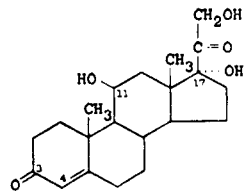
HYDROCORTISONE

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17,21-trihydroxypregn-4-ene-3,20-dione

Common Name: 17-hydroxycorticosterone

Structural Formula:



Chemical Abstracts Registry No.: 50-23-7

Trade Name	Manufacturer	Country	Year Introduced
Hydrocortone	MSD	U.S.	1952
Cortef	Upjohn	U.S.	1953
Cortril	Pfizer	U.S.	1954
Cortifan	Schering	U.S.	1954
Otosone-F	Broemmel	U.S.	1955
Cortispray	National	U.S.	1956
Domolene-HC	Dome	U.S.	1960
Texacort	Texas Pharm	U.S.	1960
Cortenema	Rowell	U.S.	1966
Lubricort	Texas Pharm	U.S.	1968
Proctocort	Rowell	U.S.	1969
Hautosone	Merrell National	U.S.	1970
Dermacort	Rowell	U.S.	1972
Rectoid	Pharmacia	U.S.	1977
Alphaderm	Norwich Eaton	U.S.	1978
H-Cort	Pharm. Assoc.	U.S.	1979
Dermolate	Schering	U.S.	1979
Clear-Aid	Squibb	U.S.	1980
Hycort	Elder	U.S.	1981
Prep-Cort	Whitehall	U.S.	1981
Corizone-5	Thompson	U.S.	1982
Flexicort	Westwood	U.S.	1982
Aeroseb	Allergan	U.S.	–
Ala-Cort	Del Ray	U.S.	–
Algicortis	Vaillant	Italy	–
Allersone	Mallard	U.S.	–
Alphacortison	Norwich-Eaton	U.S.	–
Alphaderm	Norwich	U.S.	–
Balneol-HC	Rowell	U.S.	–
Barseb -HC	Barnes-Hind	U.S.	–
Bio-Cortex	Ries	U.S.	–

Trade Name	Manufacturer	Country	Year Introduced
Carmol HC	Syntex	U.S.	–
Cleiton	Kodama	Japan	–
Cobadex	Cox	U.K.	–
Cortanal	Canada Pharmacal	Canada	–
Cort-Dome	Dome	U.S.	–
Cortes	Taisho	Japan	–
Cortesal	Pharmacia	Sweden	–
Corticaine	Glaxo	U.S.	–
Cortifair	Pharmafair	U.S.	–
Cortiment	Ferring	Sweden	–
Cortiphate	Travenol	U.S.	–
Cortisporin	Burroughs Wellcome	U.S.	–
Cortolotion	Kempthorne-Prosser	N.Z.	–
Cortril	Pfizer	U.S.	–
Cremesone	Dalin	U.S.	–
Di-Hydrotic	Legere	U.S.	–
Dioderm	Dermal	U.K.	–
Durel-Cort	Durel	U.S.	–
Ecosone	Star	U.S.	–
Efcortelan	Glaxo	U.K.	–
Egocort	Ego	Australia	–
Excerate	Foji Zoki	Japan	–
FEP	Boots	U.S.	–
Gyno-Cortisone	Lyocentre	France	–
HC-Cream	C&M Pharmacal	U.S.	–
Heb-Cort	Barnes-Hind	U.S.	–
Hidroaltesona	Alter	Spain	–
Hycor	Sigma	Australia	–
Hycort	Douglas	U.S.	–
Hycortole	Premo	U.S.	–
Hydrocort	Ferring	W. Germany	–
Hydrocortex	Kenyon	U.S.	–
Hydrofoam	U.S.V.	U.S.	–
Hydrotisona	Roussel-Lutetia	Argentina	–
Hytone	Dermik	U.S.	–
Idracemi	Farmigea	Italy	–
Lexocort	Lexington	U.S.	–
Microcort	Alto	U.S.	–
Milliderm	A.L.	Norway	–
Octicair	Pharmafair	U.S.	–
Optef	Upjohn	–	–
Otic-HC	Hauck	U.S.	–
Otobiotic	Schering	U.S.	–
Otocort	Lemmon	U.S.	–
Pedicort	Pedinol	U.S.	–
Penecort	Herbert	U.S.	–
Pyocidin	Berlex	U.S.	–
Rectocort	Welcker-Lyster	Canada	–
Rectoid	Pharmacia	Sweden	–
Sigmacort	Sigma	Australia	–
Signef	Fellows-Testagar	U.S.	–
Sterocort	Omega	Canada	–
Synacort	Syntex	U.S.	–
Tega-Cort	Ortega	U.S.	–
Vanoxide	Dermik	U.S.	–
Vioform	Ciba	U.S.	–
Viosol	Wallace	U.S.	–
Vytone	Dermik	U.S.	–

Raw Materials

Bacterium *Cunninghamella blakesleeana*
11-Desoxy-17-hydroxycorticosterone

Manufacturing Process

The following example from U.S. Patent 2,602,769 illustrates the preparation of 17-hydroxycorticosterone (compound F) from 11-desoxy-17-hydroxycorticosterone (compound S). A medium was prepared from 0.5% peptone, 2% dextrose, 0.5% soybean meal, 0.5% KH_2PO_4, 0.5% sodium chloride and 0.3% yeast extract in tap water. To 200 ml of this sterilized medium was added an inoculum of the vegetative mycella of *Cunninghamella blakesleeana*. The spores had first been transferred from a sport slant to a broth medium and the broth medium was aerobically incubated at 24°C for 24 to 72 hours in a reciprocating shaker until the development of vegetative growth. The inoculated medium containing added vegetative mycella of *Cunninghamella blakesleeana* was incubated for 48 hours at 24°C following which was added 66 mg of compound S, 11-desoxy-17-hydroxycorticosterone in solution in a minimum of ethanol, and incubation was maintained for 7 hours at 24°C. The beer containing steroid was diluted with 800 ml of acetone, shaken 1 hour on a reciprocating shaker and filtered. The cake was suspended in 500 ml of acetone, shaken another hour and again filtered. The filtrates were combined and the acetone was volatilized under reduced pressure at 50°C. Acetone was then added, if necessary, to bring the concentration to 20% acetone and this resulting aqueous acetone solution was extracted five times each with one-third volume of Skellysolve B petroleum ether to remove fatty materials. These extracts were back washed two times with one-tenth volume of 20% aqueous acetone and the washings were added to the main acetone extract.

The combined acetone extracts were extracted six times with one-fourth volume of ethylene dichloride and the ethylene dichloride extract was evaporated under vacuum to leave the steroid residue. This steroid residue was taken up in a minimum of methylene chloride and applied to the top of a column packed with 30 grams of silica which had been previously triturated with 21 ml of ethylene glycol. Then various developing mixtures, saturated with ethylene glycol, were passed over the column. Cuts were made as each steroid was eluted as determined by the lowering of the absorption of light at 240 mμ on the automatic chromatographic fraction cutter.

