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3,660,389

10,11 - DIACYLOXY - 10,11-DIHYDRO-5-TERTIARY AMINO PROPYL - 5-HYDROXY-5H-DIBENZO[a,d] CYCLOHEPTENES

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Int. Cl. C07d *87/46, 87/36*

U.S. Cl. 260—247.2 15 Claims

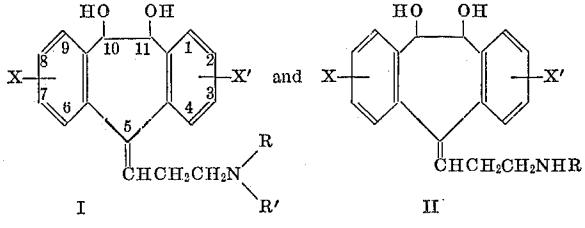
ABSTRACT OF THE DISCLOSURE

A cis or trans 3α,12β-dihydro-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxol-8-one is treated with a Grignard reagent, i.e., a tertiary aminoproplymagnesium halide, and the Grignard adduct obtained hydrolyzed to form the corresponding 5-hydroxy-5-(3-tertiary aminopropyl) derivative which is dehydrated to form the corresponding 5-(3-tertiary aminopropylidene) derivative. The resulting compound is then hydrolyzed to form the cis or trans 10,11 - dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene) - 5H-dibenzo[a,d]cycloheptene. Such compounds may be demethylated to produce the corresponding N-methylaminopropylidene compound. The compounds are useful as antidepressants.

This application is a division of application Ser. No. 723,964 filed Jan. 29, 1968, now U.S. Pat. No. 3,576,823 patented Apr. 27, 1971, which in turn is a division of application Ser. No. 296,463 filed July 22, 1963, now U.S. Pat. No. 3,390,179 patented June 25, 1968.

This invention relates to derivatives of dibenzocycloheptenes. In particular, the invention relates to 10,11-dihydro-10,11-dihydroxy - 5 - (3-substituted aminopropylidene)-5H-dibenzo[a,d]cycloheptenes and methods of preparing the same. The invention also relates to intermediates useful in the preparation of the above compounds, as well as processes for the preparation of said intermediates.

The end compounds embraced within the scope of the present invention may be represented by the following structural formulae:



wherein R is a lower alkyl radical, straight or branched chain, preferably having up to 6 carbon atoms; R′ is a lower alkyl radical, straight or branched chain, preferably having up to 6 carbon atoms and X and X′, which may be similar or dissimilar, are hydrogen, an alkyl group having up to 6 carbon atoms, an alkenyl group having up to 6 carbon atoms, halogen, trifluoromethyl, hydroxyl, an alkoxy group having up to 4 carbon atoms, mercapto, an alkylmercapto group having up to 4 carbon atoms, an alkylsulfonyl group having up to 4 carbon atoms, sulfamoyl, an alkylsulfamoyl group having up to 4 carbon atoms

or a dialkylsulfamoyl group having up to 8 carbon atoms. More than one of these substituents may be on each of the benzenoid rings. The radicals R and R′ may be similar or dissimilar and they may be linked together through an atom of carbon, nitrogen or oxygen to form a heterocyclic ring having from five to six atoms therein such as 1-piperidyl, 1-pyrrolidyl, 4-morpholinyl and 1-lower alkyl-4-piperazinyl, the lower alkyl substituent of the latter preferably having up to 4 carbon atoms.

The compounds represented by the above structural formulae may also have substituents on the propylidene side chain such as lower alkyl radicals, preferably having from 1 to 4 carbon atoms.

Representative end compounds encompassed within the scope of the present invention include:

10,11-dihydro-10,11-dihydroxy-5-[3(1-piperidyl)-propylidene]-5H-dibenzo[a,d]cycloheptene

10,11-dihydro-10,11-dihydroxy-5-[3-(1-methyl-4-piperazinyl)-propylidene]-5H-dibenzo[a,d]cycloheptene

10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

3-chloro-10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

10,11-dihydro-10,11-dihydroxy-5-(3-methylaminopropylidene)-3-methylsulfonyl-5H-dibenzo[a,d]cycloheptene

10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-3-(trifluoromethyl-5H-dibenzo[a,d]cycloheptene

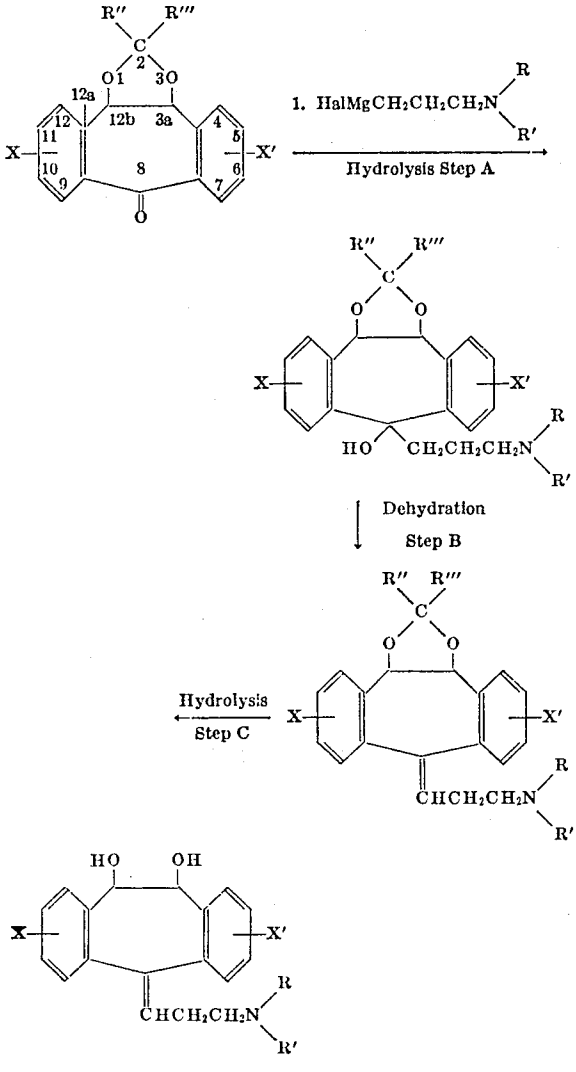
10,11-dihydro-10,11-dihydroxy-5-(3-diethylaminopropylidene)-3-dimethylsulfamoyl-5H-dibenzo[a,d]cycloheptene

The compounds represented by the above structural formulae can advantageously be employed in pharmaceutical applications because they have been found to possess anti-depressant activity. As anti-depressants, they may be administered orally in the form of tablets, powders, sustained release pellets and the like, or they may be administered orally or parenterally in the form of aqueous solutions or suspensions. When administered orally or parenterally, satisfactory results are obtained at a daily dosage level of from about 60 mg. to about 1,000 mg., preferably given in divided doses over the day or in sustained release form. The compounds are preferably administered in the form of their non-toxic acid addition salts and these salts are included within the scope of this invention.

The compounds represented by the above structural formulae exist as geometric isomers, which are determined by the steric relationships of the hydroxyl groups to each other. In order to prepare the separate isomers, it is necessary to employ an appropriate starting material in the same isomeric form as that desired of the end product. Thus, where it is desired to prepare the trans isomer of the compounds represented structurally above, a trans 3α,12β - dihydro - 8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxol-8-one is employed, whereas the cis isomers re prepared starting with a cis 10,11-dihydro-10,11-diacyloxy-5H-dibenzo[a,d]cyclohepten-5-one.

In carrying out the process, the desired ketone is treated with a Grignard reagent, namely, a tertiary aminopropylmagnesium halide and the Grignard adduct obtained hydrolyzed to form the corresponding 5-hydroxy-5-(3-tertiary aminopropyl) derivative. This is then dehydrated to form the corresponding 5-(3-tertiary aminopropylidene) derivative, which is then either hydrolyzed to form the cis or trans 10,11-dihydroxy compounds represented by structural Formula I or dealkylated and then hydrolyzed to form the cis or trans 10,11-dihydroxy compounds represented by structural Formula II.

The process for the preparation of the trans 10,11-dihydroxy compounds represented by structural Formula I may be illustrated as follows:



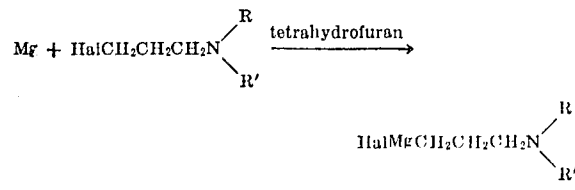
wherein Hal represents halogen, preferably chlorine or bromine and X, X', R and R' are as previously defined; and R'' and R''' are hydrogen, alkyl, aralkyl or aryl.

