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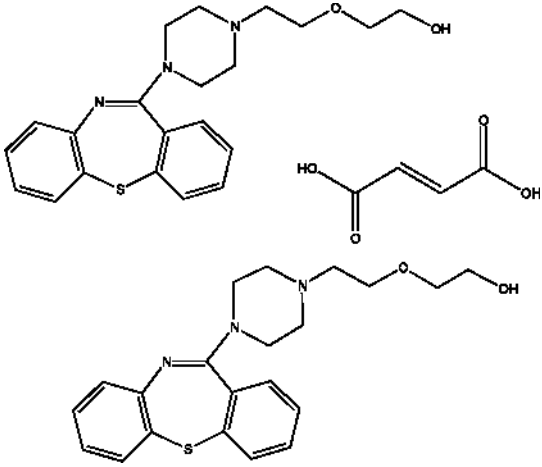
## QUETIAPINE FUMARATE

**Therapeutic Function:** Antipsychotic

**Chemical Name:** Ethanol, 2-(2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl) ethoxy)-, (E)-2-butenedioate (2:1) salt

**Common Name:** Quetiapine fumarate

**Structural Formula:**




**Chemical Abstracts Registry No.:** 111974-72-2

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Quel | Innova (IPCA) | India | - |
| Seroquel | AstraZeneca | UK | - |

**Raw Materials**

Phosphorous oxychloride
N,N-Dimethylaniline
Sodium hydroxide
Dibenzo[b,f][1,4]thiazepine-11(10-H)-one
1-(2-Hydroxyethoxy)ethylpiperazine

**Manufacturing Process**

A 2 liter round-bottom flask equipped with a magnetic stirring bar and reflux condenser with a nitrogen inlet was charged with 115.0 g (0.506 mole) of dibenzo[b,f][1,4]thiazepine-11(10-H)-one (made by the method disclosed by J. Schmutz et al. Helv. Chim. Acta., 48: 336, 1965), phosphorous oxychloride 700 ml (7.5 moles) and N,N-dimethylaniline 38.0 g (0.313 mole). The suspension was heated to gentle refluxing using a heating mantle. After 6 h of heating, the resulting amber solution was allowed to cool to room temperature (from about 18°-25°C) and was analyzed by TLC using silica gel plates, developed with ether-hexane (1:1) and detected with ultraviolet light. Analysis revealed the desired "imino chloride". Excess phosphorous oxychloride, was removed in vacuo using a rotary evaporator. The brown syrupy residue was dissolved in 1500 ml of toluene, treated with 500 ml of an ice-water mixture and stirred for 30 min. The toluene layer was separated, washed twice with 200 ml of water and dried with anhydrous magnesium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated in vacuo using a rotary evaporator to give the crude "imino chloride" as a light yellow solid: 115.15 g (92.6% yield): melting point 106°-108°C.

The above "imino chloride", 114.0 g (0.464 mole), and 1000 ml of xylene were placed in a 3 L 3-necked round bottom flask equipped with a mechanical stirrer, reflux condenser with a nitrogen inlet and a heating mantle. The resulting yellow solution was treated with 161.7 g (0.928 mole) of 1-(2-hydroxyethoxy)ethylpiperazine, rinsing with 200 ml of xylene. This reaction mixture was heated at gentle reflux for 30 h during which time a brown oil began to separate. The reaction mixture was cooled to room temperature. TLC analysis (silica gel, methanol: methylene chloride 1:9, ultraviolet light and iodine detection) indicated complete consumption of the "imino chloride". The mixture was treated with 700 ml of 1 N sodium hydroxide and 700 ml of diethyl ether. The layers were separated and the aqueous phase was extracted once with 500 ml of diethyl ether. The combined ether extract was treated with 400 ml of 1 N hydrochloric acid. The acidic extract was treated with solid sodium carbonate portionwise to give a brown oil which was extracted four times with 400 ml of methylene chloride. These methylene chloride extracts were combined and dried with anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated in vacuo using a rotary evaporator to yield the crude product as a viscous amber oil, 194.5 g, which was purified by flash chromatography as follows. The crude product in a minimum of methylene chloride was applied to a column of silica gel packed in methylene chloride. The column was eluted under nitrogen pressure with 4 L portions each of methylene chloride, and 2%, 4% and 6% methanol:methylene chloride (2:98: 4:96, 6:94 respectively). The title product began to elute with 4% methanol:methylene chloride (4:96). Combination of the pure fractions and removal of the solvent in vacuo gave the title 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperaziny]dibenzo[b,f][1,4]thiazepine 138.7 g (77.7% yield).