Band	Solvent	Tube No. (60 ml)	Crude Solids (mg)
1	Cyclohexane	1-4	11
2	Cyclohexane-methylene chloride 3:1	5-13	6.4 compound S
3	Cyclohexane-methylene chloride 1:1	14-16	3.0
4	Cyclohexane-methylene chloride 2:3	17-23	6.0 compound E
5	Cyclohexane-methylene chloride 1:4	24-38	12.2 compound F
6	Methylene chloride	39-59	4.8

A 7.7 mg portion of band 5 was taken up in a minimum of acetone and refrigerated until crystals separated. This cold acetone mixture was centrifuged and the supernatant liquid removed by pipette. To the remaining crystals, a few drops of ice-cold ether-acetone, three to one mixture, were added, shaken, recentrifuged and the supernatant wash liquid removed by pipette. The ether-acetone wash was repeated. The resulting crystals were dried under vacuum yielding 3.3 mg of pure compound F, 17-hydroxycorticosterone.

References

Merck Index 4689
Kleeman & Engel p. 470

PDR pp. 671, 684, 739, 821, 833, 908, 928, 933, 1033, 1073, 1250, 1397, 1404, 1429, 1446, 1576, 1645, 1800, 1886
OCDS Vol. 1 p. 190 (1977)
DOT 12 (9) 343 (1976)
I.N. p. 497
REM p. 967
Murray, H.C. and Peterson, D.H.; U.S. Patent 2,602,769; July 8, 1952; assigned to The Upjohn Company
Murray, H.C. and Peterson, D.H.; U.S. Patent 2,649,400; August 18, 1953; assigned to The Upjohn Company
Murray, H.C. and Peterson, D.H.; U.S. Patent 2,649,402; August 18, 1953; assigned to The Upjohn Company
Mann, K.M., Drake, H.A. and Rayman, D.E.; U.S. Patent 2,794,816; June 4, 1957; assigned to The Upjohn Company

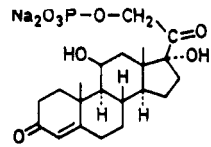
HYDROCORTISONE SODIUM PHOSPHATE

Therapeutic Function: Glucocorticoid

Chemical Name: 11β,17-Dihydroxy-21-(phosphonoxy)pregn-4-ene-3,20-dione disodium salt

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 6000-74-4; 3863-59-0 (Phosphate base)

Trade Name	Manufacturer	Country	Year Introduced
Corphos	Tilden Yates	U.S.	1959
Hydrocortone Phosphate	MSD	U.S.	1960
Cortiphate	Travenol	U.S.	1962
Ocu-Cort	Dome	U.S.	1963
Actocortin	Cooper	W. Germany	–
Efcortesol	Glaxo	U.K.	–
Flebocortid	Richter	Italy	–
Gleiton	Sankyo Zoki	Japan	–

Raw Materials

21-Iodo-11β:17α-dihydroxypregn-4-ene-3,20-dione
Phosphoric acid
Sodium hydroxide

Manufacturing Process

21-iodo-11β:11α-dihydroxypregn-4-ene-3:20-dione (5.0 g) in pure acetonitrile (125 ml) was mixed with a solution of 90% phosphoric acid (2.5 ml) and triethylamine (7.5 ml) in acetonitrile (125 ml) and boiled under reflux for 4 hours. The solvent was removed in vacuo and the residue, dissolved in ethanol (20 ml) and water (80 ml), was passed down a column of Zeo-Karb 225 (H^+ form) (60 g) made up in 20% alcohol. Elution was continued with 20%

alcohol (50 ml), 50% alcohol (50 ml) and alcohol (150 ml). The eluate was at first cloudy, but by the end of the elution it was clear and nonacid.

The eluate was titrated to pH 7 with 0.972 N NaOH (63 ml). Removal of solvent left a gum, which was boiled with methanol (400 ml) for 20 minutes. The solid insoluble inorganic phosphate was filtered off and washed with methanol (200 ml). The slightly cloudy filtrate was filtered again, and evaporated to dryness in vacuo. The residual gum dissolved readily in water (40 ml) and on addition of acetone (600 ml) to the solution a mixture of sodium salts of hydrocortisone 21-phosphate separated as a white solid. This was collected after 2 days, washed with acetone and dried at 100°C/0.1 mm/2 hr to constant weight. Yield 4.45 g.

References

Merck Index 4691
Kleeman & Engel p. 473
I.N. p. 498
REM p. 968
Elks, J. and Phillips, G.H.; U.S. Patent 2,936,313; May 10, 1960; assigned to Glaxo Laboratories, Ltd. (U.K.)

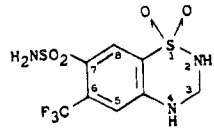
HYDROFLUMETHIAZIDE

Therapeutic Function: Diuretic, antihypertensive

Chemical Name: 3,4-dihydro-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 135-09-1

Trade Name	Manufacturer	Country	Year Introduced
Saluron	Bristol	U.S.	1959
Leodrine	Leo	France	1960
Diucardin	Ayerst	U.S.	1974
Di-Ademil	Squibb-Showa	Japan	—
Enjit	Meiji	Japan	—
Fluorodiuvis	Vis	Italy	—
Hydrenox	Boots	U.K.	—
Leodrine	Leo	France	—
Naclex	Glaxo	U.K.	—
Olmagran	Heyden	W. Germany	—
Plurine	Leo	France	—
Rivosil	Benvegna	Italy	—
Robezon	Mitsui	Japan	—
Rontyl	Leo-Sankyo	Japan	—
Vergonil	Ferrosan	Denmark	—

Raw Materials

α,α,α-Trifluoro-m-toluidine
Chlorosulfonic acid
Ammonia
Paraformaldehyde

Manufacturing Process

(a) Preparation of 5-Trifluoromethylaniline-2,4-Disulfonyl Chloride: 113 ml of chlorosulfonic acid was cooled in an ice-bath, and to the acid was added dropwise while stirring 26.6 grams of α,α,α-trifluoro-m-toluidine. 105 grams of sodium chloride was added during 1 to 2 hours, whereafter the temperature of the reaction mixture was raised slowly to 150° to 160°C, which temperature was maintained for 3 hours. After cooling the mixture, ice-cooled water was added, whereby 5-trifluoromethylaniline-2,4-disulfonyl chloride separated out from the mixture.

(b) Preparation of 5-Trifluoromethyl-2,4-Disulfamylaniline: The 5-trifluoromethylaniline-2,4-disulfonyl chloride obtained in step (a) was taken up in ether and the ether solution dried with magnesium sulfate. The ether was removed from the solution by distillation, the residue was cooled to 0°C and 60 ml of ice-cooled, concentrated ammonia water was added while stirring. The solution was then heated for one hour on a steam bath and evaporated in vacuo to crystallization. The crystallized product was 5-trifluoromethyl-2,4-disulfamylaniline, which was filtered off, washed with water and dried in a vacuum exsiccator over phosphorus pentoxide. After recrystallization from a mixture of 30% ethanol and 70% water the compound had a MP of 247° to 248°C.