The starting compound, wherein X and X' are both hydrogen and R'' and R''' are both methyl, namely, the 3α,12β - dihydro - 2,2 - dimethyl-5H-dibenzo[3,4:6,7]-cyclohepta[1,2-d]-1,3-dioxol-8-one, may be prepared in the manner described by G. L. Buchanan and D. B. Jhaveri in the J. Org. Chem. 26, 4285–4299 (1961). Those starting compounds, wherein at least one of X and X' is other than hydrogen, may be prepared from the corresponding nuclearly substituted 5H-dibenzo [a,d]-cyclohepten-5-one utilizing the procedure of G. L. Buchanan and D. B. Jhaveri, referred to above. The latter compounds may be prepared following the teachings of T. W. Campbell et al. in an article appearing in Helv. Chem. Acta, vol. 36, pages 1489–1499 (1953).

Those starting compounds, wherein R'' and R''' are other than methyl, may be prepared from the corresponding diol by treatment with an appropriate aldehyde or ketone utilizing the procedure described by G. L. Buchanan and D. B. Jhaveri for the preparation of the acetonide of the trans diol appearing in the article referred to above.

It should be noted that inasmuch as the R'' and R''' substitutents are removed during the preparation of the end compounds of this invention, the selection of the particular starting compound with respect to these substituents will be dependent only upon their ease of preparation and the removal of the R'' and R''' substituents during subsequent hydrolysis.

The Grignard reagent employed in Step A of the above process may be prepared by known procedures, but it has been found that it may be prepared in high yields as follows:



It has been found that the use of tetrahydrofuran as the solvent for the reaction results in a rapid production of the Grignard reagent in high yield.

The reaction with the Grignard reagent (Step A) is preferably initially carried out under cooled conditions such as by the use of an ice-bath, and finally may continue at room temperature. It has been found that tetrahydrofuran is a suitable solvent for carrying out the reaction and, accordingly, the ketone may be added directly to the reaction mixture in which the Grignard reagent was prepared. However, any inert solvent for the reactants may be employed.

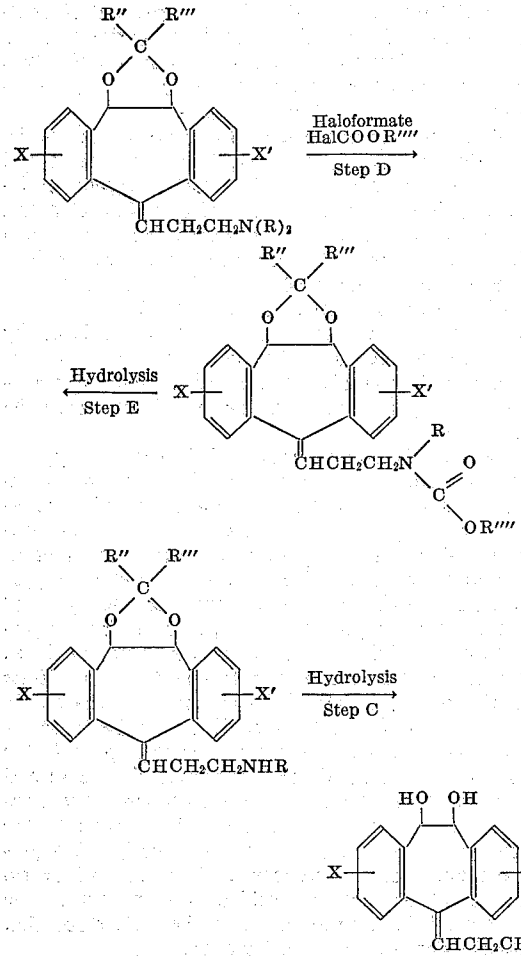
After the addition reaction is completed, the bulk of the solvent is removed by vacuum distillation, the Grignard adduct dissolved in a suitable solvent such as benzene, and hydrolyzed by the addition of water or ammonium chloride solution with cooling. The product is recovered by evaporation of the solvent after the removal of any residual inorganic material by filtration.

Conversion of the carbinol to the corresponding 5-(3-tertiary aminopropylidene) derivative (Step B) is effected by dehydration. The dehydration may be effected in conventional manner employing such commonly used dehydrating agents as acetyl chloride, acetic anhydride or thionyl chloride. The alcohol may be dehydrated directly or may be first converted to a salt such as the hydrochloride, hydrobromide or sulfate. Conversion to the salt prior to dehydration may be preferable in some cases. The reaction may be carried out at elevated temperatures, and in an excess of dehydrating agent or a solvent such as chloroform or glacial acetic acid may be employed. The desired product is recovered after rendering the mixture alkaline by extraction with a suitable solvent, and then removing the solvent.

Conversion of the compound obtained from Step B to the corresponding trans 10,11-dihydroxy compound (Step C) is effected by hydrolyzing the former in an inert solvent, preferably at elevated temperatures, and in the presence of an acidic catalyst such as, for example, p-toluenesulfonic acid, concentrated sulfuric acid, trifluoroacetic acid, dry hydrochloric acid and the like. Any number of inert solvents may be utilized, but it is preferred to employ a lower alkanol such as methanol, ethanol, isopropanol and the like. Where the product is insoluble in the solvent employed, it may be recovered by filtration and washed free of any residual acid and further purified by conventional methods. Where the product is soluble in the solvent employed, it may be recovered by evaporation of the solvent, diluting with water, neutralizing any residual acid with sufficient alkali to render the medium basic and collecting the residue by conventional methods.

The trans 10,11-dihydroxy compounds represented by structural Formula II may be prepared from the corresponding 5-(3-dialkylaminopropylidene) compound obtained in Step B above. In carrying out the process, it is preferred that the alkyl substituents attached to the nitrogen atom be the same. This is readily accomplished by appropriate selection of the Grignard reagent used to prepare the carbinol from which the tertiary aminopropylidene

compound is derived. This process may be illustrated as follows:

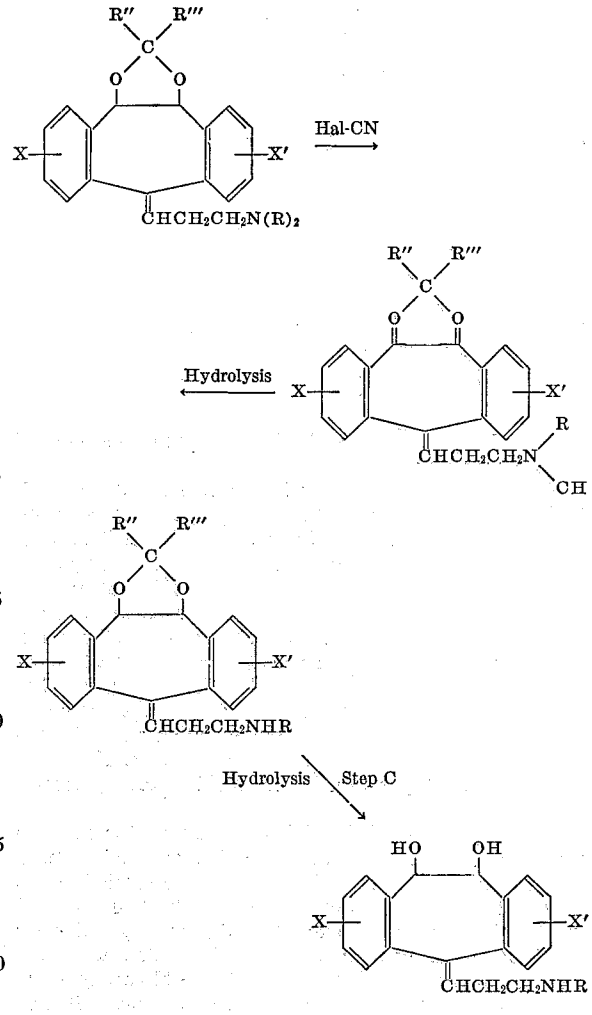


wherein Hal, X, X', R, R'' and R''' are as previously defined and R'''' is alkyl, aralkyl and aryl. However, it will be readily appreciated by those skilled in the art that inasmuch as the R'''' substituent is removed during the dealkylation step, the selection of the particular haloformate will be limited only by its availability and subsequent ease of hydrolysis of the intermediate urethane produced.

Step D of the above process involves the condensation of the tertiary amino compound with a haloformate to form the corresponding urethane intermediate. While the reaction can be carried out in the absence of a solvent, it is preferable to employ a solvent. Suitable solvents include the aromatic hydrocarbons such as benzene and toluene, aliphatic hydrocarbons such as heptane and hexane, and the halogen hydrocarbons such as chloroform and carbon tetrachlororide. The reaction may be carried out at room temperature, although an elevated temperature is preferred. At the conclusion of the reaction, the urethane is recovered, after removal of impurities, by evaporation of the solvent.

