

SPECIFICATION

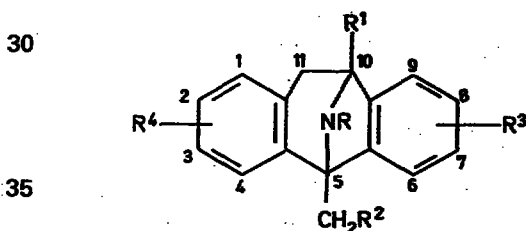
Dibenzocyclohepteneimines

- 5 This invention is concerned with 5-substituted - 10, 11-dihydro-5H-dibenzo[a,d]cyclohepten-5, 10-imines and their derivatives, pharmaceutically acceptable salts of such compounds, including optical isomers thereof. Compounds of the present invention can be used as antianxiety agents, as muscle relaxants, and in the treatment of extrapyramidal disorders such as in Parkinson's disease.

Structurally related compounds are known to have qualitatively similar utilities. For example U.S. Patent 15 3,892,756 discloses 10, 11-dihydro-5H-dibenzo[a,d]cyclohepten-5, 10-imine and derivatives which are unsubstituted at the 5-bridgehead carbon; and Belgian Patent 829,075 discloses 9, 10-dihydroanthracen-9, 10-imines and derivatives.

- 20 This invention provides certain 5-substituted - 10, 11-dihydro-5H-dibenzo[a,d]cyclohepten-5, 10-imines, novel processes for their synthesis and pharmaceutical compositions comprising them as active ingredient. Compounds of the present invention have been found surprisingly more active than the unsubstituted analogues.

The novel compounds of this invention have the structural formula:



or are pharmaceutically acceptable salts thereof, where

- 40 R is (1) hydrogen
(2) C₁₋₅ alkyl, preferably methyl or ethyl,
(3) C₂₋₅ alkenyl, preferably vinyl or allyl,
(4) (phenyl or substituted phenyl) - C₁₋₃ alkyl, preferably benzyl or substituted benzyl, where the substituent is halo such as fluoro, chloro or bromo, especially chloro, or C₁₋₃ alkyl,
(5) C₃₋₆ cycloalkyl, preferably cyclopropyl or cyclohexyl,
(6) (C₃₋₆ cycloalkyl) - (C₁₋₃ alkyl), or
50 (7) di(C₁₋₅ alkyl)amino - (C₁₋₅ alkyl), especially dimethylaminopropyl;
R' is (1) hydrogen,
(2) C₁₋₅ alkyl, preferably methyl or ethyl,
(3) C₂₋₅ alkenyl, preferably vinyl or allyl,
55 (4) phenyl - (C₁₋₃ alkyl), preferably benzyl,

(5) C₃₋₆ cycloalkyl, preferably cyclopropyl or cyclohexyl, or

- (6) (C₃₋₆ cycloalkyl) - (C₁₋₃ alkyl),
-CH₂R² is (1) C₁₋₅ alkyl, preferably methyl or ethyl,
60 (2) C₃₋₅ alkenyl, preferably allyl,
(3) phenyl - (C₁₋₃ alkyl), preferably benzyl,
(4) (C₃₋₆ cycloalkyl) - (C₁₋₃ alkyl),
(5) di(C₁₋₅ alkyl)amino - (C₁₋₅ alkyl), especially dimethylaminopropyl; or
65 (6) C₂₋₃ hydroxyalkyl, preferably hydroxyethyl;
and R³ and R⁴ are independently,
(1) hydrogen
(2) halogen, such as chloro, bromo, fluoro, or iodo,
(3) C₁₋₅ alkoxy, preferably methoxy,
70 (4) trifluoromethylthio,
(5) cyano,
(6) carboxy, or
(7) hydroxy.

A preferred group of compounds is that wherein

- 75 R' is hydrogen.

Another preferred group of compounds is that wherein R³, R⁴ and R⁵ are hydrogen.

Where R³ and/or R⁴ are other than hydrogen, it is preferred that they occupy the 2, 3, 7 or 8 positions of the tricyclic ring system.

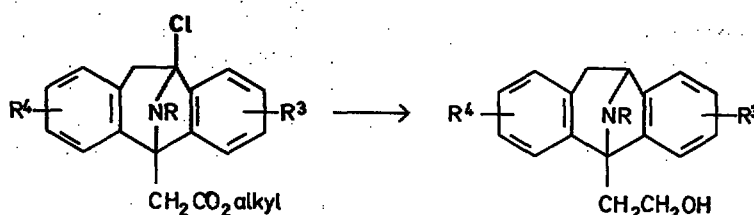
- 80 Preferred definitions for -CH₂R² are C₁₋₅ alkyl, especially methyl or ethyl, and hydroxyethyl.

Preferred definitions for R are hydrogen, C₁₋₅ alkyl or benzyl.

- 85 The novel compounds of this invention wherein R is hydrogen are generally prepared by reduction of the N-hydroxy analog. These N-hydroxy compounds are claimed in the specification of our copending application No. 8037685 (Serial No. 2061947). The preferred reducing agent is nascent hydrogen generated by the action of a metal, preferably zinc with an acid such as acetic acid at 40 to 100°C for 1 to 10 hours.

- The novel compounds are also prepared by ring closure of a 10-NHR-5-(=CHR²)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene by treatment with a strong base such as an organometallic reagent, for example, *n*-butyllithium in an ethereal solvent, such as tetrahydrofuran or 1,2-dimethoxy-ethane, at 0°C to 30°C for 5 minutes to 1 hour.

- Where -CH₂R² is C₂₋₃ hydroxyalkyl, the final step in its synthesis is reduction of the C₁₋₅ alkoxy-carbonyl precursor. The preferred reducing agent is lithium aluminium hydride in an ethereal solvent such as diethyl ether, tetrahydrofuran or 1,2-dimethoxyethane at a temperature of 15°C to 100°C until the reduction is substantially complete, which takes 1 to 6 hours. This procedure also serves to hydrogenolyse a bridgehead halo group in the exemplified synthetic scheme:



Where R is other than hydrogen, the novel compounds are prepared by alkylation of the compounds wherein R is hydrogen with the appropriate reagent of formula R-halo wherein halo represents chloro, 5 bromo or iodo. The reaction is normally conducted in an inert solvent such as benzene or toluene. However, the alkylating reagent, depending on its physical properties, may be used in sufficient excess to act as solvent. It is preferred to conduct the reaction in the presence of an acid acceptor such as an inorganic carbonate such as sodium carbonate, an organic base such as pyridine, or a basic resin. Temperatures of 50°C to 100°C may be employed over reaction times of 10 hours to 5 days.