(c) Preparation of 6-Trifluoromethyl-7-Sulfamyl-3,4-Dihydro-1,2,4-Benzothiadiazine-1,1-Dioxide: 3.2 grams of 5-trifluoromethyl-2,4-disulfamylaniline was added to a solution of 0.33 gram of paraformaldehyde in 25 ml of methyl Cellosolve (2-methoxy ethanol) together with a catalytic amount of p-toluenesulfonic acid, and the mixture was boiled with reflux for 5 hours. The solvent was then distilled off in vacuo, and the residue triturated with 30 ml of ethyl acetate. 6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide crystallized out. After recrystallization from methanol/water the substance had a MP of 272° to 273°C.

References

Merck Index 4695
Kleeman & Engel p. 474
PDR pp. 617, 709, 1606, 1999
OCDS Vol. 1 p. 358 (1977)
I.N. p. 499
REM p. 939
Lund, F., Lyngby, K. and Godtfredsen, W.O.; U.S. Patent 3,254,076; May 31, 1966; assigned to Løvens Kemiske Fabrik Ved A. Kongsted, Denmark

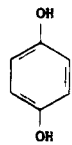
HYDROQUINONE

Therapeutic Function: Depigmentor

Chemical Name: 1,4-Benzenediol

Common Name: Quinol

Structural Formula:



Chemical Abstracts Registry No.: 123-31-9

Trade Name	Manufacturer	Country	Year Introduced
Quinnone	Dermohr	U.S.	1980
Melanek	Neutrogena	U.S.	1981
Black & White	Plough	U.S.	–
Eldopaque	Elder	U.S.	–
Eldoquin	Elder	U.S.	–
Phiaquin	Phial	Australia	–
Phiaquin	Robins	U.S.	–
Solaquin	Elder	U.S.	–

Raw Materials

Acetylene
Methanol

Manufacturing Process

Into a pressure reactor there was charged 100 ml of methanol and 1 g of diruthenium nonacarbonyl. The reactor was closed, cooled in solid carbon dioxide/acetone, and evacuated. Acetylene, to the extent of 1 mol (26 g), was metered into the cold reactor. Carbon monoxide was then pressured into this vessel at 835-980 atmospheres, during a period of 16.5 hours; while the reactor was maintained at 100°C to 150°C. The reactor was then cooled to room temperature and opened.

The reaction mixture was removed from the vessel and distilled at a pressure of 30-60 mm, and a bath temperature of 30°C to 50°C until the methanol had all been removed. The extremely viscous tarry residue remaining in the still pot was given a very crude distillation, the distillate boiling at 82°C to 132°C/2 mm. In an attempt to purify this distillate by a more careful distillation, 5.3 g of a liquid distilling from 53°C to 150°C/5 mm was collected. At this point, much solid sublimate was noted not only in this distillate but in the condenser of the still. 7 g of the solid sublimate was scraped out of the condenser of the still. Recrystallization of the sublimate from ethyl acetate containing a small amount of petroleum ether gave beautiful crystals melting at 175°C to 177°C (5 g). Infrared analysis confirmed that this compound was hydroquinone (9% conversion).

References

Merck Index 4719
PDR pp. 865, 1268
I.N. p. 499
REM p. 788
Howk, B.W. and Sauer, J.C.; U.S. Patent 3,055,949; September 25, 1962; assigned to E.I. du Pont de Nemours & Co.

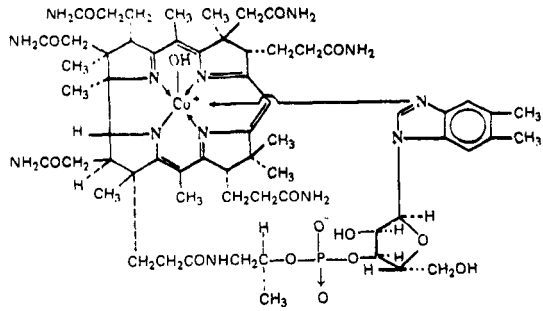
HYDROXOCOBALAMIN

Therapeutic Function: Hematopoietic vitamin

Chemical Name: Cobinamide hydroxide phosphate 3'-ester with 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole inner salt

Common Name: Vitamin B_{12a}

Structural Formula:



Chemical Abstracts Registry No.: 13422-51-0

Trade Name	Manufacturer	Country	Year Introduced
Alpha-Redisol	MSD	U.S.	1962
Ducobee-Hy	Breon	U.S.	1962
Rubramin-OH	Squibb	U.S.	1963
Hycobal-12	Canfield	U.S.	1964
Hydroxo B-12	Philips Roxane	U.S.	1964
Neo-Vi-Twel	SMP	U.S.	1964
Neo-Betalin 12	Lilly	U.S.	1964
Sustwelve	Ascher	U.S.	1964
Rubesol-LA	Central	U.S.	1965
Sytobex-X	Parke Davis	U.S.	1966
Acimexan	Cimex	Switz.	–
Anemisol	Tobishi	Japan	–
Aquo-B	Nippon Zoki	Japan	–
Aquo-Cytobion	Merck	W. Germany	–
Axlon	Albert-Roussel	W. Germany	–
Behepan	Kabi Vitrum	Sweden	–
Berubi	Redel	W. Germany	–
Bistin	Yamanouchi	Japan	–
Bradiruba	Ibirn	Italy	–
Cobalidrina	Italsuisse	Italy	–
Cobalamin H	Otsuka	Japan	–
Cobalvit	Tosi-Novara	Italy	–
Colsamine	Kanyo	Japan	–
Docevita	Boizot	Spain	–
Dolevern	Seiko	Japan	–
Erycytol	Sanabo	Austria	–
Fravit B-12	Francia	Italy	–
Fresmin S	Takeda	Japan	–
Funacomin-F	Funai	Japan	–
Hicobala	Mitaka	Japan	–
Hicobalan	Maruko	Japan	–
Hydocobamin	Hishiyama	Japan	–
Hydocomin	Sanwa	Japan	–
Hydroxo 5000	Heptatrol	France	–
Hydroxomin	Tokyo Hosei	Japan	–
Idoxo B12	Ferrosan	Denmark	–
Idro-Apavit	Locatelli	Italy	–
Idrobamina	Tiber	Italy	–
Idrocobalmin	Panther-Osfa	Italy	–
Idrospes B12	Ausonia	Italy	–
Idrozima	Labif	Italy	–