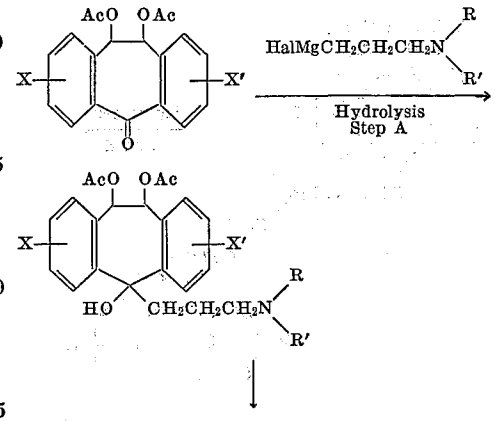
The urethane intermediate thus produced is then subjected to hydrolysis (Step E). The hydrolysis preferably may be carried out under basic conditions. After completion of the hydrolysis, the desired product is recovered in conventional manner, such as by extraction into a suitable solvent and evaporation of the solvent. Conversion to the corresponding 10,11-dihydroxy compound is accomplished using the procedure outlined in Step C.

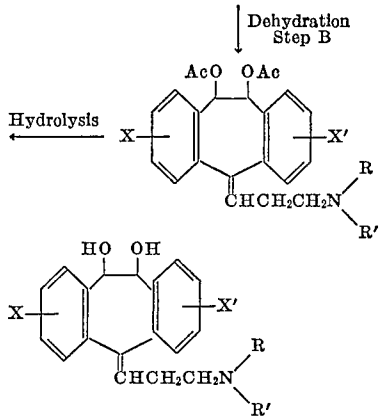
Alternatively, the dealkylation may be accomplished by treatment of the tertiary aminopropylidene compound with a cyanogen halide to form the corresponding cyanamide intermediate, and the cyanamide thus produced hydrolyzed to the corresponding secondary amine. This process may be illustrated as follows:



The tertiary amine is dissolved in a nonhydroxylic solvent such as benzene or ether and the solution slowly added to a solution of cyanogen halide in the same solvent, while stirring and permitting the alkyl halide to escape. After the reaction is complete, the basic material is separated by washing with dilute acid and the cyanamide isolated by evaporating the solvent. The cyanamide is hydrolyzed to the secondary amine in an alkaline medium, and the product recovered in conventional manner. Conversion to the corresponding 10,11-dihydroxy compound is accomplished using the procedure outlined in Step C.

The process for the preparation of the cis 10,11-dihydroxy compounds of structural Formula I may be illustrated as follows:



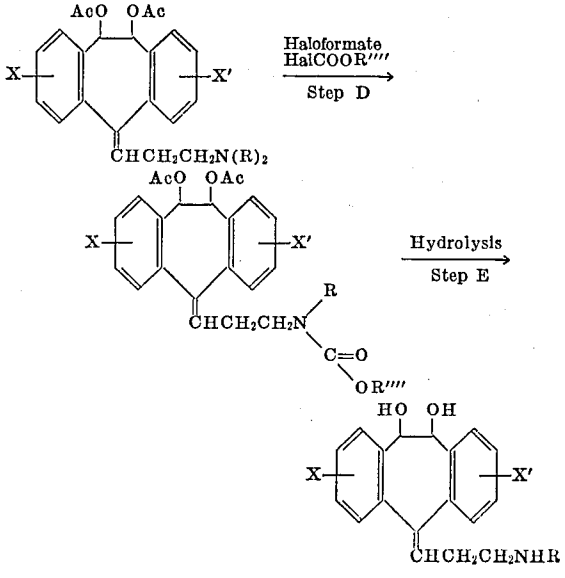


wherein Hal, X, X', R and R' are as previously defined and Ac represents acyl.

The starting compound, wherein X and X' are both hydrogen and Ac is acetyl, may be prepared in the manner described by J. Rigaudy and L. Nedelec, Bull. Soc. Chim., France (1960), pgs. 400–405. Those starting compounds, wherein at least one of X and X' is other than hydrogen, may be prepared from the corresponding nuclearly substituted 5H-dibenzo[a,d]cyclohepten-5-one utilizing the procedure of J. Rigaudy et al. previously mentioned. Those starting compounds, wherein Ac is other than acetyl, may be prepared from the corresponding diol by treatment with an appropriate acylating agent following the procedure described by J. Rigaudy et al., above cited, for the preparation of the 10,11-diacetoxy derivative.

The preparation of the Grignard reagent, the reaction with the Grignard reagent (Step A), and dehydration of the resulting carbinol (Step B), may be carried out as previously described herein. However, the hydrolysis of the 10,11-diacyloxy compound to the corresponding cis 10,11-dihydroxy compound differs from that described for the preparation of the trans 10,11-dihydroxy compounds in that the hydrolysis is effected under alkaline conditions such as by the use of potassium hydroxide and the like. Recovery of the product can be accomplished as described in Step C above, except that neutralization with alkali is unnecessary.

The preparation of the cis 10-11-dihydroxy compounds represented by structural Formula II may be accomplished by dealkylating the corresponding cis 10,11-diacyloxy-5-(3-dialkylaminopropylidene) derivative in the same manner as described for the dealkylation of the trans 5-(3-dialkylaminopropylidene) derivative, as described in Steps D and E above. This process may be illustrated as follows:



wherein Ac, Hal, R, R'''', X and X' are as previously defined.

It should be noted that the alternate method of dealkylation mentioned hereinabove for the preparation of the trans 10,11-dihydroxy compounds of structural Formula II cannot be used for the preparation of the cis 10,11-dihydroxy compounds of Formula II.

It will be readily appreciated by those skilled in the art that the compounds represented by structures I and II, in addition to the element of geometric isomerism determined by the relationship of the hydroxyls to each other, possess a second element of geometric isomerism when the dibenzocycloheptene nucleus is unsymmetrically substituted, depending on the position of the propylidene side chain relative to the nuclear substituent(s).

The separation of these isomers can be achieved by conventional techniques. While the mixture of such isomers possess pharmacological activity, in some instances the activity may be greater in one pure isomer than the other.

Inasmuch as the compounds of this invention may exist as geometric isomers with respect to the hydroxyl substituents only or with respect to both the hydroxyl substituents and the propylidene side chain, the following procedure for designating the isomers hereinabove and in the examples and claims which follow has been employed. Where isomers exist only with respect to the hydroxyl substituents, the designation of the particular isomer precedes the name of the compound. Where isomers exist as to both the hydroxyl substituents and the propylidene side chain, the designation of the isomers immediately precedes the substituent to which it refers. In those instances where insomers exist with respect to both the hydroxyl substituents and the propylidene side chain and the isomers of the latter have not been separated, then only the designation of the isomer with respect to the hydroxyl substituents is given and such designation precedes the name of the compound. However, where no designation of isomers is specified with respect to the compounds of this invention, it is to be understood that all possible stereoisomers are included.

The preparation of representative compounds encompassed within the scope of the present invention is described in the following examples which are illustrative only and are not to be construed as in any way limiting the scope of the invention.

EXAMPLE 1

Trans 3α,12β - dihydro - 2,2 - dimethyl - 8 - (3 - dimethylamino - propyl) - 8 - hydroxy - 8H - dibenzo [3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

3-dimethylaminopropylmagnesium chloride is prepared from magnesium turnings (4.05 g., 0.166 g. atom) and 3-dimethylaminopropyl chloride (20.2 g., 0.166 mole) in 150 ml. of dry tetrahydrofuran, following the method of U.S. Pat. No. 3,046,283. In a nitrogen atmosphere, a solution of trans 3α,12β-dihydro-2,2-dimethyl-8H-dibenzo[3,4:6,7] cyclohepta [1,2-d] - 1,3 - dioxol - 8 - one (23.2 g., 0.083 mole) in 100 ml. of dry tetrahydrofuran is added dropwise to the stirred solution of the Grignard reagent while cooling in an ice-bath. The mixture is allowed to come to room temperature and stirred for 2 hours. The bulk of the solvent than is distilled below 50° C. under reduced pressure. The residue is dissolved in 150 ml. of benzene and water, 20 ml. is added dropwise with stirring and cooling. The benezene layer is decanted from the gelatinous precipitate which then is extracted with four 100 ml. portions of boiling benzene. The combined benzene extracts are washed with water and extracted with three 100 ml. portions of 0.5 M citric acid. The acid extract is made basic with sodium hydroxide, and the oily base that separates is extracted into benzene. After washing the combined extracts with water and drying over anhydrous sodium sulfate, the benezene is evaporated and

the product obtained as a viscous yellow oil in a yield of 29.5 g. (96%).