15 Where R is alkyl or substituted alkyl, the compounds also may be prepared by reduction of an N-acyl compound such as alkoxycarbonyl to give methyl or other alkanoyl groups to provide the other alkyl groups. The preferred reducing system is a 20 metal hydride such as lithium aluminium hydride in an ethereal solvent such as ether, tetrahydrofuran or 1,2-dimethoxyethane. The reaction proceeds satisfactorily at room temperature but temperatures from 0°C to 50°C are appropriate with reaction times of 25 10-13 hours.

Novel compounds having substituents on the benzenoid rings are generally prepared by metathesis of the appropriate bromo or iodo compound. For example treatment with a sodium C₁₋₅ alkoxide in 30 the presence of copper dust in an inert organic solvent such as dimethyl formamide at 50-150°C for 1-10 hours yields the corresponding C₁₋₅ alkoxy compound.

The 2, 3, 7 or 8-hydroxy compounds are prepared 35 from the corresponding alkoxy, preferably methoxy, compounds by de-etherification. The preferred process comprises heating with pyridine hydrochloride at 200-220°C for 3-10 hours.

Treatment of a bromo or iodo compound with 40 cuprous cyanide in an inert organic solvent such as dimethyl formamide at reflux temperature for 1-10 hours yields the corresponding cyano compound.

Hydrolysis of the above cyano compounds with a mineral acid such as hydrochloric acid at about 50 to 45 150°C and especially at reflux temperature produces the corresponding carboxy substituted compounds.

Also treatment of the bromo or iodo compounds with bis (trifluoromethylthio) mercury and copper dust in an inert organic solvent such as dimethyl 50 formamide or quinoline at about 100-200°C for 1-10 hours yields the trifluoromethylthio derivatives.

Thus there are prepared the compounds:

3 - (or 7) - R^a - 5 - methyl - 10, 11 - dihydro - 5H - dibenzo [a, d] cyclohepten - 5, 10 - imines;
55 3 - R^a - 12 - cyclopropylmethyl - 5 - methyl - 10, 11 - dihydro - 5H - dibenzo [a, d] cyclohepten - 5, 10 - imines;
2 - R^a - 12 - dimethylaminopropyl - 5 - ethyl - 10, 11 - dihydro - 5H - dibenzo [a, d] cyclohepten - 5, 10 - 60 imines; and
7 - R^a - 5, 12 - diethyl - 10, 11 - dihydro - 5H - dibenzo [a, d] cyclohepten - 5, 10 - imines;
wherein:

R^a is C₁₋₅ alkoxy, hydroxy, cyano, carboxy or trifluoromethylthio.

The novel compounds can be resolved into their optical isomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl - *d* - tartaric acid and/or (+) - di-*p*-toluoyl - *l* - tartaric acid followed by fractional crystallization and regeneration of the free base.

70 The starting materials and processes used for preparing the intermediates used in the above described processes are fully described in the Examples.

Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the novel compounds. Acid-addition salts of the imine compounds are formed by mixing a solution of the imine with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid or phosphoric acid. Where the novel compound carries a carboxylic acid group, the invention also contemplates sodium, potassium and calcium salts thereof.

The novel imines of this invention are capable of producing anxiety relief without causing excessive sedation or sleep at a dosage level of from 0.01 to 50 mg per kilogram of body weight, preferably 0.05-10 mg/kg of body weight, on a regimen of 1-4 times a day. In addition, the novel compounds of the present invention are useful as muscle relaxants, as anticonvulsants and in the treatment of extrapyramidal disorders when indicated at comparable dosage levels. It is understood that the exact treatment level will depend upon the case history of the animal or human individual being treated and in the last 90 analysis the precise treatment level falling within the above guidelines is left to the discretion of the therapist.

Also included within the scope of the present invention are pharmaceutical compositions comprising the imines of this invention. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, or suppositories for oral, parenteral or rectal administration. A unit dose 100 contains from 0.1 to about 500 mg of active ingredient.

The following Examples representatively illustrate, but do not limit, the present invention.

EXAMPLE 1

115 5 - Methyl - 10 - 11 - dihydro - 5H - dibenzo [a, d] cyclohepten - 5, 10 - imine and oxalate salt

Step A:

Preparation of 10 - (1 - piperidyl) - 5H - dibenzo [a, d] cyclohepten - 5 - one

120 A mixture of 71.3 g of 10 - bromo - 5H - dibenzo [a, d] cyclohepten - 5 - one, 50 ml. of piperidine, 1 liter of *t*-butanol and finally 33.6 g of potassium *t*-butoxide was stirred under reflux 2 hours, then at room temperature overnight. The mixture was filtered, and concentrated to dryness. The residue was slurried with water and decanted. The residue was slurried with methanol and filtered to give 59.8 g of 10 - (1 - piperidyl) - 5H - dibenzo [a, d] cyclohepten - 5 - one, 125 m.p. 103-105°C.

Step B:**Preparation of 5-hydroxy-5-methyl-10-(1-piperidyl)-5H-dibenzo[a,d]cycloheptene**

A solution of 140 ml. of 1.8 molar methyl lithium in 5 ether and 250 ml. of ether at 5-10°C under nitrogen was treated dropwise with a solution of 59 g of 10-(1-piperidyl)-5H-dibenzo[a,d]cyclohepten-5-one in 250 ml of tetrahydrofuran. After a total of 2 hours, the mixture was poured onto ice and allowed to stand until the ice melted. The mixture was extracted well with ether and the extract was dried (Na₂SO₄), filtered, and concentrated to dryness, the residue being used directly in the next step.

Step C:**Preparation of 5-methylene-10-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene**

The carbinol from Step B was dissolved in 500 ml of 10N ethanolic hydrogen chloride and 30 ml concentrated hydrochloric acid and heated under reflux overnight. The solvent was evaporated and the residue was extracted with 500 ml of benzene. The extract was dried and concentrated to dryness. The residue was extracted with 300 ml of boiling hexane. On cooling the extract deposited 18.5 g solid which after recrystallization from hexane gave 16.5 g of 5-methylene-10-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, m.p. 84-86°C.

Step D:**Preparation of 10-hydroximino-5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene**

A mixture of 16.5 g of the oxo-compound from Step C, 6.6 g of hydroxylamine hydrochloride, 8.2 of sodium acetate and 300 ml of methanol was heated under reflux for 5 hours. The solvent was evaporated and the residue was treated with 250 ml of water. The mixture was extracted with 3 × 150 ml of ether, and the extract was dried, filtered, and evaporated to give 16.8 g of 10-hydroximino-5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, m.p. 156-160°C.

