U

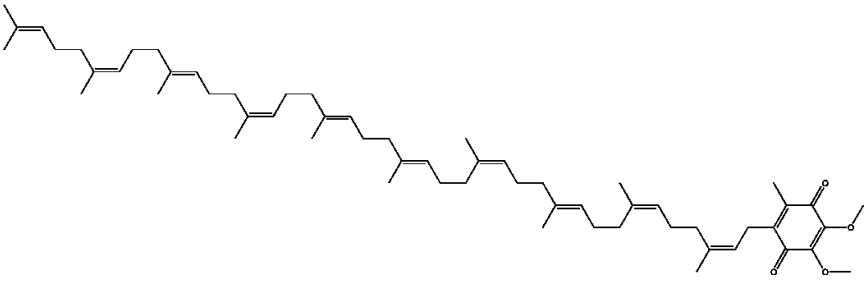
UBIDECARENONE

Therapeutic Function: Cardiovascular

Chemical Name: 2-(3,7,11,15,19,23,27,31,35,39-Decamethyl-2,6,10,14,18,22,26,30, 34,38-tetracontadecaenyl)-5,6-dimethoxy-3-methyl-p-benzoquinone

Common Name: Ubiquinone

Structural Formula:



Chemical Abstracts Registry No.: 303-98-0

Trade Name	Manufacturer	Country	Year Introduced
Neuquinon	Eisai	Japan	1974
Adelir	Teikoku Kagaku	Japan	-
Emitolon	Tatsumi	Japan	-
Heartcin	Ohta	Japan	-
Hiruton	Taisho	Japan	-
Inokiten	Nippon Chemiphar	Japan	-
Justquinon	Horita	Japan	-
Kaitron	Sawai	Japan	-
Parbinon	Santen	Japan	-
Terekol	Daigo	Japan	-
Ube-Q	Tsuruhara	Japan	-
Udekinon	Tobishi	Japan	-
Yubekinon	Hishiyama	Japan	-

Raw Materials

Nutrient medium
Bacterium Sporidiobolus ruinenii

Manufacturing Process

A small fermentation tank (5,000 parts by volume capacity) was charged with 3,000 parts by volume of a culture medium (pH 6.0) comprising 3% glucose, 1% polypepton, 0.5% yeast extract and 0.5% malt extract. The medium was sterilized by heating in a conventional manner and cooled. This medium was inoculated with 150 parts by volume of a pre-culture of *Sporidiobolus ruinenii* CBS-5001, which had been prepared by growing the same strain on a medium of the same composition as above at 28°C for one day. The inoculated medium was incubated at 28°C and under agitation at 800 rpm with sparging at a rate of 3,000 parts by volume per minute for 24 hours. During this fermentation period, the medium was maintained at pH 6.0 with ammonia and sulfuric acid.

The resultant fermentation broth was centrifuged to harvest the microbial cells, and they were washed with water and centrifuged a second time, whereupon a living cell paste was obtained. (There was obtained an amount of cells equivalent to 54 parts on a dry basis, which contained 920 μg of ubiquinone-10 per gram of dry cells.)

The moist cells were suspended in 750 parts of volume of ethanol and extracted by warming at 60°C for 1 hour. A total of 3 extractions were carried out in a similar manner and the extracts were pooled, diluted with water and further extracted three times with 1,000 parts of volume portions of n-hexane. The n-hexane layer was concentrated to dryness under reduced pressure to recover 4.12 parts of a yellow oil. This oily residue was dissolved in 6 parts by volume of benzene and passed through a column (500 parts by volume capacity) packed with Floridil (100 to 200 meshes). Elution was carried out using benzene and the eluate was collected in 10 parts by volume fractions. Each fraction was analyzed by thin-layer chromatography and color reaction and the fractions rich in ubiquinone-10 were pooled and concentrated under reduced pressure. By this procedure was obtained 0.562 part of a yellow oil. This product was dissolved in 5 parts by volume of chloroform, coated onto a thin layer plate of silica gel GF254 (silica gel with calcium sulfate) and developed with benzene. The fractions corresponding to ubiquinone-10 were extracted, whereby 0.054 part of a yellow oil was obtained. This oil was dissolved in 10 parts by volume of ethanol and allowed to cool, whereupon 0.029 part of yellow crystals of ubiquinone-10 were obtained, its melting point 48° to 50°C.

There are also synthetic routes to the ubiquinones as described in US Patents 3,068,295; 3,896,153 and 4,062,879.