The base may be converted to the hydrogen oxalate salt by treating an ethereal solution with a solution of oxalic acid (10% excess) in isopropyl alcohol. The trans 3α,12β - dihydro-2,2-dimethyl-8-(3 - dimethylaminopropyl)-8-hydroxy-8H-dibenzo-[3,4:6,7]cyclohepta[1,2 - d]-1,3-dioxole hydrogen oxalate is obtained as a white crystalline solid, M.P. 169–172° C., dec. Repeated recrystallizations from mixtures of isopropyl alcohol and absolute ether give the product, M.P. 171–173° C., dec.

Analysis.—Calc'd for $C_{23}H_{29}NO_3 \cdot C_2H_2O_4$ (percent): C, 65.62; H, 6.83; Found (percent): C, 65.08; H, 6.72.

EXAMPLE 2

Following the procedure of Example 1, the products enumerated below are obtained using the ketone of Example 1 and the Grignard reagent designated below.

Grignard reagent	Product
3-diethylaminopropyl-magnesium chloride.	Trans 8-(3-diethylaminopropyl)-3α, 12β-dihydro-2,2-dimethyl-β-hydroxy-8H-dibenzo[3,4:6,7]cyclohepta-[1,2-d]-1,3-dioxole.
3-(1-pyrrolidyl)-propyl-magnesium chloride.	Trans 3α,12β-dihydro-2,2-dimethyl-8-hydroxy-8-[3-(1-pyrrolidyl)-propyl]-8H-dibenzo[3,4:6,7]cyclohepta [1,2-d]-1,3-dioxole.
3-(1-piperidyl)-propyl magnesium chloride.	Trans 3α,12β-dihydro-2,2-dimethyl-8-hydroxy-8-[3-(1-piperidyl)-propyl]-8H-dibenzo[3,4:6,7]cyclohepta [1,2-d]-1,3-dioxole.
3-(1-ethyl-4-piperazinyl)-propylmagnesium chloride.	Trans 3α,12β-dihydro-2,2-dimethyl-8-[3-(1-ethyl-4-piperazinyl)-propyl]-8-hydroxy-8H-dibenzo-[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole.
3-(4-morpholinyl)-propyl-magnesium chloride.	Trans 3α,12β-dihydro-2,2-dimethyl-8-hydroxy-8-[3-(4-morpholinyl)-propyl]-8H-dibenzo[3,4:6,7]cyclo-hepta[1,2-d]-1,3-dioxole.
3-(N-ethyl-N-methylamino)-propylmagnesium chloride.	Trans 3α,12β-dihydro-2,2-dimethyl-8-[3-(N-ethyl-N-methylamino)-propyl]-8-hydroxy-8H-dibenzo [3,4:6,7]-cyclohepta[1,2-d]-1,3-dioxole.

EXAMPLE 3

Following the procedure of Example 1, the products enumerated below are obtained using the Grignard reagent of Example 1 and the ketone designated below.

Ketone	Product
Trans 3α,12β-dihydro-8H-dibenzo-[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxol-8-one.	Trans 3α,12β-dihydro-8-(3-dimethylaminopropyl)-8-hydroxy-8H-dibenzo-[3,4:6,7]cyclohepta-[1,2-d]-1,3-dioxole.
Trans 3α,12β-dihydro-2-phenyl-8H-dibenzo[3,4:6,7]cyclohepta-[1,2-d]-1,3-dioxol-8-one.	Trans 3α,12β-dihydro-8-(3-dimethylaminopropyl)-8-hydroxy-2-phenyl-8H-dibenzo[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole.
Trans 3α,12β-dihydro-2-methyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxol-8-one.	Trans 3α,12β-dihydro-8-(3-dimethylaminopropyl)-8-hydroxy-2-methyl-8H-dibenzo[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole.
Trans 2-benzyl-3α,12β-dihydro-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxol-8-one.	Trans 2-benzyl-3α,12β-dihydro-8-(3-dimethylaminopropyl)-8-hydroxy-8H-dibenzo[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole.
Trans 3α,12β-dihydro-2-ethyl-2-methyl-8H-dibenzo[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxol-8-one.	Trans 3α,12β-dihydro-8-(3-dimethylaminopropyl)-2-ethyl-8-hydroxy-2-methyl-8H-dibenzo-[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole.
Trans 3α,12β-dihydro-2,2-dimethyl-6-methylsulfonyl-8H-dibenzo [3,4:6,7]cyclohepta[1,2-d]-1,3-dioxol-8-one.	Trans 3α,12β-dihydro-2,2-dimethyl-8-(3-dimethylamino-propyl)-8-hydroxy-6-methyl-sulfonyl-8H-dibenzo-[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole.
Trans 6-chloro-3α,12β-dihydro-2,2-dimethyl-8H-dibenzo-[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxol-8-one.	Trans 6-chloro-3α,12β-dihydro-2,2-dimethyl-8-(3-dimethylamino-propyl)-8-hydroxy-8H-dibenzo-[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole.
Trans 3α,12β-dihydro-2,2-dimethyl-6-dimethylsulfamoyl-8H-dibenzo-[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxol-8-one.	Trans 3α,12β-dihydro-2,2-dimethyl-8-(3-dimethylamino-propyl)-6-dimethylsulfamoyl-8-hydroxy-8H-dibenzo[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole.

EXAMPLE 4

Trans 3α,12β-dihydro-2,2-dimethyl-8-(3-dimethylaminopropylidene) - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

A solution of trans 3α,12β-dimethyl-8-(3-dimethylaminopropyl)-8-hydroxy - 8H - dibenzo-[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole (1.3 g., 0.00354 mole) in 15 ml. of acetic anhydride is heated to refluxing for 4 hours. The solution is evaporated to dryness under reduced pressure and the residual syrup dissolved in 30 ml. of water. After one extraction with hexane, the aqueous layer is rendered alkaline with sodium hydroxide and the oily base extracted into benzene. The washed benzene extract is evaporated under reduced pressure, leaving the product as an oily residue weighing, typically, 950 mg. Treatment of an ethereal solution of the base with a solution of 300 mg. of oxalic acid in 3 ml. of isopropyl alcohol precipitates trans 3α,12β-dihydro-2,2-dimethyl-8-(3-dimethylaminopropylidene) - 8H - dibenzo[3,4:6,7]-cyclohepta[1,2-d]-1,3-dioxole hydrogen oxalate, M.P. 204–206° C., dec., in a yield of 1.05 g. (67.5%). The pure product from another experiment melts at 205–206° C., dec., after recrystallization from isopropyl alcohol.

Analysis.—Calc'd for $C_{23}H_{27}NO_2 \cdot C_2H_2O_4$ (percent): C, 68.32; H, 6.65; N, 319. Found (percent): C, 68.36; H, 6.72; N, 3.15.

EXAMPLE 5

Following the procedure of Example 4, the products enumerated below are obtained employing the products enumerated in Examples 2 and 3 in place of the dioxole used in Example 4.

trans 8-(3-diethylaminopropylidene)-3α,12β-dihydro-2,2-dimethyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2 - d]-1,3-dioxole

trans 3α,12β - dihydro - 2,2 - dimethyl-8-[3-(1-pyrrolidyl)-propylidene] - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 3α,12β-dihydro - 2,2 - dimethyl-8-[3-(2-piperidyl)-propylidene] - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 3α,12β-dihydro - 2,2 - dimethyl-8-[3-(1-ethyl-4-piperazinyl) - propylidene] - 8H - dibenzo[3,4:6,7]-cyclohepta[1,2-d]-1,3-dioxole

trans 3α,12β-dihydro-2,2-dimethyl-8-[3-(4-morpholinyl)-propylidene] - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 3α,12β-dihydro-2,2-dimethyl-8-[3-(N-ethyl-N-methylamino)-propylidene]-8H-dibenzo[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole

trans 3α,12β-dihydro-8-(3-dimethylaminopropylidene)-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 3α,12β-dihydro-8-(3-dimethylaminopropylidene)-2-phenyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 3α,12β-dihydro-8-(3-dimethylaminopropylidene)-2-methyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 2-benzyl-3α,12β-dihydro-8-(3-dimethylamino-propylidene-8H-dibenzo[3,4:6,7]cyclohepta [1,2-d]-1,3-dioxole

trans 3α,12β-dihydro-8-(3-dimethylaminopropylidene)-2-ethyl-2-methyl-8H-dibenzo[3,4:6,7]cyclohepta [1,2-d]-1,3-dioxole

trans 3α,12β-dihydro-2,2-dimethyl-8-(3-dimethylamino-propylidene)-6-methylsulfonyl-8H-dibenzo [3,4:6,7]-cyclohepta[1,2-d]-1,3-dioxole

trans 6-chloro-3α,12β-dihydro-2,2-dimethyl-8-(3-dimethylaminopropylidene)-8H-dibenzo[3,4:6,7]cyclohepta [1,2-d]-1,3-dioxole

trans 3α,12β-dihydro-2,2-dimethyl-8-(3-dimethylamino-propylidene)-6-dimethylsulfamoyl-8H-dibenzo [3,4:6,7]-cyclohepta[1,2-d]-1,3-dioxole

EXAMPLE 6

Trans 10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

A solution of trans 3α,12β-dihydro-2,2-dimethyl-8-(3-dimethylaminopropylidene - 8H - dibenzo - [3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole (350 mg., 0.001 mole) and p-toluenesulfonic acid monohydrate (230 mg., 0.0012 mole) in 35 ml. of absolute methanol is heated to refluxing for 4 hours. The cooled solution is neutralized with 1 ml. of 1 M potassium hydroxide in methanol and then the solvent is distilled under reduced pressure. The residue is partitioned between benzene and water and the aqueous layer re-extracted twice with benzene. The combined benzene extracts are washed with water and then evaporated to dryness under reduced pressure. Trituration of the residue with absolute ether yields the product as a white crystalline solid, M.P. 132.5–134.5° C., weighing 230 mg. (74.5%). After purification by sublimation and crystallization from a mixture of ethanol and water, an analytical sample melts at 134.5–136.5° C.