Step E:**Preparation of 10-hydroxamino-5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene**

A mixture of 15.3 of oxime from Step D, 500 ml of methanol, 12 g of sodium cyanoborohydride in 450 ml of methanol was treated dropwise with a solution of 12 ml of 12N hydrochloric in 50 ml of methanol over 5 hours, and then stirred overnight at room temperature. The solvent was evaporated, the residue was stirred with 200 ml of 1N aqueous hydrochloric acid, made alkaline with concentrated ammonium hydroxide and extracted with 3 × 175 ml of ether. The combined extracts were dried (Na₂SO₄), filtered and evaporated. The crystalline residue was washed with methanol to give 9.6 g of 10-hydroxamino-5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, m.p. 145-147°C.

Step F:**Preparation of 12-hydroxy-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine****imine**

A solution of 8.8 g of the hydroxamino compound from Step E in 200 ml of xylene was added dropwise to 80 ml of refluxing xylene. After 1 hour of refluxing the solvent was evaporated. The residue was treated with 250 ml of water and 7 ml of concentrated hydrochloric acid and the mixture was washed with 100 ml of ether and the wash was discarded. The aqueous phase was made basic with concentrated ammonium hydroxide and extracted with 3 × 100 ml of ether. The extract was dried (Na₂SO₄), filtered and evaporated. The residue was recrystallized from cyclohexane to give 8.5 g of 12-hydroxy-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine, m.p. 141-144°C.

Step G:**Preparation of 5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine and oxalate salt**

A mixture of 1.2 g of the hydroxy-imine from Step F, 7 ml of acetic acid and 1.2 g of zinc dust was heated at 60-70°C for 3.5 hours. The mixture was filtered and the filter cake was washed with 200 ml of ether and 50 ml of water. The filtrate was made basic with 5% (w/v) aqueous sodium hydroxide and extracted with ether. The extract was dried (Na₂SO₄), filtered and evaporated to dryness to give 1.1 g of product. This material (1.1 g) was dissolved in 20 ml of acetone and treated with 0.6 g of oxalic acid in 10 ml of acetone. After cooling overnight, there was collected 1.2 g of 5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine, m.p. 203-206°C (dec.), which after recrystallization from methanol/acetone, had m.p. 215-217°C (dec.).

EXAMPLE 2**5-Ethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine****Step A:****Preparation of 5-ethylidene-10-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene**

To a stirred slurry of ethyltriphenylphosphonium bromide (21 g, 0.057 mole) in ether (400 ml) was added dropwise butyllithium in hexane (48 ml, 1.3 M). To the resulting solution was added a solution of 1-(5-keto-5H-dibenzo[a,d]cyclohepten-10-yl)-4-methylpiperazine (13.5 g, 0.044 mole) in THF (100 ml). The resulting mixture was stirred and heated under reflux for 3.5 hours, cooled and poured into ice H₂O (300 ml). The organic phase was separated and the aqueous phase extracted with ether (2 × 150 ml). The combined organic solutions were concentrated under reduced pressure. The concentrate was stirred with a mixture of 1N aqueous hydrochloric acid (300 ml) and ether (300 ml). The ether phase was separated, the aqueous phase extracted with ether, and the combined ether solutions dried over Na₂SO₄, filtered and the filtrate concentrated to 100 ml. Triphenylphosphine oxide was removed by filtration and the filtrate was chromatographed on silica-gel which was eluted with chloroform to yield 10.1 g (98%) of 5-ethylidene-10-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, m.p. 93-95°C.

Following the procedure substantially as described in Example 1, Steps D through G but substituting for the 5-methylene-10-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene used in

5 Step D thereof, an equimolecular amount of 5-ethylidene-10-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, there is produced in sequence: 5-ethylidene-10-hydroximino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, (86% yield), m.p.

10 128-131°C;

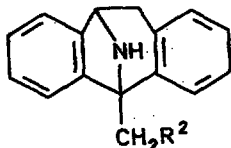
5-ethylidene-10-hydroxamino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (89% yield), m.p. 121-124°C;

5-ethyl-12-hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine, (21% yield), m.p. 112-116°C; and

5-ethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine, (90% yield) and the hydrogen oxalate salt, m.p. 240-241°C.

20 Employing the procedure substantially as described in Example 2 but substituting for the ethyltriphenylphosphonium bromide used in Step A, an equimolecular amount of a Wittig reagent of formula $(C_6H_5)_3P^+-CH_2R^2(Br^-)$, wherein $-CH_2R^2$ is $-CH_3$,

25 $-CH_2CH_2CH_3$, or $-(CH_2)_3CH_3$, there are produced the components of formula:



wherein $-CH_2R^2$ represents $-CH_3$, $-CH_2CH_2CH_3$ (m.p. 298-299.5°C as the HCl. 1/2 CH_3COCH_3) and

35 $-(CH_2)_3CH_3$.

EXAMPLE 3

5-(2-Hydroxyethyl)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine

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Step A:

Preparation of 5-ethoxycarbonylmethylene-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-10-one

Triethylphosphonoacetate, 10 g (0.045 mole) was added dropwise to a slurry of 1.9 g (0.04 mole) of sodium hydride (50% in mineral oil) in 20 ml of dry toluene under nitrogen and keeping the temperature at 30-35°C by cooling. The mixture was stirred 1 hour at room temperature. A solution of 10 g (0.0328

50 mole) of 1-(5-keto-5H-dibenzo[a,d]cyclohepten-10-yl)-4-methylpiperazine in 75 ml of dry toluene was added dropwise, keeping the temperature at 25-30°C by cooling. The mixture was stirred at room temperature for 3 hours and held at room temperature overnight. After decanting the solution, the precipitate was washed with four 25 ml portions of toluene at 65°C. The combined toluene extracts were diluted with an equal volume of ether and shaken with 75 ml of 0.5N hydrochloric acid. The aqueous

60 acid layer was separated and re-extracted with toluene-ether (1:1). The combined organic phases were washed with water, dried over magnesium sulfate, filtered, and concentrated. The oily solid obtained was freed from the bulk of the oil by collection on a sintered glass funnel and then triturated

with cyclohexane to yield 4.5 g (47%) of 5-ethoxycarbonylmethylene-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-10-one, m.p. 56-62°C.

70 Step B:

Preparation of 5-ethoxycarbonylmethyl-10,12-dihydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine

The keto-olefin from Step A, 23.4 g (0.08 mole), together with hydroxylamine hydrochloride (6.0 g), sodium acetate trihydrate (12.0 g) and wet ether (300 ml) was stirred at room temperature. After 16 hours, the precipitate was collected, washed with ether, and stirred with water (300 ml) for 1 hour. The solid was collected and dried to obtain 21.6 g (83%) of 5-ethoxycarbonylmethyl-10,12-dihydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine, m.p. 193-195°C dec.