References

Merck Index 9641
Kleeman and Engel p. 936
DOT 13 (4) 159 (1977)
I.N. p. 992

Folkers, K.A., Hoffman, C.H. and Wolf, D.E.; US Patent 3,068,295; Dec. 11, 1962; assigned to Merck and Co., Inc.
Sato, K., Inoue, S., Kijima, S. and Hamamura, K.; US Patent 3,896,153; July 22, 1975; assigned to Eisai Co., Ltd. (Japan)
Kijima, S., Yamatsu, I., Minami, N. and Inai, Y.; US Patent 4,062,879; Dec. 13, 1977; assigned to Eisai Co., Ltd. (Japan)
Nakao, Y., Kitano, K., Imada, I. and Morimoto, H.; US Patent 4,070,244; Jan. 24, 1978; assigned to Takeda Chemical Industries Ltd. (Japan).

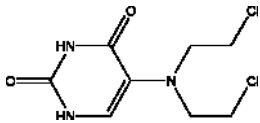
URACIL MUSTARD

Therapeutic Function: Cancer chemotherapy

Chemical Name: 5-[Bis(2-chloroethyl)amino]-2,4(1H,3H)-pyrimidinedione

Common Name: Uramustine; Demethyldopan; Chloroethaminacil

Structural Formula:



Chemical Abstracts Registry No.: 66-75-1

Trade Name	Manufacturer	Country	Year Introduced
Uracil Mustard	Upjohn	US	1962

Raw Materials

5-Aminouracil
Thionyl chloride
Ethylene oxide

Manufacturing Process

Preparation of 5-[bis(2-Hydroxyethyl)Amino] Uracil: 20 grams (0.157 mol) of 5-aminouracil was mixed with 350 ml of water, 23 ml of glacial acetic acid, and 160 ml of ethylene oxide in a one-liter flask immersed in an ice bath. The reaction mixture was stirred and allowed to come to room temperature slowly (as the ice melted), and stirring was continued for two days. A clear solution resulted to which was added 250 ml of water and 60 grams of Dowex-50 in the acid form. The mixture was stirred for 15 minutes, and the resin was collected on a filter. It was washed with water and the crude 5-[bis(2-hydroxyethyl)amino] uracil was eluted with a 10% aqueous solution of ammonium hydroxide. This eluate was evaporated to dryness, and the solid that remained was heated with 350 milliliters of isopropyl alcohol.

Undissolved substances were removed by filtration and the filtrate was concentrated on a steam bath to a volume of about 125 ml and cooled to effect crystallization. After 20 hours at room temperature the crystals that had formed were recovered, washed with isopropyl alcohol, and dried, yielding 15.61 grams (46.2%) of crystalline 5-[bis(2-hydroxyethyl)amino] uracil having a MP of 157° to 163°C. An analytical sample, obtained by several recrystallizations from isopropyl alcohol, melted at 166° to 168°C.

Preparation of 5-[bis(2-Chloroethyl)Amino] Uracil: 13 ml of thionyl chloride was added to 52 ml of diethylene glycol dimethyl ether accompanied by stirring. Heat was generated, and sulfur dioxide and hydrogen chloride were liberated. The mixture was cooled and 5.58 grams of 5-[bis(2-hydroxyethyl)amino] uracil was added, followed by 8 ml of thionyl chloride, No evidence of reaction was noted, and the reaction mixture was heated to about 40°C, gas then being evolved. After one hour at 40°C, 5 ml of thionyl chloride was added, and after 30 minutes, another 3 ml was added. The mixture was then heated to 55°C, whereupon it darkened and all of the solid dissolved. After cooling and storage at room temperature for 20 hours, three volumes of benzene was added and a dark solid precipitated. After one hour, the dark solid was collected on a filter, washed with benzene, and dissolved in a minimum of boiling methanol. Crystals formed upon cooling; and after 18 hours in the refrigerator, they were recovered on a filter, washed with cold methanol, and dried under reduced pressure, yielding 2.96 grams of 5-[bis(2-chloroethyl)amino] uracil. The product was recrystallized by dissolving in a minimum of hot methanol and adding water until the solution became cloudy; 2.25 grams of 5-[bis(2-chloroethyl)amino] uracil was recovered after cooling the mixture to 4°C for 16 hours (MP 200° to 205°C). A small sample was recrystallized again, and it melted at 198° to 204°C.