Analysis.—Calc'd for $C_{20}H_{23}NO_2$ (percent): C, 77.64; H, 7.49; N, 4.53. Found (percent): C, 77.59; H, 7.42; N, 4.47.

EXAMPLE 7

Following the procedure of Example 6, the products enumerated below are obtained using the products enumerated in Example 5 in place of the dioxole used in Example 6.

trans 5-(3-diethylaminopropylidene)-10,11-dihydro-10,11-dihydroxy-5H-dibenzo[a,d]cycloheptene
trans 10,11-dihydro-10,11-dihydroxy-5-[3-(1-pyrrolidyl)-propylidene]-5H-dibenzo[a,d]cycloheptene
trans 10,11-dihydro-10,11-dihydroxy-5-[3-(1-piperidyl)-propylidene]-5H-dibenzo[a,d]cycloheptene
trans 10,11-dihydro-10,11-dihydroxy-5-[3-(1-ethyl-4-piperazinyl)-propylidene]-5H-dibenzo[a,d] cycloheptene
trans 10,11-dihydro-10,11-dihydroxy-5-[3-(4-morpholinyl)-propylidene]-5H-dibenzo[a,d]cycloheptene
trans 10,11-dihydro-10,11-dihydroxy-5-[3-(N-ethyl-N-methylamino)-propylidene]-5H-dibenzo[a,d] cycloheptene
trans 10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene
trans 10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-3-methylsulfonyl-5H-dibenzo [a,d]cycloheptene
trans 3-chloro-10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d] cycloheptene
trans 10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-3-dimethylsulfamoyl-5H-dibenzo [a,d]cycloheptene

EXAMPLE 8

Trans 8 - [3 - (N-cyano-N-methylamino)-propylidene]-3α,12β - dihydro - 2,2 - dimethyl-8H-dibenzo[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole

In a system protected by a drying tube, and in which a nitrogen atmosphere is maintained, a solution of trans 3α,12β-dihydro - 2,2 - dimethyl - 8 - (3 - dimethylaminopropylidene) - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole (2.25 g., 0.00645 mole) in 12 ml. of dry benzene is added dropwise over a 30 minute period to a stirred solution (1.85 ml.) of 4.25 M cyanogen bromide in benzene. Stirring is continued for 1½ hours and the mixture then allowed to stand at room temperature overnight. Solvent and excess cyanogen bromide are evaporated under reduced pressure and the residue dissolved in benzene. The solution is washed with water, dilute citric acid, then with water, and evaporated to dryness under reduced pressure. The trans 8-[3-(N-cyano-N-methylamino) - propylidene] - 3α,12β - dihydro - 2,2-dimethyl - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d] - 1,3-dioxole is obtained as a yellow oily residue, weighing 1.8 g. (78%).

EXAMPLE 9

Following the procedure of Example 8, the products enumerated below are obtained employing the 8-(3-dialkylaminopropylidene) products enumerated in Example 5 in place of the dioxole used in Example 8.

trans 8-[3-(N-cyano-N-ethylamino)-propylidene]-3α,12β-dihydro-2,2-dimethyl-8H-dibenzo[3,4:6,7]cyclohepta-[1,2-d]-1,3-dioxole
trans 8-[3-(N-cyano-N-methylamino)-propylidene]-3α,12β-dihydro-8H-dibenzo[3,4:6,7]cyclohepta [1,2-d]-1,3-dioxole
trans 8-[3-(N-cyano-N-methylamino)-propylidene]-3α,12β-dihydro-2-phenyl-8H-dibenzo[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole
trans 8-[3-(N-cyano-N-methylamino)-propylidene)-3α,12β-dihydro-2-methyl-8H-dibenzo[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole
trans 2-benzyl-8-[3-(N-cyano-N-methylamino)-propylidene]-3α,12β-dihydro-8H-dibenzo[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole
trans 8-[3-(N-cyano-N-methylamino)-propylidene]3α, 12β-dihydro-2-ethyl-2-methyl-8H-dibenzo[3,4:6,7] cyclohepta[1,2-d]-1,3-dioxole
trans 8-[3-(N-cyano-N-methylamino)-propylidene]-3α, 12β-dihydro-2,2-dimethyl-6-methylsulfonyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole
trans 6-chloro-8-[3-(N-cyano-N-methylamino)-propylidene]-3α,12β-dihydro-2,2-dimethyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole
trans 8-[3-(N-cyano-N-methylamino)-propylidene]-3α, 12β-dihydro-2,2-dimethyl-6-dimethylsulfamoyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

EXAMPLE 10

Trans 3α,12β-dihydro-2,2-dimethyl-8-(3-methylaminopropylidene)-8H - dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

The oily cyanamide (1.44 g., 0.004 mole), prepared as in Example 8 above, is dissolved in a solution of potassium hydroxide (1.12 g., 0.02 mole) in 12 ml. of n-butyl alcohol and the solution is heated to refluxing in a nitrogen atmosphere for 12 hours. The solvent is distilled under reduced pressure and the residue partitioned between hexane and water. After two re-extractions of the aqueous layer with hexane, the combined hexane extracts are washed with water and extracted with 50 ml. of 0.1 M citric acid. The acid extract is rendered alkaline with sodium hydroxide and the oily base extracted into benzene. The washed and dried benzene extract is evaporated to dryness under reduced pressure, leaving the product as an oily residue weighing, typically, 920 mg.

The base may be converted to the hydrogen oxalate salt by treating an ethanolic solution with a solution of oxalic acid (10% excess) in absolute ethanol. Analytically pure trans 3α,12β-dihydro-2,2-dimethyl-8-(3-methylaminopropylidene) - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole hydrogen oxalate from another experiment melts at 224° C., dec., after repeated recrystallizations from absolute ethanol.

Analysis.—Calc'd for $C_{22}H_{25}NO_2 \cdot C_2H_2O_4$ (percent): C, 67.75; H, 6.40; N, 3.29. Found (percent): C, 67.78; H, 6.32; N, 3.41.

Conversion of the oily base (900 mg.) to the p-toluenesulfonate salt by treating an ethereal solution with a solution of p-toluene sulfonic acid monohydrate (5% excess) in absolute ethanol, affords the white crystalline salt, M.P. 148–150° C., dec., in a yield of 950 mg.

EXAMPLE 11

Following the procedure of Example 10, the products enumerated below are obtained employing the products

enumerated in Example 9 in place of the cyanamide used in Example 10.

trans 3α,12β-dihydro-2,2-dimethyl-8-(3-ethylamino-propylidene)-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole
trans 3α,12β-dihydro-8-(3-methylaminopropylidene)-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole
trans 3α,12β-dihydro-8-(3-methylaminopropylidene)-2-phenyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole
trans 3α,12β-dihydro-2-methyl-8-(3-methylamino-propylidene)-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole
trans 2-benzyl-3α,12β-dihydro-8-(3-methylamino-propylidene)-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole
trans 3α,12β-dihydro-2-ethyl-2-methyl-8-(3-methylamino-propylidene)-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole
trans 3α,12β-dihydro-2,2-dimethyl-8-(3-methylamino-propylidene)-6-methylsulfonyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole
trans 6-chloro-3α,12β-dihydro-2,2-dimethyl-8-(3-methyl-aminopropylidene)-8H-dibenzo[3,4:6,7]cyclohepta-[1,2-d]-1,3-dioxole
trans 3α,12β-dihydro-2,2-dimethyl-6-dimethylsulfamoyl-8-(3-methylaminopropylidene)-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

EXAMPLE 12

Trans 10,11-dihydro-10,11 dihydroxy-5-(3-methylamino-propylidene)-5H-dibenzo[a,d]cycloheptene

A solution of trans 3α,12β-dihydro-2,2-dimethyl-8-(3-methylaminopropylidene) - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d]1,3-dioxole p-toluenesulfonate (700 mg., 0.00138 mole) and p-toluenesulfonic acid monohydrate (60 mg., 0.000316 mole) in 60 ml. of absolute methanol is heated to refluxing for 4 hours. The cooled solution is neutralized with 1.5 ml. of 1 M potassium hydroxide in methanol and then the solvent is distilled under reduced pressure. The residue is partitioned between benzene and water and the aqueous layer re-extracted with benzene. The combined benzene extracts are washed with water and then evaporated to dryness under reduced pressure, leaving the product as an oily solid residue. Sublimation of the product at 142° C. and 0.1 mm. affords white crystals, M.P. 153–155° C., weighing, typically, 120 mg. (30%). An analytical sample is obtained by crystallization from a mixture of ethanol and water and resublimation, and melts at 154–156° C.