85 Step C:

Preparation of 5-ethoxycarbonylmethyl-10-hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine

The N-hydroxyimine from Step B, 21 g (0.0646 mole), was suspended in glacial acetic acid (125 ml) and zinc dust (16 g) was added in portions over 15 minutes. After the exothermic reaction had subsided, the mixture was stirred and heated in an oil bath at 65°C for 3 hours. The cooled mixture was filtered and the filtrate was evaporated under reduced pressure. The residual syrup was dissolved in water (500 ml) and the filtered solution was made basic with 15% aqueous sodium hydroxide. The precipitate was collected, washed with water, and dried to yield 15 g of 5-ethoxycarbonylmethyl-10-hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine, m.p. 186-189°C dec. A filtered solution of this product in boiling acetone (350 ml) was treated with 7N ethanolic hydrogen chloride (7 ml). The precipitate of the hydrochloride salt was collected, washed with ether, and dried to obtain 14.35 g (64%), m.p. 247-250°C dec.

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Step D:

110 Preparation of 10-chloro-5-ethoxycarbonylmethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine

The hydrochloride salt of the product from Step C, 17.8 g (0.0515 mole) was slurried in thionyl chloride (250 ml) and the mixture was heated to refluxing. After the ensuing exothermic reaction subsided the mixture was heated at reflux for 20 minutes when the solid had dissolved completely. The thionyl chloride was evaporated under reduced pressure and the last traces were removed by repeated co-evaporation with toluene. The residue was triturated with acetone and dried to give 15.35 g (81%), m.p. 223-227°C dec., of 10-chloro-5-ethoxycarbonylmethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrochloride.

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Step E:

Preparation of 5-(2-hydroxyethyl)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine

130 The hydrochloride from Step D, 15.3 g (0.042

mole), was added in portions to a slurry of lithium aluminum hydride (5.6 g, 0.147 mole) in ether (200 ml) and tetrahydrofuran (200 ml). The mixture was stirred at reflux for 3 hours, then cooled to 0°C, and hydrolyzed by the dropwise addition of water (4 ml) and 10% aqueous sodium hydroxide (4 ml.). After dilution with ether, the precipitate was collected, suspended in chloroform (250 ml) and stirred at room temperature for 1 hour. The mixture was filtered and the filtrate was combined with the previously obtained ethereal filtrate. Solvents were evaporated under reduced pressure and the solid obtained was recrystallized from 95% ethanol to yield 8.6 g of 5 - (2 - hydroxyethyl) - 10, 11 - dihydro - 5H - dibenzo [a, d] cyclohepten - 5, 10 - imine, m.p. 181-184°C. Recrystallization from 70% ethanol gave m.p. 182-184°C.

A suspension of this product (4.4 g) in warm absolute ethanol (20 ml) was treated with 7N ethanolic hydrogen chloride (2.5 ml) and the mixture was stirred until all of the solid dissolved. Dilution with ether precipitated the hydrochloride salt; 4.8 g, m.p. 263-265°C. Recrystallization from acetonitrile gave m.p. 262-264°C dec.

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Example 4

3 - (and 7) - Bromo - 5 - methyl - 10, 11 - dihydro - 5H - dibenzo [a, d] cyclohepten - 5, 10 - imine

30 Step A:

Preparation of 3, 10, 11 - tribromo - 5H - dibenzo - [a, d] cyclohepten - 5 - one

A solution of bromine (53 g., 0.33 mole) in glacial acetic acid (125 ml.) was added dropwise to a stirred slurry of 3 - bromo - 5H - dibenzo [a, d] cyclohepten - 5 - one (71.25 g., 0.25 mole) in glacial acetic acid (775 ml.). After the mixture had been stirred at room temperature for several hours, the solid was collected, washed with glacial acetic acid and dried; yield, 105.8 g (95%), m.p. 173-175°C.

40 Step B:

Preparation of 3, 10 - dibromo - 5H - dibenzo [a, d] cyclohepten - 5 one and 3, 11 - dibromo - 5H - dibenzo [a, d] cyclohepten - 5 - one

45 The product from Step A was added to a stirred solution of sodium hydroxide (28 g., 0.7 mole) in methanol (2 liter). The thick mixture was stirred at reflux for 1 1/4 hours. After cooling, the solid was collected, washed with methanol and then with water, and dried to obtain 81 g. (90%) of the mixture of 3, 10 - dibromo - 5H - dibenzo [a, d] cyclohepten - 5 - one and 3, 11 - dibromo - 5H - dibenzo [a, d] cyclohepten - 5 - one, m.p. 146-156°C.

55 Step C:

Preparation of 3 - bromo - 10 - (4 - methyl - piperazinyl) - 5H - dibenzo [a, d] cyclohepten - 5 - one and 3 - bromo - 11 - (4 - methylpiperazinyl) - 5H - dibenzo [a, d] cyclohepten - 5 - one

60 Potassium tert-butoxide (6.8 g., 0.06 mole) was added to a stirred slurry of 3, 10 - dibromo - 5H - dibenzo [a, d] cyclohepten - 5 - one and 3, 11 - dibromo - 5H - dibenzo [a, d] cyclohepten - 5 - one (18.2 g., 0.005 mole), 4 - methylpiperazine (10 ml.), and dry tert-butyl alcohol (200 ml.) at room temperature

and under nitrogen. The dark orange mixture was heated to refluxing for 2 hours and then stirred at room temperature overnight. The mixture was poured into approximately 800 ml. of ice and water and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. The mixture of 3 - bromo - 10 - (4 - methylpiperazinyl) - 5H - dibenzo [a, d] cyclohepten - 5 - one and 3 - bromo - 11 - (4 - methylpiperazinyl) - 5H - dibenzo [a, d] cyclohepten - 5 - one was obtained as a residual red-yellow gum; yield, 19.4 g. 100%.

Step D:

80 Preparation of 3 - bromo - 5 - methyl - 10 - (4 - methylpiperazinyl) - 5H - dibenzo [a, d] cyclohepten - 5 - ol and 3 - bromo - 5 - methyl - 11 - (4 - methylpiperazinyl) - 5H - dibenzo [a, d] cyclohepten - 5 - ol

85 Methylolithium, 35 ml. of a 1.6 M solution in ether, was added dropwise to a stirred solution of the product from Step C (18 g., 0.047 mole) in ether (200 ml) and tetrahydrofuran (60 ml) cooled in an ice bath and under nitrogen. Stirring was continued at room temperature for 3 hours. The mixture was cooled in ice and hydrolyzed by the dropwise addition of water. After dilution with ether and water, the layers were separated and the aqueous phase was re-extracted with ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate and evaporated. The mixture of 3 - bromo - 5 - methyl - 10 - (4 - methylpiperazinyl) - 5H - dibenzo - [a, d] cyclohepten - 5 - ol and 3 - bromo - 5 - methyl - 11 - (4 - methylpiperazinyl) - 5H - dibenzo [a, d] cyclohepten - 5 - ol was obtained as a residual dark yellow glass; yield, 18 g. (96%).