References

Merck Index 9652
Kleeman and Engel p. 936
I.N. p. 995
REM p. 1157
Lyttle, D.A.; US Patent 2,969,364; January 24, 1961; assigned to Upjohn Company.

URAPIDIL

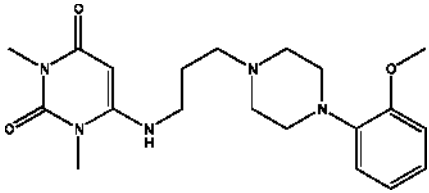
Therapeutic Function: Hypotensive

Chemical Name: 1,3-Dimethyl-4-[γ-[4-(o-methoxyphenyl)piperazinyl-(1)]-propyl-amino]uracil

Common Name: -

Chemical Abstracts Registry No.: 34661-75-1

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Ebrantil	Byk Gulden	W. Germany	1978
Ebrantil	Byk Gulden	Switz.	1983

Raw Materials

N-(o-Methoxyphenyl)-N'-(3-aminopropyl)piperazine
1,3-Dimethyl-4-chlorouracil

Manufacturing Process

20.6 g (0.083 mol) of N-(o-methoxyphenyl)-N'-(3-aminopropyl)-piperazine and 15.7 g (0.09 mol) of 1,3-dimethyl-4-chlorouracil were boiled for 15 hours in 100 ml triethylamine. The excess triethylamine was then distilled off in vacuo and the residue was dissolved in 300 ml 1 N hydrochloric acid with subsequent filtration. The filtrate thus obtained was cooled with ice and 2 N aqueous ammonic solution was slowly added with stirring. As soon as the first precipitation appeared, a few crystals of the desired product were added to the solution. The ammoniacal suspension was stirred for one more hour, the precipitate filtered off by suction and washed with 200 ml water.

The material was purified by recrystallization from ethanol with the addition of activated carbon. In this manner 242 g 1,3-dimethyl-4-[γ-[4-(o-methoxyphenyl]-piperizinyl-(1)]propylamino] uracil having a melting point of 156°C were obtained corresponding to a yield of 75%. The purification may also be effected by boiling the material in acetone to result in similar yields.

References

Merck Index 9669
DFU 3 (5) 397 (1978)
Kleeman and Engel p. 937
DOT 10 (2) 72 and (10) 551 (1982)
I.N. p.995
Klemm, K., Schoetensack, W. and Prusse, W.; US Patent 3,957,786; May 18, 1976; assigned to Byk Gulden

UROKINASE

Therapeutic Function: Anticoagulant

Chemical Name: A complex enzyme

Common Name: -

Chemical Abstracts Registry No.: 9039-53-6

Trade Name	Manufacturer	Country	Year Introduced
Abbofinase	Abbott	UK	1962
Uronase	Mochida	Japan	1970
Urokinase	Choay	France	1973
Urokinase	Choay	Italy	1975
Urokinase	Serono	W. Germany	1978
Abbokinase	Abbott	US	1978
Breokinase	Breon	US	1979
Abbokinase	Abbott	W. Germany	1980
Abbokinase	Abbott	France	1980
Ukidan	Serono	Sweden	1983
Abbokinase	Abbott	Sweden	1983
Actosolv	Behring Werke	W. Germany	-

Raw Materials

Human urine
Sodium benzoate
Hydrogen chloride

Manufacturing Process

In 20 liters of human urine is dissolved 1,200 grams of sodium benzoate (6% weight by volume). The solution is acidified with aqueous hydrochloric acid (assay about 7.5% HCl) to a pH of 4.5 resulting in a heavy precipitation. This requires 10% of the original urine volume, or about 2 liters of aqueous hydrochloric acid. The suspension is stirred 20 minutes and is then allowed to stand for about 30 minutes. The mixture so obtained is filtered on a Buchner funnel that has been prepared with a precoat of benzoic acid crystals over filter paper. The filter cake is washed with a saturated benzoic acid solution, then sucked dry. The benzoic acid cake with the adsorbed urokinase weighs 2,060 grams.

The filter cake is stirred with 3.1 liters of acetone. The volume of acetone used is about 1.5 times the weight of the cake resulting in about a 65% acetone concentration. The benzoic acid dissolves in the acetone and the urokinase flocculates out. Sodium benzoate, about 1% of the weight of the cake, or 21 grams, is added to speed up the formation of the precipitate. The suspension of crude urokinase in acetone is filtered on a Buchner funnel using filter paper precoated with a diatomaceous silica product (Celite 505). The precipitate is washed with acetone until the filtrate is water clear. The precipitate is then washed with ether and air dried. The yield of powder so obtained is 2.3 grams.