Trade Name	Manufacturer	Country	Year Introduced
Laseramin	Choseido	Japan	–
Longicobal	Farber-R.E.F.	Italy	–
Masblon H	Fuso	Japan	–
Natur B12	Panthox & Burck	Italy	–
Nichicoba	Nichiiko	Japan	–
Novobedouze	Bouchara	France	–
OH-B1Z	Morishita	Japan	–
Oxobemin	Vitrum	Sweden	–
Rasedon	Sawai	Japan	–
Red	Neopharmed	Italy	–
Red-B	Kowa	Japan	–
Redisol H	Merck-Banyu	Japan	–
Rossobivit	Medici	Italy	–
Rubitard B12	Proter	Italy	–
Runova	Squibb-Sankyo	Japan	–
Solco H	Tobishi	Japan	–
Tsuerumin S	Mohan	Japan	–
Twelvmin	Mohan	Japan	–
Vigolatin	Kowa	Japan	–

Raw Materials

Vitamin B_{12} (cyanocobalamin)
Hydrogen

Manufacturing Process

A solution containing 26.3 mg of vitamin B_{12} in 15 ml of water was shaken with 78 mg of platinum oxide catalyst and hydrogen gas under substantially atmospheric pressure at 25°C for 20 hours. Hydrogen was absorbed. During the absorption of hydrogen the color of the solution changed from red to brown. The solution was separated from the catalyst and evaporated to dryness in vacuo. The residue was then dissolved in 1 ml of water and then diluted with about 6 ml of acetone.

After standing for several hours a small amount of precipitate (about 2 to 3 mg) was formed and was then separated from the solution. This solution was diluted with an additional 2 ml of acetone and again allowed to stand for several hours. During this time about 4 to 5 mg of noncrystalline precipitate formed. This solid was separated from the solution and an additional 2 ml of acetone was added to the solution. On standing, vitamin B_{12a} began to crystallize in the form of red needles. After standing for 24 hours, the crystalline material was separated, yield 12 mg. By further dilution of the mother liquor with acetone additional crystalline precipitate formed (from U.S. Patent 2,738,302).

References

Merck Index 4720
Kleeman & Engel p. 475
I.N. p. 500
REM pp. 1020, 1023
Kaczka, E.A., Wolf, D.E. and Folkers, K.; U.S. Patent 2,738,301; March 13, 1956; assigned to Merck & Co., Inc.
Kaczka, E.A., Wolf, D.E. and Folkers, K.; U.S. Patent 2,738,302; March 13, 1956; assigned to Merck & Co., Inc.

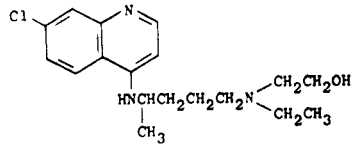
HYDROXYCHLOROQUINE SULFATE

Therapeutic Function: *Antimalarial*

Chemical Name: 2-[[4-[(7-chloro-4-quinolinyl)amino] pentyl] ethylamino] ethanol sulfate

Common Name: –

Structural Formula:



(base)

Chemical Abstracts Registry No.: 747-36-4; 118-42-3 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Plaquenil	Winthrop	U.S.	1956
Plaquenil	Winthrop	France	1960
Ercoquin	Erco	Denmark	–
Eroquin	Shionogi	Japan	–
Oxiklorin	Orion	Finland	–
Quensyl	Winthrop	W. Germany	–
Rhyumapirine S	Nichiiko	Japan	–
Toremonil	Iwaki	Japan	–

Raw Materials

1-Chloro-4-pentanone
N-Ethyl-N-2-hydroxyethylamine
4,7-Dichloroquinoline
Sulfuric acid
Ammonia
Hydrogen
Phosphoric acid

Manufacturing Process

A mixture of 323 grams of 1-chloro-4-pentanone, 480 grams of N-ethyl-N-2-hydroxyethylamine and 400 grams of sodium chloride (to aid in subsequent filtration) in 1.3 liters of xylene was heated with stirring on a steam bath for two hours and then refluxed for three hours. After standing overnight, the mixture was filtered and the filter cake washed with xylene. The filtrate was fractionally distilled, yielding 207.3 grams of a fraction distilling at 89° to 90°C at 0.35 mm; n_D^{25} = 1.4600. This fraction, 1-(N-ethyl-N-2-hydroxyethylamino)-4-pentanone, was used in the next step of the synthesis. A sample of the fraction was further purified by distillation through a column and gave an analytically pure sample of 1-(N-ethyl-N-2-hydroxyethylamino)-4-pentanone, boiling at 85° to 87°C at 0.4 mm.

The 1-(N-ethyl-N-2-hydroxyethylamino)-4-pentanone from above (284.2 grams) was dissolved in 300 grams of 28% ammoniacal methanol and reduced catalytically with Raney nickel (at an initial pressure of 1,000 pounds) at room temperature. After 24 hours the catalyst was filtered off and the product distilled in vacuo through a column, yielding 254 grams of a fraction distilling at 88.5° to 96°C at 0.3 mm and comprising mainly 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine. An analytical sample of this fraction distilled at 93°C at 0.6 mm.

A mixture of 90 grams of 4,7-dichloroquinoline, 90 grams of phenol, 1 gram of potassium iodide and 132 grams of 5-(N-ethyl-N-2-hydroxyethylamino)-2-pentylamine from above was heated with stirring for 13 hours at 125° to 130°C. Methanol (1.9 liters) was added and the the mixture was filtered with charcoal. The filtrate was treated with 270 cc of a solution of 100 grams of phosphoric acid in 300 cc of methanol. The walls of the flask containing the filtrate were scratched with a glass rod and the mixture was allowed to stand for two days. The solid was filtered off, washed with methanol and dried, yielding 101 grams of crude 7-chloro-4-[5-(N-ethyl-N-2-hydroxyethylamino)-2-pentyl] aminoquinoline diphosphate, MP 155° to 156°C.

Additional quinoline diphosphate was obtained as a gummy mass from the filtrate by concentrating the latter to about half its volume and adding acetone. The crude gummy diphosphate was dissolved in water, basified with ammonium hydroxide and the resulting liberated basic quinoline extracted with chloroform. After removal of the chloroform by distillation, the residue was dissolved in ether and crystallization was induced by scratching the walls of the flask with the glass rod. About 30 grams of the crude quinoline base, melting at 77° to 82°C, separated. Recrystallization of this material from ethylene dichloride or ethyl acetate yielded the purified 7-chloro-4-[5-(N-ethyl-N-2-hydroxyethylamino)-2-pentyl] aminoquinoline, MP 89° to 91°C.

The base may then be dissolved in ethanol and precipitated as the sulfate by reaction with an equimolar quantity of sulfuric acid.

References

Merck Index 4729
Kleeman & Engel p. 476
PDR p. 1926
OCDS Vol. 1 p. 342 (1977)
I.N. p. 502
REM p. 1220
Surrey, A.R.; U.S. Patent 2,546,658; March 27, 1951; assigned to Sterling Drug Inc.

