Q

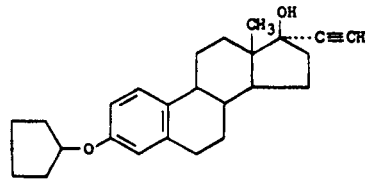
QUINESTROL

Therapeutic Function: Estrogen

Chemical Name: 3-(cyclopentyloxy)-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17-ol

Common Name: 17α-ethinylestradiol 3-cyclopentyl ether

Structural Formula:



Chemical Abstracts Registry No.: 152-43-2

Trade Name	Manufacturer	Country	Year Introduced
Estrovis	Goedecke	W. Germany	1968
Estrovis	Warner	U.K.	1969
Estrovis	Warner-Lambert	U.S.	1979
Agalacto-Quilea	Elea	Argentina	—
Basaquines	Boehr. Mann.	—	—

Raw Materials

17α-Ethynyl estradiol
Cyclopentyl bromide

Manufacturing Process

A solution of 1.5 grams of 17α-ethynyl estradiol in 50 cc of absolute ethanol is added slowly to a mixture of 3 grams of cyclopentyl bromide and 2 grams of potassium carbonate. This mixture is heated to reflux and stirred for 3 hours, then filtered. Most of the alcohol is eliminated by distillation and the resulting solution diluted with water, and cooled in an ice-bath. The product which precipitates is collected by filtration, washed and dried. After recrystallization from methanol the 3-cyclopentyl ether of 17α-ethynyl estradiol shows a melting point of 107° to 108°C.

References

Merck Index 7959
Kleeman & Engel p. 797
PDR p. 1347
DOT 17 (4) 163 (1981)
I.N. p. 832

REM p. 988
Ercoli, A.; U.S. Patent 3,159,543; December 1, 1964; assigned to Francesco Vismara SpA, Italy
Ercoli, A., Gardi, R. and Pedrali, C.; U.S. Patent 3,231,567; January 25, 1966; assigned to Francesco Vismara SpA, Italy

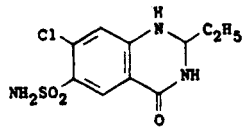
QUINETHAZONE

Therapeutic Function: Diuretic

Chemical Name: 7-chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxo-6-quinazolinesulfonamide

Common Name: Chinethazonum

Structural Formula:



Chemical Abstracts Registry No.: 73-49-4

Trade Name	Manufacturer	Country	Year Introduced
Hydromox	Lederle	U.S.	1962
Aquamox	Lederle	U.K.	–

Raw Materials

7-Chloro-2-ethyl-6-sulfamyl-4-quinazolinone
Sodium borohydride

Manufacturing Process

For preparation of the desired tetrahydroquinazolinone, 103 parts of aluminum chloride were added to 25,000 parts by volume of diethylene glycol dimethyl ether while cooling in an ice bath. The mixture was then stirred with warming and 200 parts of 7-chloro-2-ethyl-6-sulfamyl-4-quinazolinone added. A second solution of 140 parts of sodium borohydride in 7,000 parts of dry diethylene glycol dimethyl ether was then added gradually. An orange mixture resulted which was kept at 85°C until the reaction was complete. The reaction mixture was then cooled to approximately 0°C and 4,000 parts of water slowly added. Dilute HCl was then added to form a strongly acidic clear solution which was evaporated to dryness. Following this, the solid was triturated with cold water to yield 90 parts of a solid. Fibrous crystals were obtained by recrystallization from 50% acetone.