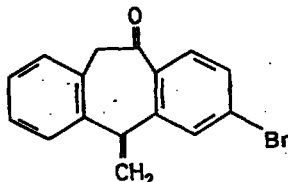
Step E:

105 Preparation of 3 - bromo - 5 - methylene - 10, 11 - dihydro - 5H - dibenzo [a, d] cyclohepten - 10 - one and 7 - bromo - 5 - methylene - 10, 11 - dihydro - 5H - dibenzo [a, d] cyclohepten - 10 - one

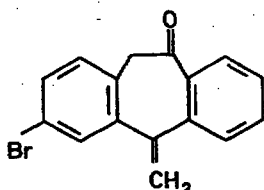
A mixture of the product from Step D (18 g., 0.045 mole), 95% ethanol (80 ml.), 7N ethanolic hydrogen chloride (40 ml.), and 6N aqueous hydrochloric acid (80 ml.) was stirred at room temperature for 30 minutes and at reflux temperature for 1 hour. The mixture consisted of a brown oily lower phase and an aqueous alcoholic upper phase. The latter was decanted and the alcohol was stripped *in vacuo*. The residual aqueous mixture was extracted with chloroform. The previously obtained brown oil was dissolved in chloroform and the combined chloroform phases were washed with water and dried over anhydrous magnesium sulfate. Evaporation of the filtered extract left the crude product as a residual dark yellow glass. This material was chromatographed on a silica gel column, eluting with toluene. Evaporation of the appropriately combined fractions left the partially purified product as an oily solid (8.5 g.). Trituration with cyclohexane afforded one of the isomers of the product as a white solid; yield, 2.6 g., m.p. 125-158°C. Two recrystallizations from cyclohexane gave m.p. 158-163°C. Evaporation of the first cyclohexane-mother liquor left the remaining isomer of the product as a dark yellow oil.

Trituration with three successive 10 ml. portions of hexane afforded a yellow solid; yield, 3.3 g., m.p. 75-83°C. Two recrystallizations from hexane gave m.p. 84-89°C.

- 5 The higher melting isomer (m.p. 160-164°C) has structural formula:



- 10 and is named 7-bromo-5-methylene-10,11-
15 dihydro-5H-dibenzo[a,d]cyclohepten-10-one.
The other isomer, 3-bromo-5-methylene-10,11-
-dihydro-5H-dibenzo[a,d]cyclohepten-10-one
(m.p. 84-91°C) has structural formula:



Step F through I:

Preparation of 3 (and 7)-bromo-5-methyl-10,11-
dihydro-5H-dibenzo[a,d]cyclohepten-5,10-
imine

Employing the procedure substantially as described in Example 1, Steps D through G, but substituting for the 5-methylene-10-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene employed therein, an equimolecular amount of the corresponding 3- and 7-bromo-compounds there is produced in sequence the following:

(Step F):

3 (and 7)-bromo-10-hydroximino-5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, m.p.'s 171-175°C and 179-181°C respectively;

(Step G):

3 (and 7)-bromo-10-hydroxamino-5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, m.p.'s 149-153°C and 136-139°C respectively;

(Step H):

3 (and 7)-bromo-12-hydroxy-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine, m.p.'s 175-180°C and 187-189°C respectively;

and

(Step I):

3 (and 7)-bromo-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrochloride, m.p.'s >300°C.

Similarly prepared are:

8-bromo-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine;

2-bromo-5-ethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine; and

7-bromo-5-ethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine.

EXAMPLE 5

10,11-Dihydro-5,12-dimethyl-5H-dibenzo[a,d]cyclohepten-5,10-imine fumaric acid salt

Step A:

Preparation of 10,11-dihydro-12-ethoxycarbonyl-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine

- 70 A mixture of 1.15 g of 10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine, 1.0 g of anhydrous sodium carbonate, 1 ml of ethyl chloroformate and 10 ml of dry benzene was stirred at reflux temperature for 2 hours. The mixture was filtered and the filtrate was evaporated *in vacuo* to give 1.45 g of white crystalline 10,11-dihydro-12-ethoxycarbonyl-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine, m.p. 80-83°C.

Step B:

Preparation of 10,11-dihydro-5,12-dimethyl-5H-dibenzo[a,d]cyclohepten-5,10-imine

- A solution of the urethan from Step A in 15 ml of absolute ether was added dropwise to a slurry of 190 mg of lithium aluminum hydride in 15 ml of absolute ether with stirring and under nitrogen. After 24 hours at room temperature, the mixture was cooled in an ice bath and hydrolyzed by the dropwise addition of the minimum volume of water containing a few drops of 5% (w/v) aqueous sodium hydroxide. After dilution with ether, the mixture was filtered. The filtrate was evaporated *in vacuo* to give 1.1 g of the free base of the product as a colorless oil. This was combined with 0.9 g of similar material and dissolved in 25 ml of ethyl acetate. A warm solution of 1.2 g of fumaric acid in 12 ml of methanol was added. The fumaric acid salt which crystallized was collected and was recrystallized from methanol-ethyl acetate to give 2.1 g of 10,11-dihydro-5,12-dimethyl-5H-dibenzo[a,d]cyclohepten-5,10-imine fumaric acid salt, m.p. 186-188°C.

EXAMPLE 6

12-Benzyl-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine

- A mixture of 2.45 g of 10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine, 1.9 g of benzyl chloride, 3.2 g of anhydrous sodium carbonate and 50 ml of dry benzene was stirred at reflux temperature for 4 days. The mixture was filtered and the filtrate was evaporated *in vacuo* to give 3.1 g of the product as an oily solid, m.p. 107-111°C. This was recrystallized twice from 95% ethanol to give 1.85 g of white crystalline 12-benzyl-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine, m.p. 111-114°C.

EXAMPLE 7

12-Allyl-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine

- A mixture of 2.45 g of 10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine, 1.8 g of allyl bromide, 3.0 g of anhydrous sodium carbonate and 50 ml of dry benzene was stirred at reflux temperature for 20 hours. The mixture was filtered and the filtrate was evaporated *in vacuo* to give 1.2 g of the oily free base of the product. This was dissolved in 5 ml of acetone and added to a warm solution of 0.75 g of fumaric acid in 75 ml of acetone. The salt which crystallized was collected and recrystallized

from acetone to give 1.45 g of white crystalline 12-allyl-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine fumaric acid salt, m.p. 180-182°C.