A portion of a 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperaziny]dibenzo[b,f][1,4]thiazepine 2.1 g (5.47 mmol) was dissolved in 20 ml of ethanol and treated with 0.67 g (5.7 mmol) of fumaric acid. Upon heating, complete solution was effected for a few minutes after which the salt began to crystallize. After 1 h at room temperature, the resulting solid was collected by filtration and dried in vacuo in a drying pistol over refluxing

ethanol to give the 11-[4-[2-(2-Hydroxyethoxy)ethyl]-1-piperaziny]dibenzo[b,f][1,4]thiazepine, hemifumarate, 2.4 g, melting point 172°-173°C.

**References**

Parikh B.V. et al.; Patent WO 97/45124; Dec. 4, 1997; Assigned: Zeneca Limited [GB/GB]; Stanhope Gate, London Wiy 6LN (GB)
Warawa E.J., Migler B.M.; US Patent No. 4,879,288; Nov. 7, 1989; Assigned: ICI Americas INC., Wilmington, Del.

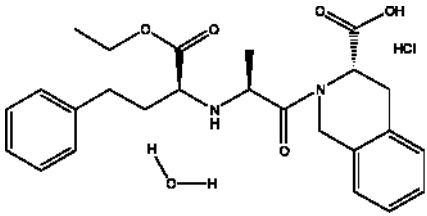
# QUINAPRIL HYDROCHLORIDE HYDRATE

**Therapeutic Function:** Antihypertensive

**Chemical Name:** 3-Isoquinolinecarboxylic acid, 1,2,3,4-tetrahydro-2-(2-((1-(ethoxycarbonyl)-3-phenylpropyl)amino)-1-oxopropyl)-, monohydrochloride, (3S-(2(R*(R*)),3R*))-, monohydrate

**Common Name:** Quinapril hydrochloride

**Structural Formula:**




**Chemical Abstracts Registry No.:** 90243-99-5; 85441-61-8 (Base)

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Accupril | Warner | - | - |
| Accupril | Pfizer | - | - |
| Accupril | Teva Pharmaceuticals | USA | - |
| Accupril | Parke-Davis | - | - |
| Accupro | Parke Davis GmbH/Godecke AG | - | - |

**Raw Materials**

t-Butyl alanine
Triethylamine
Benzyl alcohol
Hydrogen
Ethyl 2-bromo-4-phenylbutanoate
Hydrogen chloride
Polyphosphoric acid
Palladium on carbon

**Manufacturing Process**

A solution of 2.0 g of t-butyl alanine (S-form) and 3.78 g of ethyl 2-bromo-4-phenylbutanoate in 25 ml of dimethylformamide was treated with 1.8 ml of triethylamine and the solution was heated at 70°C for 18 h. The solvent was removed at reduced pressure and the residue was mixed with water and extracted with ethyl ether. The organic layer was washed with water and dried over magnesium sulfate. Concentration of the solvent at reduced pressure gave the oily t-butyl ester of the intermediate which was found to be sufficiently pure by gas liquid chromatography for further use. A solution of 143.7 g of this t-butyl ester in 630 ml of trifluoroacetic acid was stirred at room temperature for one hour. The solvent was removed at reduced pressure and the residue was dissolved in ethyl ether and again evaporated. This operation was repeated. Then the ether solution was treated dropwise with a solution of hydrogen chloride gas in ethyl ether until precipitation ceased. The solid, collected by filtration, was a mixture of diastereoisomers, melting point 153°-165°C.