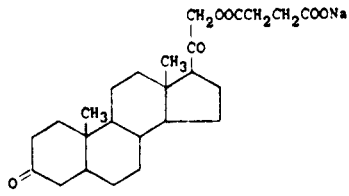
HYDROXYDIONE SODIUM SUCCINATE

Therapeutic Function: General anesthetic

Chemical Name: 21-(3-Carboxy-1-oxopropoxy)-5β-pregnane-3,20-dione sodium salt

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 53-10-1

Trade Name	Manufacturer	Country	Year Introduced
Viadril	Pfizer	U.S.	1957
Predion	V.N.I.Kh.F.I.	USSR	–

Raw Materials

Desoxycorticosterone
Hydrogen
Succinic anhydride

Manufacturing Process

A solution of 20 g of desoxycorticosterone in 190 ml of absolute ethanol was stirred in an atmosphere of hydrogen in the presence of 1.68 g of 25% palladium on calcium carbonate

catalyst. After 20 hours, approximately 1 molar equivalent of hydrogen had been absorbed and hydrogen uptake had ceased. The catalyst was removed by filtration and the filtrate evaporated in vacuo to yield 20 g of nearly pure product, MP 135°C to 140°C. The crude product was demonstrated to be free of starting material by paper chromatography. A highly purified product was obtained by recrystallization from acetone-water with cooling in an ice bath, yield 14.5 g, MP 152°C to 154°C. The product was characterized by analysis and by absence of ultraviolet absorption.

A solution of 14 g of 21-hydroxypregnane-3,20-dione and of 14 g of recrystallized succinic anhydride in 140 ml of dry pyridine was allowed to stand at room temperature for 18 hours, then cooled in an ice bath and poured in a fine stream into 1.5 liters of ice water. Excess pyridine was neutralized with 3 N hydrochloric acid and the solution further diluted with 2 liters of ice water. The precipitated product was filtered, washed with water and dried in vacuo at 50°C affording 18 g of solid MP 192°C to 195°C. Recrystallization of a small sample afforded analytically pure material, MP 200°C.

References

Merck Index 4734
I.N. p. 502
Laubach, G.D.; U.S. Patent 2,708,651; May 17, 1955; assigned to Chas. Pfizer & Co., Inc.

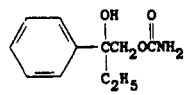
HYDROXYPHENAMATE

Therapeutic Function: Minor tranquilizer

Chemical Name: 2-Phenyl-1,2-butanediol-1-carbamate

Common Name: Oxyfenamate

Structural Formula:



Chemical Abstracts Registry No.; 50-19-1

Trade Name	Manufacturer	Country	Year Introduced
Listica	Armour	U.S.	1961
Listica	Armour Montagu	France	1975

Raw Materials

2-Phenyl-1,2-butanediol
Ethyl chloroformate
Ammonia

Manufacturing Process

2-Phenyl-2-hydroxy-butyl carbamate was prepared by the following method:

49.81 g of 2-phenyl-1,2-butanediol and 25.01 g of pyridine were dissolved in 500 ml of benzene and cooled to 5°C. 34.01 g of ethyl chloroformate was added over a period of ¾ hour at 4°C to 8°C. The reaction mixture was warmed to room temperature and stirred for 2 hours and then extracted with 100 cc each of the following:

Water, 15% hydrochloric acid, 10% sodium bicarbonate and finally water. The solvent was stripped off. The residual oil was mixed with 300 ml of 28% aqueous ammonia for 1 hour. The ammonia and water were vacuum distilled at a temperature of 40°C or less. Then 300 cc of carbon tetrachloride was added and the solution dried with sodium sulfate. The solution was cooled at 0°C and then filtered. The crystals were washed with cold carbon tetrachloride and vacuum dried. The yield was 57 g of dried product having a melting point of 55°C to 56.5°C.

References

Merck Index 4756
OCDS Vol. 1 p. 220 (1977)
I.N. p. 718
Sifferd, R.H. and Braitberg, L.D.; U.S. Patent 3,066,164; November 27, 1962; assigned to Armour Pharmaceutical

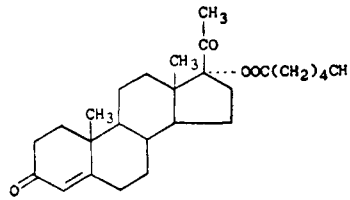
HYDROXYPROGESTERONE CAPROATE

Therapeutic Function: Progestin

Chemical Name: 17-[(1-oxohexyl)oxy] pregn-4-ene-3,20-dione

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 630-56-8

Trade Name	Manufacturer	Country	Year Introduced
Delalutin	Squibb	U.S.	1956
Hyproval	Tutag	U.S.	1976
Corluton Depot	I.E. Kimya Evi	Turkey	—
Caprogen Depot	Kanto	Japan	—
Depolut	Taro	Israel	—
Depot-Progen	Hokoriku	Japan	—
Hormofort	Kobanyai	Hungary	—
Idrogestene	Farmila	Italy	—
Kaprogest	Polfa	Poland	—
Lutopron	Cipla	India	—
Pergestron	Dexter	Spain	—
Primolut-Depot	Schering	U.K.	—
Prodox	Legere	U.S.	—
Proge	Mochida	Japan	—
Progestron-Depo	Galenika	Yugoslavia	—

Raw Materials

17α-Oxypregnene-(5)-ol-(3)-one-(20)-acetate-(3)

Caproic acid anhydride
Hydrogen chloride
Cyclohexanone

Manufacturing Process

40 grams of 17α-oxypregnene-(5)-ol-(3)-one-(20)-acetate-(3) is brought to reaction with 22 grams of p-toluol sulfonic acid and 850 cc of caproic acid anhydride under a nitrogen atmosphere for 5 days at room temperature or 2½ days at 37°C. The excess anhydride is blown off with steam in the presence of 200 cc of pyridine and the distillation residue is extracted with ether and worked up as usual. The remaining oil is brought to crystallization with pentane and the raw 17α-oxypregnenolone-3-acetate-17-caproate is recrystallized from methanol. The crystals are needle-like and have a MP of 104° to 105°C. This substance is partially saponified by refluxing for 1 hour in 1,800 cc of methanol in the presence of 13 cc of concentrated hydrochloric acid. After evaporation of the methanol under vacuum, the dry residue is recrystallized from isopropyl ether or methanol (dense needles). The thus obtained 17α-oxypregnenolone-17-caproate melts at 145° to 146.5°C.

By oxidation in 100 cc of absolute toluol with 425 cc of cyclohexanone and 155 cc of a 20% aluminum isopropylate solution in absolute toluol and after repeated crystallizations from isopropyl ether or methanol, 24 grams of pure 17α-oxyprogesterone-17-caproate is obtained, MP 119° to 121°C (dense needles).