- 5 Employing the procedure of Example 7, but substituting for the allyl bromide and the 10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-

imine used therein a compound of formula R-I and 5-R²CH₂-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine, described in Table II, there are produced the 5-R²CH₂-12-R-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imines also described in Table II, in accordance with the following reaction:

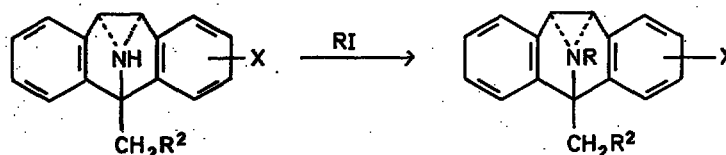


TABLE II

R ²	R	X
-H		H (m.p. 132.5-135.5°C)
-H		H (m.p. 111-113°C hydrogen oxalate)
-H		H (m.p. 115.5-117°C)
-CH ₃		H (m.p. 163-164°C)
-CH ₂ CH ₃		H (m.p. 132.5-135.5°C)
H		H (m.p. 112-114.5°C)
H		H (m.p. 111-113°C, base)
H		3-Br
-CH ₃	-(CH ₂) ₃ N(CH ₂) ₃	2-Br
-CH ₃	-C ₂ H ₅	7-Br

- 15 **EXAMPLE 8**
5,10,12-Trimethyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5,10-imine hydrochloride

Step A:

- 20 Preparation of 10-amino-5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

To a stirred slurry of zinc dust (.9 g, 0.138 mole) in 100 ml of glacial acetic acid stirred in an oil bath at 65° was added 10-hydroxamino-5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (10 g, 42 mmole). The mixture was stirred in the oil bath for 2 hours, cooled, and quenched in 500 ml of water.

The mixture was made basic with concentrated ammonia, then extracted with ether. The combined ether layers were washed with water, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was recrystallized from hexane to give 7.8 g, m.p. 84.5-86.5°.

35 Step B:

Preparation of 10-isocyano-5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

To a solution of 10-amino-5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (8.1 g, 36.6 mmole) in chloroform (180 ml) was added sodium

hydroxide pellets (4.42 g, 0.11 mole) benzyl-triethylammonium chloride (0.42 g, 1.8 mmole) and water (0.5 ml). The mixture was stirred under nitrogen until the sodium hydroxide pellets dissolved (ca 4 hours), treated with anhydrous potassium carbonate, filtered, and evaporated to dryness *in vacuo*. The resulting oil was dissolved in chloroform (180 ml), treated with another 1.5 g (37.5 mmole) of sodium hydroxide and 0.2 g (.86 mmole) of benzyl-triethylammonium chloride, and stirred overnight under nitrogen. The mixture was again dried over potassium carbonate, filtered, and evaporated to dryness *in vacuo*. The resulting oil was chromatographed on 120 g of silica gel, and eluted with methylene chloride. The combined product fractions were evaporated to dryness *in vacuo* and the resulting solid was recrystallized from ether to give 4 g of solid, m.p. 96-98°.

20 Step C:

Preparation of 10-isocyano-10-methyl-5-methylene-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene

Diisopropylamine (1.1 g, 10.9 mmole) in 25 ml of dry tetrahydrofuran was stirred in a dry ice/acetone bath. Under a nitrogen blanket, this solution was treated with n-butyllithium/hexane (5.0 ml of 2.2M solution) added dropwise over 10 minutes. After 5 minutes, a solution of 10-isocyano-5-methylene-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene (2.4 g, 10.4 mmole) in 25 ml of dry tetrahydrofuran was added dropwise (over 45 minutes) to the lithium diisopropylamide solution. The resulting deep red solution was stirred in the cold for 15 minutes then treated with methyl iodide (4.56 g, 32 mmole) added all at once. The mixture was stirred 2 hours in the cold and an additional 1 hour at room temperature. The solvent was removed *in vacuo* and the residue chromatographed on 75 g of silica gel, eluted with methylene chloride. The combined product fractions were evaporated *in vacuo* to give 2.2 g (86%) solid. Recrystallization from ether gave, m.p. 146-147.5°C.

Step D:

Preparation of 10-methyl-10-methylamino-5-methylene-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene hydrogen chloride

10-isocyano-10-methyl-5-methylene-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene (1.8 g, 7.3 mmole), dissolved in dry ether (100 ml) was added dropwise to a slurry of lithium tetrahydridoaluminate (0.53 g, 14 mmole) in ether (40 ml) stirred under nitrogen. The mixture was heated at reflux for 1 hour, cooled, and the excess hydride decomposed by careful dropwise addition of 1.5 ml of ice water. The suspension was filtered and the solids washed twice with ether. The combined ether fractions were evaporated *in vacuo* to 1.8 g of oil. This oil, dissolved in 10 ml of absolute ethanol was treated with a slight excess of 8N ethanolic HCl and cooled to give 1.7 g (81%) of powder, m.p. 238-240° (d).

Step E:

Preparation of 5,10,12-trimethyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine hyd-

rogen chloride.

10-Methyl-10-methylamino-5-methylene-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene (1.6 g, 6.4 mmole) was dissolved in dry tetrahydrofuran (40 ml). To this solution, stirred at room temperature under nitrogen, was added n-BuLi (3.0 ml of a 2.2M solution in hexane) dropwise over 5 minutes. The mixture was stirred 10 minutes, then treated with 3 ml of ice water. The tetrahydrofuran was removed under vacuum and the residue taken up in ether. The ether solution was washed with water, dried over sodium sulfate, filtered, and evaporated to dryness *in vacuo*. The resulting oil was chromatographed on 120 g of silica gel, eluted with methylene chloride and 1%, 1.5%, 2%, 3%, and 5% methanol in methylene chloride.

The combined product fractions were evaporated to dryness *in vacuo*, dissolved in 50 ml of absolute ethanol, and treated with a slight excess of 8N ethanolic HCl. The solvent was removed *in vacuo* and the residual solid recrystallized from 20 ml of absolute ethanol to give 5,10,12-trimethyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine hydrogen chloride m.p. 295-296.5°C.

Similarly prepared are:

10-allyl-5,12-dimethyl-; 5,10-diethyl-12-methyl-; 10-cyclopropyl-5,12-dimethyl-; and 10-cyclopropylmethyl-5,12-dimethyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine.

EXAMPLE 9

Optical Resolution

Racemic 5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine (3.93 g, 0.0178 mole) and (-) di-p-toluoyl-d-tartaric acid (6.88 g, 0.0178 mole) are dissolved in 21 ml of acetone. The solution is seeded and after several hours of standing at room temperature, the crystalline salt is collected. This product is recrystallized repeatedly from acetone to constant rotation. The salt is suspended in cold water, stirred with aqueous sodium hydroxide and the base is extracted into ether. The washed and dried ether extract is evaporated to dryness under reduced pressure leaving (-) 5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine as the residual solid, m.p. 71.5-73.5°C.