In order to separate the preferred, S,S-isomer, a suspension of 10.0 g of the mixture in 200 ml of methylene chloride was stirred at room temperature for five min and filtered; the solid was washed with additional methylene chloride and finally ether. The solid material, melting point 202°-208°C (dec.) was the less preferred diastereoisomer having the R,S-configuration (S referring to the portion derived from L-alanine). The preferred S,S-diastereoisomer was recovered from the filtrate after concentration and trituration of the residue with ether; melting point 137°-139°C. The free amino acid (S,S-form) was prepared by treatment of an aqueous solution of the hydrochloride with saturated sodium acetate. The ethyl α-[(1-carboxyethyl)amino]benzenebutanoate hydrochloride (S,S) was filtered, washed efficiently with cold water and recrystallized from ethyl acetate; melting point 149°-151°C.

Benzyl alcohol, 750 ml, was treated with 150 g of commercial polyphosphoric acid and warmed and stirred at 90°C to obtain a homogeneous mixture. Solid 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (S-form) 165.2 g was added. The mixture was stirred 4 h at 95°-105°C and then allowed to stand at room temperature for 18 h. A solution of 18.5 g gaseous hydrochloric acid in 2.5 L of anhydrous ether was added, and the product separated slowly on cooling overnight. Filtration gave the crude tetrahydro-3-isoquinolinecarboxylic acid phenylmethyl ester hydrochloride (S-form). This was purified by recrystallization from ethanol twice to give material with melting point 190.5°-191°C.

Ethyl 7α-[(1-carboxyethyl)amino]benzenebutanoate hydrochloride (S,S) was coupled with 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid phenylmethyl ester free base (S-form) yield 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid phenylmethyl ester maleate (S,S,S) 61%; melting point 151°-153°C (recrystallized from ethyl acetate).

2-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl[amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, phenylmethyl ester, maleate, (S,S,S) was dissolved in tetrahydrofuran was catalytically debenzylated with hydrogen and 20% Pd/carbon at low pressure. The catalyst was filtered off and the 2-

[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid hydrochloride hydrate (S,S,S) was precipitated as a relatively nonhydroscopic solid by the addition of a 10 fold quantity of ether. Melting point 105°-120°C; yield: 56%.

**References**

Hoefle M. L., Klutchko S.; US Patent No. 4,344,949; August 17, 1982; Assigned: Warner-Lambert Company, Morris Plains, N.J.

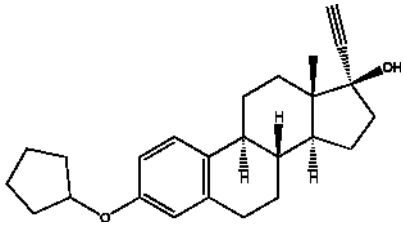
# QUINESTROL

**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 | UK | 1969 |
| Estrovis | Warner Lambert | US | 1979 |
| Agalacto-Quilea | Elea | Argentina | - |
| Basaquines | Boehringer Mannheim | - | - |

**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 17$\alpha$-ethynyl estradiol shows a melting point of 107° to 108°C.

**References**

Merck Index 7959
Kleeman and Engel p. 797
PDR p. 1347
DOT 17 (4) 163 (1981)
I.N. p. 832
REM p. 988
Ercoli, A.; US Patent 3,159,543; December 1, 1964; assigned to Francesco Vismara SpA, Italy
Ercoli, A., Gardi, R. and Pedrali, C.; US Patent 3,231,567; January 25, 1966; assigned to Francesco Vismara SpA, Italy

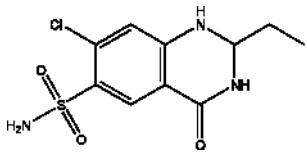
# QUINETHAZONE

**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 | US | 1962 |
| Aquamox | Lederle | UK | - |

**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 and 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.; US Patent 2,976,289; March 21, 1961; assigned to American Cyanamid Company

