

1074081



PATENT SPECIFICATION

1074081

NO DRAWINGS

Date of Application and filing Complete Specification: June 8, 1964.
No. 23655/64.

Application made in United States of America (No. 286,962) on June 11, 1963.
Application made in United States of America (No. 306,639) on Sept. 4, 1963.

Complete Specification Published: June 28, 1967.

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Index at acceptance:—C2 C(1F1B, 1F1C2, 1F1C5, 1F1C6, 1F1D3, 1F2C2, 1F2C5, 1F2C6, 1F2D3, 1H1A2, 1H1A3, 1H1C3, 1Q2, 1Q6C, 1Q7A, 1Q8A, 1Q9A, 1Q9B, 1Q9C, 1Q9D1, 1Q9F2, 1Q9L, 1Q11D, 1Q11G, 1Q11J, 2A3, 2A5, 2A6, 2A13, 2A14, 2B2A4, 2B2G2, 2B2G10, 2B2J, 2B3A4, 2B3B, 2B3E, 2B3F, 2B3G1, 2B3G2, 2B3G7, 2B4A4, 2B4F, 2B4G1, 2B4G2, 2B4G10, 2B18, 2B40D, 2B40F, 2B40G, 2B40H1, 2B40H2, 2B40J1, 2B40J2, 2B40J3, 2B40J4, 2B40K, 2B45D1, 2D6, 2D43A, 2D43B, 2D43C, 2D43D, 2D43E, 2D43F, 2D43J, 2D43S4, 2D48, 2R16, 2R17, 2R18, 3A10E3A4, 3A10E3C4, 3A10E5A, 3A10E5F1C, 3A10E5F2A, 3A13A3A4, 3A13A3B2, 3A13A3B3, 3A13A3C, 3A13A3F3, 3A13A3K, 3A13A3L, 3A14A3C, 3A14A5, 3A14A7B, B4A1, B4A2, B4A4, B4B, B4C, B4D, B4H)

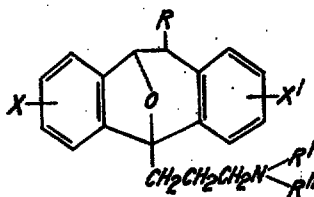
Int. Cl.:—C 07 d 21/00

COMPLETE SPECIFICATION

5,10-Epoxy-5-(Aminopropyl) Dibenzocycloheptenes

We, MERCK & CO., INC., a body corporate organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to dibenzocycloheptene compounds. Certain compounds provided by the present invention have the formula:

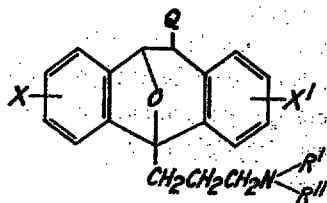


in which R is a hydrogen atom, a hydroxy, oxo, hydroxyimino, amino, C₁₋₆ alkylamino, or di(C₁₋₆ alkyl)amino radical, or R represents a hydroxy and a C₁₋₆ alkyl radical attached to the same carbon atom; NR'R'' is a C₁₋₆ alkylamino or di(C₁₋₆ alkyl)amino radical or a saturated heterocyclic amino radical containing five or six atoms in the ring and in which any hetero atoms, apart from the N shown are nitrogen (either unsubstituted or C₁₋₄ alkylated), or oxygen and each of X and X' is a hydrogen or halogen atom or a C₁₋₆ alkyl, C₂₋₆ alkenyl, trifluoromethyl, hydroxyl, C₁₋₄ alkoxy, mercapto, C₁₋₄ alkylthio, C₁₋₄ alkylsulfonyl, sulfamoyl, C₁₋₄ alkylsulfamoyl or di(C₁₋₄ alkyl)sulfamoyl radical, more than one substituent being optionally present on each benzene ring.

Preferably, if NR'R'' is a heterocyclic radical, it is 1-piperidyl, 1-pyrrolidyl, 4-morpholinyl, or 1-(C₁₋₄ alkyl)-4-piperazinyl. Hereinafter, compounds having the above formula in which NR'R'' is a di(C₁₋₆ alkyl)amino group or a saturated heterocyclic amino group will be referred to as compounds of Formula I, compounds in which NR'R'' is a mono(C₁₋₆ alkyl)amino group will be referred to as compounds of Formula II.

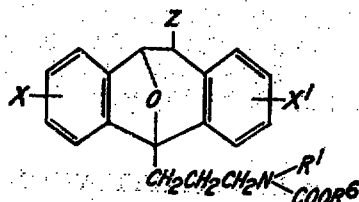
[Price 4s. 6d.]