The acetone mother liquor from the initial crystallization of the (-)-isomer is evaporated to dryness under reduced pressure. A suspension of the residual glass in cold water is stirred with aqueous sodium hydroxide and the base is extracted into ether. The washed and dried ether extract is concentrated to obtain the optically impure (+)-base as the residual solid. This product (2.27 g, 0.0103 mole) and (+) di-p-toluoyl-l-tartaric acid (3.9 g, 0.0103 mole) are dissolved in 20 ml of acetone. After several hours of standing at room temperature, the crystalline salt is collected and recrystallized repeatedly from acetone to constant rotation. The salt is reconverted to the base in the manner previously described to obtain (+) 5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine, m.p. 72-74°C.

EXAMPLE 10

Tablet Preparation

Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0, and

100.0 mg, respectively, of 10, 11 - dihydro - 5 - methyl - 12 - benzyl - 5H - dibenzo [a, d] cyclohepten - 5, 10 -

imine are prepared as illustrated below.

TABLE FOR DOSES CONTAINING FROM
1-25 MG OF THE ACTIVE COMPOUND

	Amount — mg		
10, 11 - dihydro - 5 - methyl - 12 - benzyl 5H - dibenzo [a, d] cyclohepten - 5, 10 - imine	1.0	2.0	25.0
Microcrystalline cellulose	49.25	48.75	37.25
Modified food corn starch	49.25	48.75	37.25
Magnesium stearate	0.50	0.50	0.50

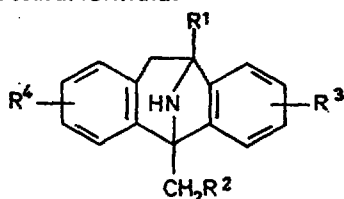
TABLE FOR DOSES CONTAINING FROM
26-100 MG OF THE ACTIVE COMPOUND

	Amount — mg		
10, 11 - dihydro - 5 - methyl - 12 - benzyl 5H - dibenzo [a, d] cyclohepten - 5, 10 - imine	26.0	50.0	100.0
Microcrystalline cellulose	25.0	100.0	200.0
Modified food corn starch	2.21	4.25	8.5
Magnesium stearate	.39	0.75	1.5

All of the active compound, lactose, and a portion
5 of the corn starch are mixed and granulated to a 10%
corn starch paste. The resulting granulation is
sieved, dried and blended with the remainder of the
corn starch and the magnesium stearate. The result-
ing granulation is then compressed into tablets con-
taining 1.0 mg, 2.0 mg, 25.0 mg, 26.0 mg, 50.0 mg,
10 and 100.0 mg of active ingredient per tablet. Other
tablets are prepared using the same procedures and
the equivalent amounts of excipients along with
equivalent amounts of any of the novel compounds
15 of the present invention.

CLAIMS

1. A process for the preparation of a compound
of the structural formula:



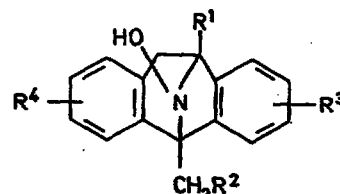
in which

- 20 R is (1) hydrogen,
(2) C₁₋₅ alkyl,
(3) C₂₋₅ alkenyl,
(4) phenyl - (C₁₋₃ alkyl),
(5) halophenyl - (C₁₋₃ alkyl),
25 (6) (C₁₋₃ alkyl)phenyl - (C₁₋₃ alkyl),
(7) C₃₋₆ cycloalkyl,
(8) (C₃₋₆ cycloalkyl) - (C₁₋₃ alkyl), or
(9) di(C₁₋₅ alkyl)amino - (C₁₋₅ alkyl);
R¹ is (1) hydrogen,
30 (2) C₁₋₅ alkyl,
(3) C₂₋₅ alkenyl,
(4) phenyl - (C₁₋₃ alkyl),
(5) C₃₋₆ cycloalkyl, or
(6) (C₃₋₆ cycloalkyl) - (C₁₋₃ alkyl),
35 -CH₂R² is (1) C₁₋₅ alkyl,
(2) C₃₋₅ alkenyl,

- (3) phenyl - (C₁₋₃ alkyl),
(4) (C₃₋₆ cycloalkyl) - (C₁₋₃ alkyl),
(5) di(C₁₋₅ alkyl)amino - (C₁₋₅ alkyl), or
40 (6) C₂₋₃ hydroxyalkyl; and
R³ and R⁴ are independently
(1) hydrogen,
(2) halogen,
(3) C₁₋₅ alkoxy,
45 (4) trifluoromethylthio,
(5) cyano,
(6) carboxy, or
(7) hydroxy;

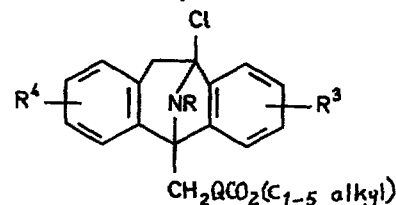
which comprises

- 50 (a) reduction of a compound of formula:



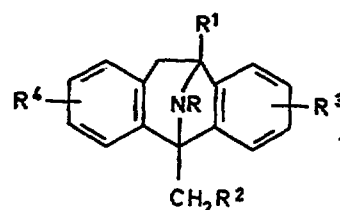
to produce the compound in which R is hydrogen;

- (b) reduction of a compound of formula:



where Q is a single bond or a methylene group, to
produce the compound in which CH₂R² is C₂₋₃ hyd-
55 roxyalkyl;

- (c) alkylation of a compound of formula:



100.0 mg, respectively, of 10, 11 - dihydro - 5 - methyl - 12 - benzyl - 5H - dibenzo [a, d] cyclohepten - 5, 10 -

imine are prepared as illustrated below.