Four batches of urokinase, obtained in this manner from 202 liters of urine, is pooled, amounting to 23.5 grams. The combined urokinase is suspended in

750 ml of 0.1 M phosphate-saline buffer at pH 6.2, stirred to dissolve the urokinase and centrifuged to remove the Celite. The residue is extracted two more times with 500 ml portions of 0.1 M phosphate-saline buffer. The combined extracts are filtered and labelled Extract 1.The residue is extracted three more times with 600 ml portions of buffer, the combined extracts are filtered and labelled Extract 2.

The clarified solution of the first phosphate-saline buffer extract, 1,320 ml, is passed through 110 cm of Amberlite XE-64 ion exchange resin contained in a column 10 cm in diameter. The resin exchange column has a hold-up volume of about 2.8 liters. The second extract (Extract 2) of the Celite residue, 1,720 ml, is then passed through the same exchange column. The column is washed with 11.4 liters of the phosphate-saline buffer. Then the adsorbate is eluted with 9 liters of 0.5 M sodium chloride. The eluate is dialyzed through a viscose regenerated cellulose membrane against distilled water. The active fractions within the dialysis sacs, totaling 4,940 ml, are pooled and lyophilized. The yield is 2.5 grams having an activity of 415,000 units or 166 units per milligram.

References

Merck Index 9693
Kleeman & Engel p. 937
PDR p. 502
I.N. p. 997
REM p. 1038
Singher, H.O. and Zuckerman, L.; US Patent 2,961,382; November 22, 1960; assigned to Ortho Pharmaceutical Corporation
Kjeldgaard, N.O. and Herlev, J.P.; US Patent 2,983,647; May 9, 1961; assigned to Lovens kemiske Fabrik ved A. Kongsted, Denmark
Singher, H.O. and Zuckerman, L.; US Patent 2,989,440; June 20, 1961; assigned to Ortho Pharmaceutical Corporation
Doczi, J.; US Patent 3,081,236; March 12, 1963; assigned to Warner-Lambert Pharmaceutical Company

URSODIOL

Therapeutic Function: Gallostone dissolving agent, Hepatoprotectant

Chemical Name: Cholan-24-oic acid, 3,7-dihydroxy-, (3α,5β,7β)-

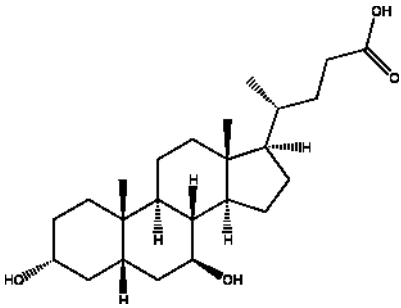
Common Name: Ursodeoxycholic acid; Ursodiol; Ursotan

Chemical Abstracts Registry No.: 128-13-2

Raw Materials

Acetic acid
Sodium
Hydrochloric acid
Chenodeoxycholanic acid
Chromium(VI) oxide

Structural Formula:



Trade Name	Manufacturer	Country	Year Introduced
Actigall	Novartis	-	-
Actigall	Axcan Scandipharm Inc.	-	-
Livera	Shin Poong	-	-
Ursodeoxycholic acid	ABCR GmbH and Co. KG	-	-
Solvobil	Master	-	-
Solvobil	Recordati	-	-
Ursacol	Zambon Italia S.r.l.	-	-

Manufacturing Process

Chenodeoxycholanic acid was dissolved in acetic acid and to this solution aqueous solution of CrO_3 was added. As a result 3,7-diketodeoxycholanic acid was obtained, yield 95%, melting point 145°C.

15.0 g of 3,7-diketodeoxycholanic acid were dissolved in 80 ml of toluene, then petroleum ether 30 ml were added. 3,7-Diketodeoxycholanic acid as an oil precipitate was obtained, melting point 152°-154°C.

10.0 g of 3,7-diketodeoxycholanic acid were dissolved in 300 ml butanol, heated to 120°-130°C on bath and then sodium metallic 13.0 g were added. After that to this mixture hydrochloric acid was added for neutralization. Ursodeoxychlolanic acid was obtained, yield 9.4 g, melting point 193°C (recrystallization from ethyl acetate).

References

Sato M.T.; EU Patent No. 1,372,109; September 23, 1963; Assigned: Tokyo Tanabe Co Ltd resident au Japon