References

Merck Index 4761
Kleeman & Engel 479
PDR p. 1033
OCDS Vol. 1 pp. 176, 190 (1977)
DOT 19 (2) 112 (1983)
I.N. p. 505
REM p. 991
Kaspar, E., Pawlowski, K.H., Junkmann, K. and Schenck, M.; U.S. Patent 2,753,360; July 3, 1956; assigned to Firma Schering AG, Germany

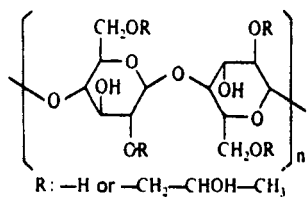
HYDROXYPROPYL CELLULOSE

Therapeutic Function: Topical protectant; ophthalmic vehicle

Chemical Name: Cellulose 2-hydroxypropyl ether

Common Name: Hyprolose

Structural Formula:



Chemical Abstracts Registry No.: 9004-64-2

Trade Name	Manufacturer	Country	Year Introduced
Lacrisert	MSD	U.S.	1981

Raw Materials

Cotton linters
Sodium hydroxide
Propylene oxide
Acetic acid

Manufacturing Process

Charge:

	Parts
Purified cotton linters	1
Tertiary butanol	10
Water	1.4
Sodium hydroxide	0.1
Hexane	9.5
Propylene oxide	2.85

Procedure:

The tertiary butanol, water and sodium hydroxide were mixed and the mixture cooled to 20°C. The purified cotton linters were added to the mixture and aged at 20°C for one hour while stirring. Excess liquid was filtered off the resulting alkali cellulose so that the resulting alkali cellulose filter cake weighed 3.08 parts. This filter cake was broken up and slurried in the hexane, placed in a pressure vessel the pressure of which was increased to 100 psig with nitrogen, and then the pressure was vented to 5 psig. The propylene oxide was added to the pressure vessel and then the pressure was increased to 25 psig with nitrogen. The resulting charge was heated to 85°C in 30 minutes and then reacted at this temperature and 25 psig pressure for six hours. The charge was cooled to 30°C, the pressure vessel vented and 0.14 part of glacial acetic acid added. The excess hexane was filtered off from the resulting hydroxypropyl cellulose product, the product was purified by washing with hot water (85°C to 95°C) and then dried at 130°C using a two-roll drum drier.

References

Merck Index 4763
PDR p. 1191
DOT 18 (7) 338 (1982)
I.N. p. 509
REM p. 1298
Klug, E.D.; U.S. Patent 3,278,521; October 11, 1966; assigned to Hercules, Inc.

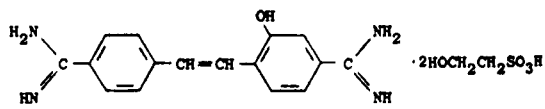
HYDROXYSTILBAMIDINE ISETHIONATE

Therapeutic Function: Systemic fungicide

Chemical Name: 2-hydroxy-4,4'-stilbenedicarboxamidine di(β-hydroxyethanesulfonate)

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 533-22-2; 495-99-8 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Hydroxystilbamidin Isethionate	Merrell-National	U.S.	1954
Hydroxystilbamide	May & Baker	U.K.	–

Raw Materials

2-Nitro-p-tolunitrile
Stannous chloride
Sulfuric acid
Ammonia
4-Cyanobenzaldehyde
Sodium nitrate
Hydrogen chloride
Isethionic acid

Manufacturing Process

Preparation of 2-Nitro-4,4'-Dicyanostilbene: 10 grams of 2-nitro-p-tolunitrile and 8.1 grams of 4-cyano-benzaldehyde were heated to 170° to 180°C, 1.2 and 0.6 cc of piperidine were added at quarter-hour intervals, heating was continued for a further one and a quarter hours, the product cooled, triturated with glacial acetic acid and filtered. The residue was crystallized from glacial acetic acid as yellow needles, MP 290°C.

Preparation of 2-Amino-4,4'-Dicyanostilbene: 10.0 grams of 2-nitro-4,4'-dicyanostilbene thus prepared were suspended in 200 cc of glacial acetic acid and a hot solution of 50 grams of stannous chloride ($SnCl_2 \cdot 2H_2O$) in 50 cc of concentrated hydrochloric acid was quickly added. Rapid reaction occurred and the boiling was continued for a further 4 minutes, the reaction mixture was cooled, filtered, and the stannous chloride residue decomposed with 25% aqueous caustic soda solution. The liberated amine crystallized from glacial acetic acid as yellow needles, MP 232°C.

Preparation of 2-Hydroxy-4,4'-Dicyanostilbene: 10 grams of 2-amino-4,4'-dicyanostilbene thus prepared were dissolved in 400 cc of boiling glacial acetic acid and 200 cc of dilute sulfuric acid added; the solution was suddenly chilled and diazotized over one and a half hours at 5° to 10°C with sodium nitrate (3.0 grams/15 cc H_2O). The diazonium salt solution was decomposed by boiling for 15 minutes with 600 cc of 55% aqueous sulfuric acid solution; the solution was diluted, cooled and filtered. The residue crystallized from ethyl alcohol as lemon yellow prismatic needles, MP 296°C.

Preparation of 2-Hydroxy-4,4'-Diamidinostilbene Dihydrochloride: 10 grams of 2-hydroxy-4,4'-dicyanostilbene were suspended in 250 cc of absolute ethyl alcohol and the mixture saturated with dry hydrogen chloride at 0°C. The whole was left for eight days at room temperature. The imino-ether hydrochloride formed was filtered off, washed with dry ether and dried in the air for a short time. It was then added to 250 cc of 10% ethyl alcoholic ammonia and the whole heated for 5 hours at 45°C. The 2-hydroxy-4,4'-diamidinostilbene dihydrochloride which separated was crystallized from 10% hydrochloric acid. It forms pale yellow needles, MP 357°C (decomposition).

Preparation of the Final Isethionate Product: The diisethionate may be produced by treating a solution of the dihydrochloride with alkali carbonate, separating and dissolving the resultant base in aqueous isethionic acid and precipitating the diisethionate with acetone. The product may be purified by dissolving in hot methyl alcohol containing a trace of water followed by precipitation by the cautious addition of acetone. The diisethionate has a MP of 286°C.