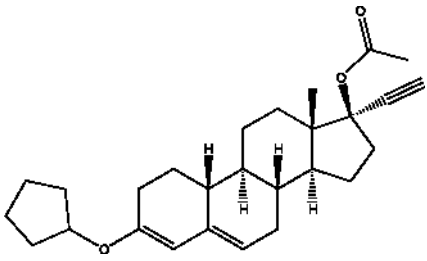
# QUINGESTANOL ACETATE

**Therapeutic Function:** Progestin

**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**

Lithium
Acetic anhydride
3-Cycloethylenedioxy-10-cyano-17α-ethynyl-19-nor-δ(5)-androstene-17β-ol
Ammonia
Cyclopentanol

**Manufacturing Process**

The starting material for the purposes of this discussion is 3-cycloethylenedioxy-10-cyano-17α-ethynyl-19-nor-$\Delta^5$-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-nortestosterone 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 and Engel p. 798
DOT 9 (5) 182 (1973)
I.N. p. 833
Ercoli, A. and Gardi, R.; US Patent 3,159,620; December 1, 1964; assigned to Francesco Vismara S.p.A. (Italy)

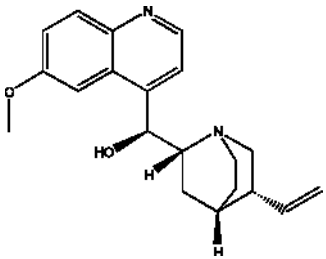
# QUINIDINE

**Therapeutic Function:** Antiarrhythmic

**Chemical Name:** Cinchonan-9-ol, 6'-methoxy-, (9S)-

**Common Name:** Chinidin; β-Chinin; Chinotin; Cinchotin; Conchinin; Conquinine; Kinidin; Pitauine; Quinidine; β-Quinine

**Structural Formula:**




**Chemical Abstracts Registry No.:** 56-54-2

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Quinidine | Glaxo Smithkline | - | - |
| Natcardine | Franco Indian Pharmaceuticals Ltd. | - | - |

**Raw Materials**

Quinine
Benzophenone
Sulfuric acid

**Manufacturing Process**

100 g quinine, 60 g benzophenone in 1 L of dry toluene and 50 g sodium methylate refluxed for 12 hours at 105°-110°C. Then 150 g absolute isopropanol was added and the mixture refluxed for 6 hours. After cooling the solution was extracted with deluted $H_2SO_4$, the sodium hydroxide was added to an acidic extract. The precipitate of the diastereoisomers was filtered off and washed with water to neutral pH. They was divided by usual methods (with help of tartrate or rhodanide). Yield: 45% quinidine and 45% quinine.

**References**

Dietrich H. et al; D.B. Patent No. 877,611; 8 July 1949; Assigned to C.F.Boehringer and Soehne G.m.b.H., Manheim-Waldorf.

# QUINIDINE POLYGALACTURONATE

**Therapeutic Function:** Antiarrhythmic

**Chemical Name:** D-Galacturonic acid, homopolymer, compd. with (9S)-6'-methoxycinchonan-9-ol

**Common Name:** -

**Structural Formula:** Quinidine polygalacturonate

**Chemical Abstracts Registry No.:** 65484-56-2

| Trade Name | Manufacturer | Country | Year Introduced |
|---|---|---|---|
| Cardioquin | Purdue Frederick | US | 1960 |
| Cardioquin | N.A.P.P. | UK | 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 methanol 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.; US Patent 2,878,252; March 17, 1959; assigned to Synergistics, Inc.

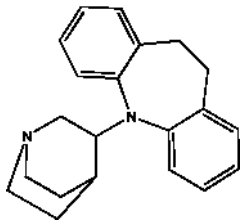
# QUINUPRAMINE

**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 10 N 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 and 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