Analysis.—Calc'd for $C_{19}H_{21}NO_2$ (percent): C, 77.26; H, 7.17; N, 4.74. Found (percent): C, 77.48; H, 7.12; N, 4.77.

EXAMPLE 13

Following the procedure of Example 12, the products enumerated below are obtained employing the products enumerated in Example 11 in place of the dioxole used in Example 12.

trans 10,11-dihydro-10,11-dihydroxy-5-(3-ethylamino-propylidene)-5H-dibenzo[a,d]cycloheptene
trans 10,11-dihydro-10,11-dihydroxy-5-(3-methylamino-propylidene)-5H-dibenzo[a,d]cycloheptene
trans 10,11-dihydro-10,11-dihydroxy-5-(3-methylamino-propylidene)-3-methylsulfonyl-5H-dibenzo[a,d] cycloheptene
trans 3-chloro-10,11-dihydro-10,11-dihydroxy-5-(3-methylaminopropylidene)-5H-dibenzo[a,d] cycloheptene
trans 10,11-dihydro-10,11-dihydroxy-3-dimethyl-sulfamoyl-5-(3-methylaminopropylidene)-5H-dibenzo-[a,d]cycloheptene

EXAMPLE 14

Cis 10,11-diacetoxy-10,11-dihydro-5-(3-dimethylamino-propyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene

3-dimethylaminopropylmagnesium chloride is prepared from magnesium turnings (4.86 g., 0.2 g. atom) and 3-dimethylaminopropyl chloride (24.3 g., 0.2 mole) in 75 ml. of dry tetrahydrofuran following the method of U.S. Pat. No. 3,046,283. In a nitrogen atmosphere, the solution of the Grignard reagent is added dropwise to a stirred suspension of cis 10,11-diacetoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (30.0 g., 0.0925 mole) in 60 ml. of tetrahydrofuran while cooling in an ice-bath. The mixture is stirred in the cold for 2 hours and the bulk of the solvent then is distilled below 50° C. under reduced pressure. The residue is dissolved in benzene and water, 30 ml. is added with stirring and cooling. The benzene is decanted and the gelatinous precipitate washed by decantation with boiling benzene. The combined benzene extracts are extracted repeatedly with 0.5 M citric acid. The acid extract is rendered alkaline with sodium hydroxide and the oily base extracted into benzene. Evaporation of the washed and dried benzene extract under reduced pressure leaves a yellow glass which is extracted into 1 l. of cyclohexane. The solution is filtered from insoluble material and the solvent evaporated. Crystallization of the residual solid from a mixture of ether and hexane gives a first crop of product, M.P. 135–136° C., weighing 12.4 g. A second crop of 8.1 g., M.P. 132–134° C., is obtained from the mother liquor. An analytical sample melts at 134–135° C. after recrystallization from a mixture of ether and hexane.

Analysis.—Calc'd for $C_{24}H_{29}NO_5$ (percent): C, 70.05; H, 7.10; N, 3.40. Found (percent): C, 70.23; H, 7.09; N, 3.37.

EXAMPLE 15

Following the procedure of Example 14, the products enumerated below are obtained employing the ketone of Example 14 and the Grignard reagent designated below.

Grignard reagent	Product
3-diethylaminopropylmagnesium chloride.	Cis 10,11-diacetoxy-5-(3-dethylaminopropyl)-10,11-dihydro-5-hydroxy-5H-dibenzo[a,d]cycloheptene.
3-(1-pyrrolidyl)-propylmagnesium chloride.	Cis 10,11-diacetoxy-10,11-dihydro-5-hydroxy-5[3-(1-pyrrolidyl)-propyl]-5H-dibenzo[a,d]-cycloheptene.
3-(1-piperidyl)-propylmagnesium chloride.	Cis 10,11-diacetoxy-10,11-dihydro-5-hydroxy-5-[3-(1-piperidyl)-propyl]-5H-dibenzo[a,d]-cycloheptene.
3-(1-ethyl-4-piperazinyl)-propylmagnesium chloride.	Cis 10,11-diacetoxy-10,11-dihydro-5-[3-(1-ethyl-4-piperazinyl)-propyl]-5-hydroxy-5H-dibenzo[a,d]cycloheptene.
3-(4-morpholinyl)-propylmagnesium chloride.	Cis 10,11-diacetoxy-10,11-dihydro-5-hydroxy-5-[3-(4-morpholinyl)-propyl]-5H-dibenzo[a,d]-cycloheptene.
3-(N-ethyl-N-methylamino)-propylmagnesium chloride.	Cis 10,11-diacetoxy-10,11-dihydro-5-[3-(N-ethyl-N-methylamino)-propyl]-5-hydroxy-5H-dibenzo[a,d]cycloheptene.

EXAMPLE 16

Following the procedure of Example 14, the products enumerated below are obtained employing the Grignard reagent of Example 14 and the ketone designated below.

Ketone	Product
Cis 10,11-dihydro-10,11-dipropionyloxy-5H-dibenzo-[a,d] cyclohepten-5-one.	Cis 10,11-dihydro-5-(3-dimethylaminopropyl)-10,11-dipropionyloxy-5-hydroxy-5H-dibenzo[a,d]-cycloheptene.
Cis 10,11-dibutyryloxy-10,11-dihydro-5H-dibenzo-[a,d] cyclohepten-5-one.	Cis 10,11-dibutyryloxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]-cycloheptene.
Cis 10,11-dibenzoyloxy-10,11-dihydro-5H-dibenzo-[a,d] cyclohepten-5-one.	Cis 10,11-dibenzoyloxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene.
Cis 10,11-dicaproyloxy-10,11-dihydro-5H-dibenzo-[a,d] cyclohepten-5-one.	Cis 10,11-dicaproyloxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]-cycloheptene.

Ketone	Product
Cis 3-chloro-10,11-diacetoxy-10,11-dihydro-5H-dibenzo [a,d]cyclohepten-5-one.	Cis 3-chloro-10,11-diacetoxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene.
Cis 10,11-diacetoxy-10,11-dihydro-3-methylsulfonyl-5H-dibenzo[a,d]-cyclohepten-5-one.	Cis 10,11-diacetoxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-3-methylsulfonyl-5H-dibenzo[a,d] cycloheptene.
Cis 10,11-diacetoxy-10,11-dihydro-3-dimethylsulfamoyl-5H-dibenzo[a,d]-cyclohepten-5-one.	Cis 10,11-diacetoxy-10,11-dihydro-5-(3-dimethylaminopropyl)-3-dimethylsulfamoyl-5-hydroxy-5H-dibenzo [a,d]-cycloheptene.

EXAMPLE 17

Cis 10,11-diacetoxy-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

A solution of cis 10,11-diacetoxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H - dibenzo[a,d]cycloheptene (19.5 g., 0.0475 mole) in 300 ml. of acetic anhydride is heated to refluxing for 4 hours. The solution is evaporated to dryness under reduced pressure and the residual oil partitioned between 0.5 M citric acid and benzene. After repeated washing with benzene, the aqueous acid layer is rendered alkaline with sodium hydroxide and the oily base extracted into benzene. Evaporation of the washed and dried benzene extract leaves the product as an oily residue weighing, typically, 18.0 g. (96.5%).

The base may be converted to the hydrogen oxalate salt by treating an ethanolic solution with a solution of oxalic acid (10% excess) in absolute ether. Cis 10,11-diacetoxy-10,11 - dihydro - 5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrogen oxalate precipitates as a white crystalline solid which melts at 165–166° C. after one recrystallization from a mixture of absolute ethanol and absolute ether.

Analysis.—Calc'd for $C_{24}H_{27}NO_4 \cdot C_2H_2O_4$ (percent): C, 64.58; H, 6.05; N, 2.90. Found (percent): C, 64.31; H, 5.84; N, 2.79.