References

Merck Index 4768
Kleeman & Engel p. 480
I.N. p. 506
REM p. 1230
Ewins, A.J.; U.S. Patent 2,510,047; May 30, 1950; assigned to May & Baker Ltd., England

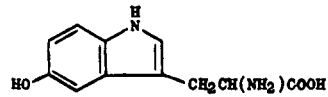
HYDROXYTRYPTOPHAN

Therapeutic Function: CNS stimulant

Chemical Name: 5-hydroxytryptophan

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 56-69-9

Trade Name	Manufacturer	Country	Year Introduced
Quietim	Nativelle	France	1973
Tript-Oh	Sigma Tau	Italy	1980
Levothym	Karlspharma	W. Germany	1980

Raw Materials

4-Benzyloxyaniline HCl
Hydrochloric acid
Sodium hydroxide
Diethylacetylamino malonate
Sodium nitrite
Stannous chloride
Acrolein
Hydrogen

Manufacturing Process

Preparation of 4-Benzyloxyphenylhydrazine: 200 grams 4-benzyloxyaniline hydrochloride was suspended in a mixture of 264 ml concentrated hydrochloric acid, 528 ml water and 732 grams crushed ice. A solution of 62.4 grams sodium nitrite in 136 ml water was added below the surface of the stirred suspension at -10±2°C during 10 minutes. After stirring for 1 hour at 0°C, the suspension was treated with acid-washed charcoal and filtered.

The filtrate was cooled and maintained at -8°C while a solution of 500 grams of stannous chloride in 760 ml concentrated hydrochloric acid was added with stirring. The mixture was stirred for 2 hours at -8°C and the 4-benzyloxyphenylhydrazine hydrochloride which separated was filtered off and washed with water. The product was crystallized by adding 800 ml hot water to a 3 liter solution in ethanol and had a MP of 185° to 189°C (yield 168.5 grams, 79%).

Preparation of Ethyl α-Acetylamino-α-Carbethoxy-β-(5-Benzyloxy-Indolyl-3)-Propionate: 4-benzyloxyphenylhydrazine hydrochloride was converted to the corresponding base 2 to 3 hours before use: 28 grams of the hydrochloride was suspended in 500 ml chloroform and shaken with 55 ml 2 N sodium hydroxide in 100 ml water. The chloroform was separated and the aqueous phase reextracted with chloroform (2 x 100 ml). After washing with 100 ml water, the chloroform solution was dried over sodium sulfate, filtered and evaporated at 30° to 35°C, leaving 4-benzyloxyphenylhydrazine as a friable buff-colored solid (23 grams, 97% from hydrochloride).

6.1 grams freshly distilled acrylic aldehyde (acrolein) in 9.7 ml chlorobenzene was added at 30°C over 30 minutes to a stirred suspension of 24.2 grams diethyl acetylaminomalonate in 37.5 ml chlorobenzene containing a catalytic amount (0.25 ml) of 50% w/v aqueous sodium hydroxide. After a further 30 minutes the resultant solution was warmed and 23 grams 4-benzyloxyphenylhydrazine was added at 45°C. The mixture was stirred and heated at 65° to 70°C for 1 hour to complete condensation, when a red solution was formed.

The resultant chlorobenzene solution was added to 440 ml N sulfuric acid and the suspension was refluxed with stirring for 6 hours. The product was extracted with chloroform (250 + 100 ml), and the chloroform solution washed with water (3 x 100 ml), separated and dried over sodium sulfate. After filtration and concentration at 40°C to 100 ml, 300 ml light petroleum (BP 40° to 60°C) was added to the warm chloroform-chlorobenzene solution. 33.1 grams ethyl α-acetylamino-α-carbethoxy-β-(5-benzyloxyindolyl-3)-propionate crystallized on cooling from the mixture. It was recrystallized by dissolving in 200 ml benzene and adding 100 ml light petroleum (BP 60° to 80°C) at the boiling point. After cooling, the buff crystals were collected, washed with cold benzene/light petroleum (1:1) mixture (50 ml), and dried at 55°C (yield 26.0 grams, 54%, MP 164° to 165°C).

Preparation of α-Acetylamino-α-Carboxy-β-(5-Benzyloxy-Indolyl-3)-Propionic Acid: 18 grams ethyl α-acetylamino-α-carbethoxy-β-(5-benzyloxy-indolyl-3)-propionate was suspended in 85 ml water containing 8.5 grams sodium charcoal. The suspension was refluxed for 4 hours, decolorizing charcoal added, and the solution filtered hot through Hyflo Supercel.

After cooling in ice to 10°C, the solution was acidified with 24 ml concentrated hydrochloric acid. The solid which separated was filtered off, washed with water (3 x 30 ml) and dried in vacuo over silica gel, to give α-acetylamino-α-carboxy-β-(5-benzyloxy-indolyl-3)-propionic acid, MP 144° to 146°C (15.0 grams, 95%) sufficiently pure for use in the next stage.

Preparation of α-Acetylamino-β-(5-Benzyloxy-Indolyl-3)-Propionic Acid: 15 grams α-acetylamino-α-carboxy-β-(5-benzyloxy-indolyl-3)-propionic acid was suspended in 225 ml water and the suspension refluxed and stirred in a stream of nitrogen until evolution of carbon dioxide ceased (about 2 hours). After cooling somewhat, 120 ml ethyl alcohol was added and the suspension refluxed until the product dissolved. Charcoal was added to the solution the mixture filtered hot, and the filter-cake washed with 50 ml hot 50% aqueous ethanol. α-Acetylamino-β-(5-benzyloxy-indolyl-3)-propionic acid, MP 164° to 166°C, which crystallized from the filtrate on cooling, was collected, washed with an ice-cold mixture of 15 ml ethanol and 45 ml water, and dried in vacuo over silica gel (yield 11.1 grams, 83%).

Preparation of 5-Benzyloxytryptophan: 11 grams α-acetylamino-β-(5-benzyloxy-indolyl-3)-propionic acid was suspended in a solution of 12 grams sodium hydroxide in 90 ml water and refluxed for 24 hours. Charcoal was added to the resultant solution and the mixture filtered hot. 150 ml 2 N hydrochloric acid was added to the filtrate at 70°C and 5-benzyloxytryptophan crystallized on cooling. After washing with water and drying in vacuo over silica gel, the amino acid (6.9 grams, 71%) had MP (sealed evacuated tube) 232°C, with softening, finally melting at 237° to 238°C (decomposition). Charcoal was added to the filtrate, which was filtered hot and adjusted to pH 2. On cooling a second crop of 5-benzyloxytryptophan was obtained (2.2 grams, 23%), MP (sealed evacuated tube) 230°C, with softening, finally melting at 233° to 237°C (decomposition). The overall yield of 5-benzyloxytryptophan was 9.1 grams (94%).

Preparation of 5-Hydroxytryptophan: 0.4 gram palladium chloride and 1.7 grams acid-washed charcoal were suspended in 157 ml water and hydrogenated at room temperature and atmospheric pressure until no further hydrogen uptake occurred. A suspension of 14.2 grams 5-benzyloxytryptophan in 175 ml ethyl alcohol was added and the mixture hydrogenated under similar conditions. A hydrogen uptake slightly in excess of theory was obtained. The suspension was warmed for a few minutes on the steam bath and filtered hot. The filter-cake was washed with hot water (3 x 20 ml) and the filtrate evaporated to 20 ml under reduced pressure in a nitrogen atmosphere.