References

Merck Index 7960
Kleeman & Engel p. 797
PDR p. 1010
OCDS Vol. 1 p. 354 (1977)
I.N. p. 833
REM p. 940
Cohen, E. and Vaughan, J.R., Jr.; U.S. Patent 2,976,289; March 21, 1961; assigned to American Cyanamid Company

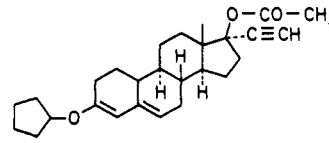
QUINGESTANOL ACETATE

Therapeutic Function: Gestagen

Chemical Name: 19-Norpregna-3,5-dien-20-yn-17-ol-3-(cyclopentyloxy) acetate (17α)

Common Name: —

Structural Formula:



Chemical Abstracts Registry No.: 3000-39-3; 10592-65-1 (Base)

Trade Name	Manufacturer	Country	Year Introduced
Demovis	Parke Davis	Italy	1972
Demovis	Vister	Italy	—
Delovis	Substantia	France	—

Raw Materials

3-Cycloethylenedioxy-10-cyano-17α-ethynyl-19-nor-Δ^5-androstene-17β-ol
Lithium
Ammonia
Acetic anhydride
Cyclopentanol

Manufacturing Process

The starting material for the purposes of this discussion is 3-cycloethylenedioxy-10-cyano-17α-ethynyl-19-nor-Δ^5-androstene-17β-ol (I).

A solution of 10-cyano-3-monoketal (I) in 60 cc of dry ether and 60 cc of dry dioxane is dropped into 400 cc of liquid ammonia. Then, 1.2 g of lithium in small pieces are introduced over a period of 90 minutes and the mixture is maintained under stirring until the blue color of the solution is discharged.

10 g of ammonium chloride are added and the stirring is continued for some hours longer at room temperature. The moist ammonia is left to evaporate cautiously, maintaining the mixture on water-bath and diluting the resulting solution with water. After repeated extractions with ether, an oily residue is obtained consisting of a mixture of $\Delta^{5(6)}$ and $\Delta^{5(10)}$ isomers of 17α-ethynyl-19-nor-androstene-17β-ol-3-one 3-ethylene ketal (II).

To a solution of 1 g of the mixture of 3-ketal-isomers of compound (II) in 10 cc of acetic anhydride is added a solution of 700 mg of p-toluenesulfonic acid in 7 cc of acetic anhydride. The reaction mixture is kept at room temperature and under stirring for 5 hours. After some time a crystalline product begins to precipitate and the precipitation is complete by diluting with water. The precipitate is filtered and crystallized from methanol to give 17α-ethynyl-19-nor-testosterone 3,17-diacetate (III), melting point 175°C to 178°C.

A solution of 1 g of the diacetate (III) in 100 cc of n-heptane containing 2.5 cc of cyclopentanol and 50 mg of p-toluenesulfonic acid is heated under reflux for 20 hours. After cooling, a few drops of pyridine are added and the solvent is eliminated by evaporation under vacuum. The residue is taken up with methanol to give 3-cyclopentyl enolether of 17α-ethynyl-19-nortestosterone acetate which, after recrystallization from methanol, melts at 182°C to 184°C.

References

Kleeman & Engel p. 798
DOT 9 (5) 182 (1973)
I.N. p. 833
Ercoli, A. and Gardi, R.; U.S. Patent 3,159,620; December 1, 1964; assigned to Francesco Vismara S.p.A. (Italy)

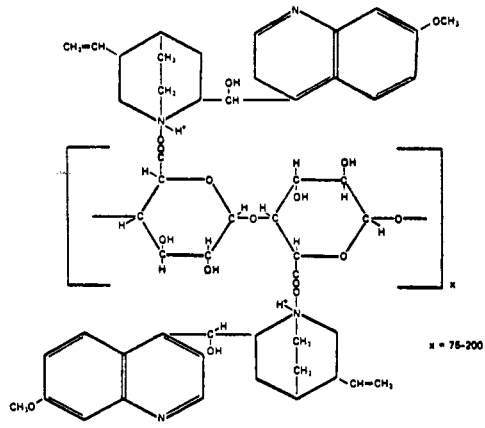
QUINIDINE POLYGALACTURONATE

Therapeutic Function: Antiarrhythmic

Chemical Name: See structural formula

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 65484-56-2

Trade Name	Manufacturer	Country	Year Introduced
Cardioquin	Purdue Frederick	U.S.	1960
Cardioquin	N.A.P.P.	U.K.	1970
Cardioquine	Berenguer-Beneyto	Spain	–
Galactoquin	Mundipharma	W. Germany	–
Galatturil-Chinidina	Francia	Italy	–
Naticardina	Chinoin	Italy	–
Neochinidin	Brocchieri	Italy	–
Ritmocor	Malesci	Italy	–