EXAMPLE 18

Following the procedure of Example 17, the products enumerated below are obtained employing the products enumerated in Examples 15 and 16 in place of the dibenzocycloheptene used in Example 17.

cis 10,11-diacetoxy-5-(3-diethylaminopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene
cis 10,11-diacetoxy-10,11-dihydro-5-[3-(1-pyrrolidyl)-propylidene]-5H-dibenzo[a,d]cycloheptene
cis 10,11-diacetoxy-10,11-dihydro-5-[3-(1-piperidyl)-propylidene]-5H-dibenzo[a,d]cycloheptene
cis 10,11-diacetoxy-10,11-dihydro-5-[3-(1-ethyl-4-piperazinyl)-propylidene]-5H-dibenzo[a,d]cycloheptene
cis 10,11-diacetoxy-10,11-dihydro-5-[3-(4-morpholinyl)-propylidene]-5H-dibenzo[a,d]cycloheptene
cis 10,11-diacetoxy-10,11-dihydro-5-[3-(N-ethyl-N-methylamino)-propylidene]-5H-dibenzo[a,d]cycloheptene
cis 10,11-dihydro-5-(3-dimethylaminopropylidene)-10,11-dipropionyloxy-5H-dibenzo[a,d]cycloheptene
cis 10,11-dibutyryloxy-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene
cis 10,11-dibenzoyloxy-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene
cis 10,11-dicaproyloxy-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene
cis 3-chloro-10,11-diacetoxy-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene
cis 10,11-diacetoxy-10,11-dihydro-5-(3-dimethylaminopropylidene)-3-methylsulfonyl-5H-dibenzo[a,d]cycloheptene
cis 10,11-diacetoxy-10,11-dihydro-5-(3-dimethylaminopropylidene)-3-dimethylsulfamoyl-5H-dibenzo[a,d]-cycloheptene

EXAMPLE 19

Cis 10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

A solution of cis 10,11-diacetoxy-10,11-dihydro-5-(3-dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene (1.6 g., 0.00417 mole) and potassium hydroxide (1.6 g., 0.024 mole) in 70 ml. of absolute methanol is heated to refluxing for 15 minutes. The solvent is evaporated under reduced pressure and the residue treated with 50 ml. of water. The precipitate is collected, washed with water, and recrystallized from a mixture of ethanol and water to obtain the product as a white crystalline solid, M.P. 173–175° C., weighing 1.05 g. (81%). A purified sample from another experiment melts at 171–174° C. after sublimation at 155° C. and 0.05 mm.

Analysis.—Calc'd for $C_{20}H_{23}NO_2$ (percent): C, 77.64; H, 7.49; N, 4.53. Found (percent): C, 77.64; H, 7.50; N, 4.53.

EXAMPLE 20

Following the procedure of Example 19, the products enumerated below are obtained employing the products enumerated in Example 18 in place of the dibenzocycloheptene used in Example 19.

cis 5-(3-diethylaminopropylidene)-10,11-dihydro-10,11-dihydroxy-5H-dibenzo[a,d]cycloheptene
cis 10,11-dihydro-10,11-dihydroxy-5-[3-(1-pyrrolidyl)-propylidene]-5H-dibenzo[a,d]cycloheptene
cis 10,11-dihydro-10,11-dihydroxy-5-[3-(1-piperidyl)-propylidene]-5H-dibenzo[a,d]cycloheptene
cis 10,11-dihydro-10,11-dihydroxy-5-[3-(1-ethyl-4-piperazinyl)propylidene]-5H-dibenzo[a,d]cycloheptene
cis 10,11-dihydro-10,11-dihydroxy-5-[3-(4-morpholinyl)-propylidene]-5H-dibenzo[a,d]cycloheptene
cis 10,11-dihydro-10,11-dihydroxy-5-[3-(N-ethyl-N-methylamino)-propylidene]-5H-dibenzo[a,d]cycloheptene
cis 10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene
cis 3-chloro-10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene
cis 10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-3-methylsulfonyl-5H-dibenzo[a,d]cycloheptene
cis 10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-3-dimethylsulfamoyl-5H-dibenzo[a,d] cycloheptene

EXAMPLE 21

Cis 5 - [3-(N-carbethoxy-N-methylamino)-propylidene]-10,11 - diacetoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

A solution of cis 10,11-diacetoxy-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene (7.86 g., 0.02 mole) in 40 ml. of dry benzene is added dropwise over a 90 minute period to a stirred solution of 8 ml. of ethyl chloroformate in 20 ml. of dry benzene. The mixture then is stirred at reflux for 2½ hours. After cooling and diluting with 50 ml. of benzene, the solution is washed with 3 N hydrochloric acid and then with water. Benzene is distilled under reduced pressure, leaving cis 5-[3-(N-carbethoxy-N-methylamino)-propylidene]-10,11-diacetoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene as an oily residue weighing, typically, 7.85 g. (87%).

EXAMPLE 22

Following the procedure of Example 21, the products enumerated below are obtained employing the 5-(3-dialkylaminopropylidene) products enumerated in Example 18 in place of the dibenzocycloheptene used in Example 21.

cis 5-[3-(N-carbethoxy-N-ethylamino)-propylidene]-10,11-diacetoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

cis 5-[3-(N-carbethoxy-N-methylamino)-propylidene]-10,11-dihydro-10,11-dipropionyloxy-5H-dibenzo[a,d]cycloheptene

cis 5-[3-(N-carbethoxy-N-methylamino)-propylidene]-10,11-dibutyryloxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

cis 5-[3-(N-carbethoxy-N-methylamino)-propylidene]-10,11-dibenzoyloxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

cis 5-[3-(N-carbethoxy-N-methylamino)-propylidene]-10,11-dicaproyloxy-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene

cis 5-[3-(N-carbethoxy-N-methylamino)-propylidene]-3-chloro-10,11-diacetoxy-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene

cis 5-[3-(N-carbethoxy-N-methylamino)-propylidene]-10,11-diacetoxy-10,11-dihydro-3-methylsulfonyl-5H-dibenzo[a,d]cycloheptene

cis 5-[3-(N-carbethoxy-N-methylamino)-propylidene]-10,11-diacetoxy-10,11-dihydro-3-dimethylsulfamoyl-5H-dibenzo[a,d]cycloheptene

EXAMPLE 23

Following the procedure of Example 21, the products enumerated below are obtained employing the haloformate designated below in place of ethyl chloroformate.

Haloformate	Product
Benzyl chloroformate	Cis 5-[3-(N-carbobenzoxy-N-methylamino)-propylidene]-10,11-diacetoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene.
Phenyl chloroformate	Cis 5-[3-(N-carbophenoxy-N-methylamino)-propylidene]-10,11-diacetoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene.
Propyl chloroformate	Cis 5-[3-(N-carbopropoxy-N-methylamino)-propylidene]-10,11-diacetoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene.

EXAMPLE 24

Following the procedure of Example 21, the products enumerated below are obtained employing the 8-(3-dialkylaminopropylidene) products enumerated in Example 5 in place of cis 10,11-diacetoxy-10,11-dihydro-5-(3-dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene.

trans 8-[3-(N-carbethoxy-N-ethylamino)-propylidene]-3α,12β-dihydro-2,2-dimethyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 8-[3-(N-carbethoxy-N-methylamino)-propylidene]-3α,12β-dihydro-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 8-[3-(N-carbethoxy-N-methylamino)-propylidene[-3α,12β-dihydro-2-phenyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 8-[3-(N-carbethoxy-N-methylamino)-propylidene]-3α,12β-dihydro-2-methyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 2-benzyl-8-[3-(N-carbethoxy-N-methylamino)-propylidene]-3α,12β-dihydro-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 8-[3-(N-carbethoxy-N-methylamino)-propylidene]-3α,12β-dihydro-2-ethyl-2-methyl-8H-dibenzo[3,4:6,7]-cyclohepta[1,2-d]-1,3-dioxole

trans 8-[3-(N-carbethoxy-N-methylamino)-propylidene]-3α,12β-dihydro-2,2-dimethyl-6-methylsulfonyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 8-[3-(N-carbethoxy-N-methylamino)-propylidene]-6-chloro-3α,12β-dihydro-2,2-dimethyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

trans 8-[3-(N-carbethoxy-N-methylamino)-propylidene]-3α,12β-dihydro-2,2-dimethyl-6-dimethylsulfamoyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxole

EXAMPLE 25

Following the procedure of Example 21, the products enumerated below are obtained employing trans 3α,12β-dihydro-2,2-dimethyl-8-(3 - dimethylaminopropylidene)-8H - dibenzo[3,4:6,7]cyclohepta[1,2-d] - 1,3 - dioxole in place of cis 10,11-diacetoxy-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene and the haloformates designated below in place of ethyl chloroformate.