The resultant mass of colorless crystals was triturated with 250 ml ice-cold ethyl alcohol under hydrogen, filtered, and washed with cold ethyl alcohol (2 x 15 ml). The 5-hydroxytryptophan (6.9 grams, 69%) had MP (sealed evacuated tube) 288°C, with softening, finally melting at 249° to 247°C (decomposition). Concentration of the liquors under reduced pressure in a nitrogen atmosphere, and trituration as before, gave a second crop (0.9 gram, 9%). The combined crops (7.8 grams) were dissolved in 120 ml hot water, charcoal added,

and the mixture filtered hot. The filtrate was concentrated in a nitrogen atmosphere under reduced pressure and ethyl alcohol added. The 5-hydroxytryptophan then crystallized as colorless microneedles (6.5 grams, 65%), had MP (sealed evacuated tube) 290°C, with slight softening, finally melting at 295° to 297°C (decomposition).

References

Merck Index 4771
DOT 9 (6) 224 (1973), 10 (9) 323 & 10, 262 (1974)
REM p. 1083
Ash, A.S.F.; British Patent 845,034; August 17, 1960; assigned to May & Baker Ltd., U.K.

HYDROXYUREA

Therapeutic Function: Cancer chemotherapy

Chemical Name: Hydroxycarbamide

Common Name: –

Structural Formula: $H_2NCONHOH$

Chemical Abstracts Registry No.: 127-07-1

Trade Name	Manufacturer	Country	Year Introduced
Hydrea	Squibb	U.K.	1967
Hydrea	Squibb	U.S.	1968
Litalir	Heyden	W. Germany	1968
Hydrea	Squibb	France	1969
Biosuppressin	Biogal	Hungary	–
Hidroks	Yurtoglu	Turkey	–
Onco-Carbide	Simes	Italy	–

Raw Materials

Hydroxylamine hydrochloride
Sodium cyanate

Manufacturing Process

The procedure may be illustrated by the following equations relating to the preparation of hydroxyurea from hydroxylamine hydrochloride:

(1) $R_4N^+Cl^- + NaNCO \rightarrow R_4N^+NCO^- + NaCl$

(2) $R_4N^+NCO^- + H_2NOH{\cdot}HCl \rightarrow R_4N^+Cl^- + HO\overset{H}{\underset{|}{N}}{-}CO{-}NH_2$

Equation (1) shows the simple conversion of a quaternary ammonium anion exchange resin from the chloride form to the cyanate form. Equation (2) shows the reaction of the resin in the cyanate form with hydroxylamine hydrochloride whereby hydroxyurea is formed and the anion Cl^- is retained by the quaternary resin.

A 90 x 6 cm column was packed with 2 kg of granular Amberlite IRA-410 resin in the chloride form (a vinylpyridine/divinylbenzene copolymer quaternized with dimethyl sulfate and converted to chloride) and washed with 3 kg of a 10% aqueous solution of sodium

cyanate. This changed the resin from the chloride to the cyanate form. Sodium chloride and excess sodium cyanate were then washed from the column with distilled water until the effluent failed to give a white precipitate with silver nitrate. The reaction of equation (2) was conducted by elutriating the column with a solution of 105 grams (1.5 mols) of hydroxylamine hydrochloride in 400 ml water at about 15°C.

A hot (50° to 70°C) reaction zone developed near the top of the column and about 30 minutes was required for this hot zone to descend the full length of the column. The reaction solution was followed in the column by 2.5 liters of distilled water. Collection of the product was begun when hydroxyurea could be detected in the effluent, as indicated by a black precipitate on warming a sample with a silver nitrate test solution. All the effluents were combined and vacuum evaporated at 35°C to give 90 grams of tan residue corresponding to 79% yield of crude product. After recrystallization from 100 ml of water heated to 75°C, the colorless product was dried in a vacuum desiccator over phosphorus pentoxide to give 60.6 grams (53% yield) of hydroxyurea, MP 133° to 136°C.

References

Merck Index 4772
Kleeman & Engel. p. 476
PDR p. 1746
I.N. p. 501
REM p. 1155
Graham, P.J.; U.S. Patent 2,705,727; April 5, 1955; assigned to E.I. du Pont de Nemours and Company

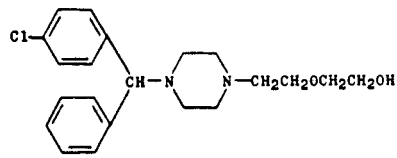
HYDROXYZINE HYDROCHLORIDE

Therapeutic Function: Tranquilizer

Chemical Name: 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethoxy] ethanol hydrochloride

Common Name: —

Structural Formula:



(base)

Chemical Abstracts Registry No.: 2192-20-3; 68-88-2 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Atarax	UCB	France	1956
Atarax	Roerig	U.S.	1956
Vistaril	Pfizer	U.S.	1958
Quiess	O'Neal Jones	U.S.	1958
Hyzine	Hyrex	U.S.	1980
Orgatrax	Organon	U.S.	1980
Durrax	Dermik	U.S.	1983
Alamon	Grelan	Japan	—
Arcanax	Arcana	Austria	—
Atazina	Panthox & Burck	Italy	—

Trade Name	Manufacturer	Country	Year Introduced
Disron	Teikoku	Japan	–
Masmoran	Pfizer	W. Germany	–
Marax	Roerig	U.S.	–
Neucalm	Legere	U.S.	–
Neurozina	Farge	Italy	–
Theozine	Schein	U.S.	–

Raw Materials

N-Mono-1-p-chlorobenzohydrylpiperazine
1-Chloro-2-(2-hydroxyethoxy)ethane
Sodium hydroxide
Hydrogen chloride

Manufacturing Process

A mixture of 0.1 mol of N-mono-1-p-chlorobenzohydrylpiperazine and 0.1 mol of 1-chloro-2-(2-hydroxy-ethoxy)-ethane is heated for 3 hours to 150°C. The mass is then taken up in 100 ml of benzene and 100 ml of a 10% aqueous solution of NaOH; decanting takes place, and the benzene solution is washed with water and the solvent is evaporated. Vacuum distilling of the residue yields 1-p-chlorobenzohydryl-4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazine, BP 220°C/0.5 mm Hg.

The corresponding dihydrochloride is prepared by dissolving this base in about twice its weight of alcohol, by treating it with excess of gaseous HCl and by precipitating it with ether. The solvent is decanted and the residue, dissolved in a minimum of alcohol, crystallizes on the addition of ether, MP 193°C.

References

Merck Index 4773
Kleeman & Engel p. 480
PDR pp. 832, 872, 993, 1033, 1288, 1416, 1520, 1528, 1606, 1989, 1999
OCDS Vol. 1 p. 59 (1977)
I.N. p. 506
REM p. 1071
Morren, H.; U.S. Patent 2,899,436; August 11, 1959; assigned to Union Chimique Belge Societe Anonyme, Belgium