TABLE FOR DOSES CONTAINING FROM
1-25 MG OF THE ACTIVE COMPOUND

	Amount — mg		
10, 11 - dihydro - 5 - methyl - 12 - benzyl 5H - dibenzo [a, d] cyclohepten - 5, 10 - imine	1.0	2.0	25.0
Microcrystalline cellulose	49.25	48.75	37.25
Modified food corn starch	49.25	48.75	37.25
Magnesium stearate	0.50	0.50	0.50

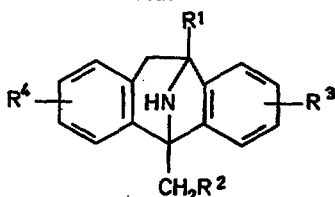
TABLE FOR DOSES CONTAINING FROM
26-100 MG OF THE ACTIVE COMPOUND

	Amount — mg		
10, 11 - dihydro - 5 - methyl - 12 - benzyl 5H - dibenzo [a, d] cyclohepten - 5, 10 - imine	26.0	50.0	100.0
Microcrystalline cellulose	25.0	100.0	200.0
Modified food corn starch	2.21	4.25	8.5
Magnesium stearate	.39	0.75	1.5

All of the active compound, lactose, and a portion
5 of the corn starch are mixed and granulated to a 10%
corn starch paste. The resulting granulation is
sieved, dried and blended with the remainder of the
corn starch and the magnesium stearate. The result-
ing granulation is then compressed into tablets con-
10 taining 1.0 mg, 2.0 mg, 25.0 mg, 26.0 mg, 50.0 mg,
and 100.0 mg of active ingredient per tablet. Other
tablets are prepared using the same procedures and
the equivalent amounts of excipients along with
equivalent amounts of any of the novel compounds
15 of the present invention.

CLAIMS

1. A process for the preparation of a compound
of the structural formula:

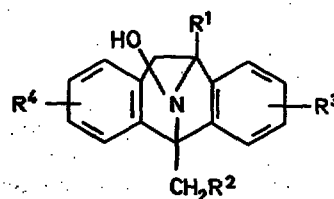


in which

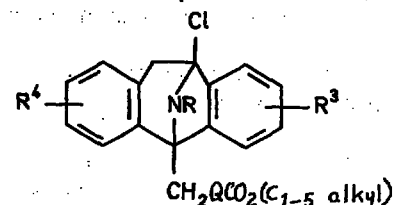
- 20 R is (1) hydrogen,
(2) C₁₋₅ alkyl,
(3) C₂₋₅ alkenyl,
(4) phenyl - (C₁₋₃ alkyl),
(5) halophenyl - (C₁₋₃ alkyl),
25 (6) (C₁₋₃ alkyl)phenyl - (C₁₋₃ alkyl),
(7) C₃₋₆ cycloalkyl,
(8) (C₃₋₆ cycloalkyl) - (C₁₋₃ alkyl), or
(9) di(C₁₋₅ alkyl)amino - (C₁₋₅ alkyl);
R¹ is (1) hydrogen,
30 (2) C₁₋₅ alkyl,
(3) C₂₋₅ alkenyl,
(4) phenyl - (C₁₋₃ alkyl),
(5) C₃₋₆ cycloalkyl, or
(6) (C₃₋₆ cycloalkyl) - (C₁₋₃ alkyl),
35 -CH₂R² is (1) C₁₋₅ alkyl,
(2) C₃₋₅ alkenyl,

- (3) phenyl - (C₁₋₃ alkyl),
(4) (C₃₋₆ cycloalkyl) - (C₁₋₃ alkyl),
(5) di(C₁₋₅ alkyl)amino - (C₁₋₅ alkyl), or
40 (6) C₂₋₃ hydroxyalkyl; and
R^a and R^b are independently
(1) hydrogen,
(2) halogen,
(3) C₁₋₅ alkoxy,
45 (4) trifluoromethylthio,
(5) cyano,
(6) carboxy, or
(7) hydroxy;
which comprises

- 50 (a) reduction of a compound of formula:

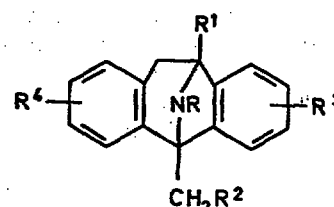


to produce the compound in which R is hydrogen;
(b) reduction of a compound of formula:



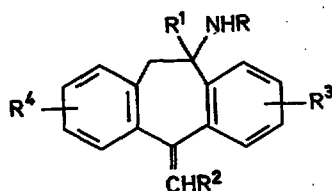
where Q is a single bond or a methylene group, to
produce the compound in which CH₂R² is C₂₋₃ hyd-
55 roxyalkyl;

(c) alkylation of a compound of formula:



to produce the compound in which R is other than hydrogen;

(d) treatment of a compound of formula:



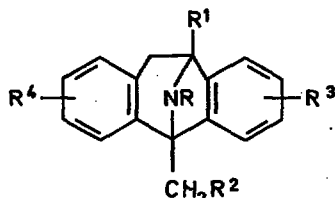
with a strong base;

- 5 (e) treatment of the compound in which R³ and/or R⁴ is bromo with a sodium or potassium C₁₋₅ alkoxide, with cuprous cyanide or with bis(trifluoromethylthio)mercury and copper dust to produce a compound in which R³ and/or R⁴ is/are C₁₋₅

10 alkoxy, cyano, or trifluoromethylthio respectively;

(f) hydrolysis of the compound in which R³ and/or R⁴ is/are cyano or C₁₋₅ alkoxy to produce a compound in which R³ and/or R⁴ is/are carboxy or hydroxy respectively.

- 15 2. A compound of the structural formula:



or a pharmaceutically acceptable salt thereof in which R, R¹, R³, R⁴ and -CH₂R² are as defined in claim 1.

3. A compound as claimed in Claim 2 in which R¹
20 is hydrogen.

4. A compound as claimed in Claim 2 in which R¹, R³ and R⁴ are hydrogen, R is hydrogen, lower alkyl or benzyl; and -CH₂R² is lower alkyl or hydroxyethyl.

5. 5-Methyl-10,11-dihydro-5H-dibenzo[a,d]
25 cyclohepten-5,10-imine.

6. 12-Benzyl-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine.

7. 12-(4-Chlorobenzyl)-5-methyl-10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5,10-
30 imine.

8. A pharmaceutical composition comprising a pharmaceutical carrier and a compound as claimed in Claim 2.

9. A pharmaceutical composition comprising a
35 pharmaceutical carrier and a compound as claimed in Claim 3.

10. A pharmaceutical composition comprising a pharmaceutical carrier and a compound as claimed in Claim 4.

- 40 11. A process that produces a compound as claimed in Claim 2, substantially as hereinbefore described in any one of Examples 1 to 9.

12. A compound as claimed in Claim 2 when prepared by a process as claimed in Claim 1 or 11.

- 45 13. A composition as claimed in Claim 8, substantially as hereinbefore described with reference to any one of the formulations set out in Example 10.

14. A compound as claimed in Claim 2 in the

form of a salt with maleic acid.

- 50 15. A maleic acid salt of a compound as claimed in any one of Claims 3 to 7.

16. A (+) or (-) optical isomer of a compound as claimed in any one of Claims 2 to 7, 14 and 15.

17. A pharmaceutical composition comprising a
55 pharmaceutical carrier and a compound as claimed in any one of Claims 5, 6, 7, 14, 15 and 16.

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