Haloformate	Product
Benzyl chloroformate	trans 8-[3-(N-carbobenzoxy-N-methylamino)-propylidene]-3α,12β-dihydro-2,2-dimethyl-8H-dibenzo[3,4:6,7]cyclohepta-[1,2-d]-1,3-dioxole.
Phenyl chloroformate	trans 8-[3-(N-carbophenoxy-N-methylamino)-propylidene]-3α,12β-dihydro-2,2-dimethyl-8H-dibenzo[3,4:6,7]cyclohepta-[1,2-d]-1,3-dioxole.
Propyl chloroformate	trans 8-[3-(N-carbopropoxy-N-methylamino)-propylidene]-3α,12β-dihydro-2,2-dimethyl-8H-dibenzo[3,4:6,7]cyclohepta-[1,2-d]-1,3-dioxole.

EXAMPLE 26

Cis 10,11-dihydro-10,11-dihydroxy-5-(3-methylaminopropyl)-5H-dibenzo[a,d]cycloheptene

A solution of the oily urethane (2.8 g., 0.0076 mole) obtained in Example 21 and potassium hydroxide (2.5 g., 0.04 mole) in 25 ml. of n-butyl alcohol is stirred and heated to refluxing in a nitrogen atmosphere for 6 hours. The solvent is distilled under reduced pressure and the residue partitioned between benzene and water. After re-extraction of the aqueous phase, the combined benzene extracts are washed with water and then extracted with 15 ml. and 10 ml. portions of 0.5 M citric acid. The acid extract is rendered alkaline with sodium hydroxide and the oily base extracted into benzene. The washed and dried benzene extract is concentrated to a small volume. The product separates as a white crystalline solid and is collected, washed with benzene, and dried to obtain 1.05 g. (47%), M.P. 140–143° C. The pure product from another experiment melts at 143–145° C. after repeated crystallizations from benzene and from mixtures of ethanol and water.

Analysis.—Calc'd for $C_{19}H_{21}NO_2$ (percent): C, 77.26; H, 7.17; N, 4.74. Found (percent): C, 77.34; H, 7.18; N, 4.59.

EXAMPLE 27

Following the procedure of Example 26, the products enumerated below are obtained employing the products enumerated in Examples 22 and 23 in place of the urethane used in Example 26.

cis 10,11-dihydro-10,11-dihydroxy-5-(3-ethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

cis 10,11-dihydro-10,11-dihydroxy-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

cis 3-chloro-10,11-dihydro-10,11-dihydroxy-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

cis 10,11-dihydro-10,11-dihydroxy-5-(3-methylaminopropylidene)-3-methylsulfonyl-5H-dibenzo[a,d]cycloheptene

cis 10,11-dihydro-10,11-dihydroxy-3-dimethylsulfamoyl-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

EXAMPLE 28

Following the procedure of Example 26, the products enumerated below are obtained employing the products enumerated in Examples 24 and 25 in place of the urethane used in Example 26.

trans 10,11-dihydro-10,11-dihydroxy-5-(3-ethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

trans 10,11-dihydro-10,11-dihydroxy-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

trans 3-chloro-10,11-dihydro-10,11-dihydroxy-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

trans 10,11-dihydro-10,11-dihydroxy-5-(3-methylaminopropylidene)-3-methylsulfonyl-5H-dibenzo[a,d]cycloheptene

trans 10,11-dihydro-10,11-dihydroxy-3-dimethylsulfamoyl-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

EXAMPLE 29

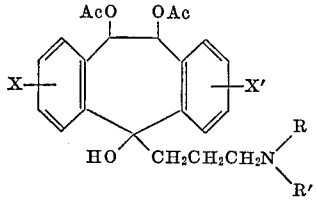
Cis 10,11-dihydro-10,11-dihydroxy-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

A solution of 5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene (1.06 g., 0.00386 mole) in 7 ml. of dry benzene and 0.6 ml. of dry pyridine is treated with a solution of osmium tetroxide (1.0 g., 0.00394 mole) in 6 ml. of dry benzene and the mixture allowed to stand at room temperature for 10 days. The solution is decanted from the black precipitate which separates and the solid washed once with 25 ml. of benzene by decantation. The benzene solution and washings are filtered through diatomaceous earth. The combined precipitate and diatomaceous earth are suspended in 60 ml. of 95% ethanol and heated to refluxing for 45 minutes with 25 ml. of a saturated aqueous solution of sodium sulfite. After filtering the mixture through diatomaceous earth, the filtrate is evaporated under reduced pressure until a dark oil separates. The residue is diluted with an equal volume of water and the oily base extracted into benzene. Evaporation of the washed and dried benzene extract leaves the product as an oily solid residue weighing 450 mg. Purification by sublimation at 155° C. and 0.1 mm. and crystallization of the sublimate from a mixture of ethanol and water affords the product as a white crystalline solid, M.P. 172.5–175.5° C., in a yield of 250 mg. (20%).

Analysis.—Calc'd. for $C_{20}H_{23}O_2N$ (percent): C, 77.64; H, 7.49. Found (percent): C, 77.41; H, 7.49.

What is claimed is:

1. A compound of the formula



wherein R and R' are lower alkyl radicals having up to 6 carbon atoms or R and R' form with the nitrogen atom piperidino, pyrrolidino, morpholino or 4-lower alkyl of 1 to 6 carbon atoms piperazino; X and X' are selected from the group consisting of hydrogen, lower alkyl up to 6 carbon atoms, lower alkenyl up to 6 carbon atoms, halogen, trifluoromethyl, hydroxyl, lower alkoxy up to 4 carbon atoms, mercapto, loweralkyl mercapto up to 4 carbon atoms, loweralkyl sulfonyl up to 4 carbon atoms, sulfamoyl, loweralkyl sulfamoyl up to 4 carbon atoms and diloweralkyl sulfamoyl up to 8 carbon atoms; and Ac represents acyl selected from acetyl, propionyl, butyryl, benzoyl or caproyl.

2. 10,11 - diacetoxy - 10,11 - dihydro - 5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene.

3. Cis 10,11 - diacetoxy - 5 - (3 - diethylaminopropyl)-10,11 - dihydro - 5 - hydroxy - 5H - dibenzo[a,d]cycloheptene according to claim **1**.

4. Cis 10,11 - diacetoxy - 10,11 - dihydro - 5 - hydroxy-5 - [3 - (1 - pyrrolidyl)-propyl] - 5H - dibenzo[a,d]cycloheptene according to claim **1**.

5. Cis 10,11 - diacetoxy - 10,11 - dihydro - 5 - hydroxy-5 - [3 - (1 - piperidyl)-propyl] - 5H - dibenzo[a,d]cycloheptene according to claim **1**.

6. Cis 10,11 - diacetoxy - 10,11 - dihydro - 5 - [3 - (1-ethyl - 4 - piperazinyl)-propyl] - 5 - hydroxy - 5H - dibenzo[a,d]cycloheptene according to claim **1**.

7. Cis 10,11 - diacetoxy - 10,11 - dihydro - 5 - hydroxy-5 - [3 - (4 - morpholinyl)-propyl] - 5H - dibenzo[a,d] cycloheptene according to claim **1**.

8. Cis 10,11 - diacetoxy - 10,11 - dihydro - 5 - [3-(N-ethyl-N-methylamino)-propyl] - 5 - hydroxy - 5H - dibenzo[a,d]cycloheptene according to claim **1**.

9. Cis 10,11 - dihydro - 5 - (3 - dimethylaminopropyl)-10,11 - dipropionyloxy - 5 - hydroxy - 5H - dibenzo[a,d] cycloheptene according to claim **1**.

10. Cis 10,11 - dibutyryloxy - 10,11 - dihydro - 5 - (3-dimethylaminopropyl) - 5 - hydroxy - 5H - dibenzo[a,d] cycloheptene according to claim **1**.

11. Cis 10,11 - dibenzoyloxy - 10,11 - dihydro-5-(3-dimethylaminopropyl) - 5 - hydroxy - 5H - dibenzo[a,d] cycloheptene according to claim **1**.

12. Cis 10,11 - dicaproyloxy - 10,11 - dihydro - 5 - (3-dimethylaminopropyl) - 5 - hydroxy - 5H - dibenzo[a,d] cycloheptene according to claim **1**.

13. Cis 3-chloro - 10,11 - diacetoxy - 10,11 - dihydro-5-(3-dimethylaminopropyl) - 5 - hydroxy - 5H - dibenzo [a,d]cycloheptene according to claim **1**.

14. Cis 10,11 - diacetoxy - 10,11 - dihydro - 5 - (3-dimethylaminopropyl) - 5 - hydroxy - 3 - methylsulfonyl-5H-dibenzo[a,d]cycloheptene according to claim **1**.

15. Cis 10,11 - diacetoxy - 10,11 - dihydro - 5 - (3-dimethylaminopropyl) - 3 - dimethylsulfamoyl-5-hydroxy-5H-dibenzo[a,d]cycloheptene according to claim **1**.

No references cited.

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