Raw Materials

Polygalacturonic acid
Quinidine

Manufacturing Process

100 grams of polygalacturonic acid are dissolved in 1 liter of a 60% (v/v) mixture of meth-

anol and water. The neutralization equivalent of the polygalacturonic acid is determined by titration with tenth-normal alkali on an aliquot sample. A stoichiometric equivalent of quinidino alkaloid dissolved in 2,500 cc of 80% methanol is slowly added, with continued stirring.

The pH of the reaction mixture is taken both before and after the addition of the last portion of the quinidine-methanol solution. The mixture is gently warmed (30° to 50°C), and the pH determined at 20 minute intervals. At the end of 4 hours, or when the reaction has gone to completion as evidenced by the pH of the mixture (between pH 6.5 and 7.5), the stirring is then stopped and the mixture cooled to 0°C and filtered. The solvent is evaporated to dryness under reduced pressure, utilizing as little heat as is feasible. The dried residue is powdered and suspended in 10 volumes of methanol and filtered. The insoluble powder is dried, and is quinidine polygalacturonate, melting at 180°C with decomposition.

References

Merck Index 7966
PDR p. 1433
OCDS Vol. 1 p. 339 (1977)
I.N. p. 833
REM p. 859
Halpern, A.; U.S. Patent 2,878,252; March 17, 1959; assigned to Synergistics, Inc.

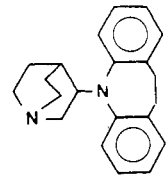
QUINUPRAMINE

Therapeutic Function: Antidepressant

Chemical Name: 5-(3-Quinuclidinyl)-10,11-dihydro-dibenzo[b,f]azepine

Common Name: –

Structural Formula:



Chemical Abstracts Registry No.: 31721-17-2

Trade Name	Manufacturer	Country	Year Introduced
Kinupril	Fournier	France	1979

Raw Materials

Iminodibenzyl
Sodium amide
3-Phenylsulfonyloxyquinuclidine

Manufacturing Process

3.9 g of iminodibenzyl were added in one batch to a suspension of 0.96 g of sodium amide in 50 ml of anhydrous toluene. The mixture was heated to reflux temperature for a period of 6

hours. A solution of 5.34 g of 3-phenylsulfonyloxyquinuclidine in 15 ml of anhydrous toluene was added dropwise over a period of 75 minutes to the suspension at reflux temperature and the latter was maintained for 150 minutes after the completion of the addition. The reaction mixture was cooled to ambient temperature and treated with 75 ml of distilled water and 75 ml of ethyl acetate.

The decanted aqueous phase was extracted three times with a total of 150 ml of ethyl acetate. The combined organic solutions were filtered over Clarcel and extracted three times with a total of 150 ml of an iced normal aqueous methane-sulfonic acid solution. The combined acid extracts were rendered alkaline on an ice bath with 30 ml of 10N caustic soda solution. The separated oil was extracted four times with a total of 200 ml of ether. The combined ethereal extracts were washed twelve times with a total of 360 ml of distilled water, dried over anhydrous magnesium sulfate in the presence of 0.3 g of animal charcoal and evaporated under reduced pressure on a water bath at 40°C. The oily residue obtained (3.8 g) was dissolved in 30 ml of boiling acetonitrile. After cooling for 2 hours at 3°C, the crystals formed were separated, washed with 5 ml of acetonitrile and dried at ambient temperature at low pressure. 1.6 g of 5-(3-quinuclidinyl)-10,11-dihydro-dibenzo[b,f] azepine, melting point 150°C, were obtained.

References

Merck Index 8006
DFU 3 (7) 548 (1978)
Kleeman & Engel p. 799
DOT 16 (4) 122 (1980)
I.N. p. 835
Gueremy, C. and Wirth, P.C.; British Patent 1,252,320; November 3, 1971; assigned to Societe Generale De Recherches Et D'Applications Scientifiques Sogeras