Other compounds provided in accordance with the present invention have the formula:



in which X, X', R' and R'' are as defined above and Q is an ethylenedithio or trimethylenedithio radical, or, but only when NR'R'' is a di(C₁₋₆ alkyl)amino radical, an acyloxy or C₂₋₆ alkanoylamino radical.

Other compounds provided in accordance with the present invention have the formula:



in which R' is a C₁₋₆ alkyl radical, R⁶ is an alkyl, aralkyl, or aryl radical, Z is a hydrogen atom or an amino, dialkylamino, oxo, acyloxy, C₂₋₆ alkanoylamino, or hydroxyimino radical, and X and X' are as defined above.

The invention also provides non-toxic acid-addition salts of the compounds of Formulae I and II.

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

10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - [3 - (1 - piperidyl) - propyl] - 5H - dibenzo[a,d]cycloheptene;

10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - [3 - (1 - methyl - 4 - piperazinyl) - propyl] - 5H - dibenzo[a,d]cycloheptene;

10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene;

10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene;

7 - chloro - 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene;

10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hydroxy - imino - 3 - methylsulfonyl - 5H - dibenzo[a,d]cycloheptene.

11 - methylamino - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene.

11 - diethylamino - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene.

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

10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - methylaminopropyl) - 3 - methylsulfonyl - 5H - dibenzo[a,d]cycloheptene.

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

10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - diethylaminopropyl) - 3 - dimethylsulfamoyl - 5H - dibenzo[a,d]cycloheptene.

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

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

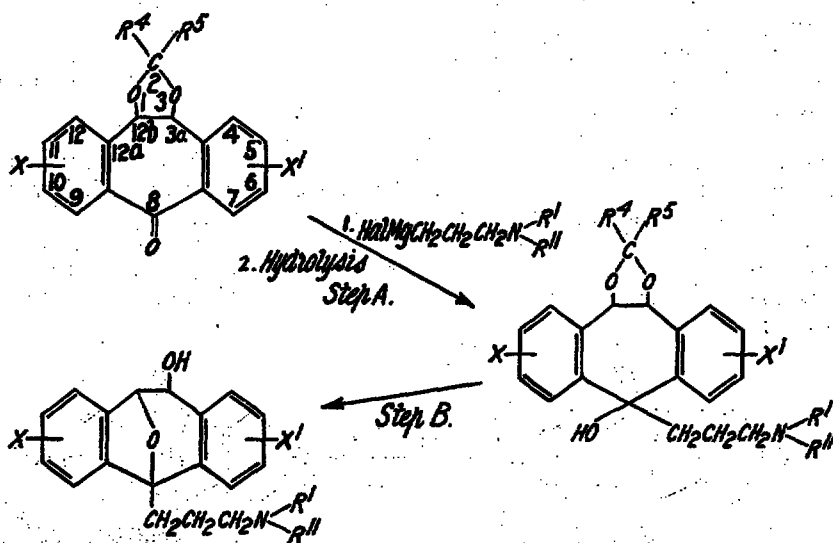
10,11 - dihydro - 5,10 - epoxy - 5 - (3 - methylaminopropyl) - 3 - methylsulfonyl - 5H - dibenzo[a,d]cycloheptene.

10,11 - dihydro - 5,10 - epoxy - 5 - (3 - dimethylaminopropyl) - 3 - trifluoromethyl - 5H - dibenzo[a,d]cycloheptene.

10,11 - dihydro - 5,10 - epoxy - 5 - (3 - diethylaminopropyl) - 3 - dimethylsulfamoyl - 5H - dibenzo[a,d]cycloheptene.

Compounds represented by the above structural formulae, other than those containing the group $-\text{COOR}_6$, possess anti-depressant activity and can advantageously be used in pharmaceutical applications. Pharmaceutical compositions containing such compounds and an inert diluent or carrier form part of the present invention. As anti-depressants, said compounds may be administered orally in the form of tablets, powders, or sustained-release pellets, 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 one mg. to about 300 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, which are included within the scope of this invention.

The compounds of structural formula I, wherein R is hydroxyl and X, X', R' and R'' are as defined for Formula I, may be prepared by treating a 3a,12b - dihydro - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d] - 1,3 - dioxolan - 8 - one with a Grignard reagent, namely, a tertiaryaminopropylmagnesium halide in an inert organic solvent, and hydrolysing the Grignard adduct obtained to form the corresponding 3a,12b - dihydro - 8 - hydroxy - 8 - (3 - tertiaryaminopropyl) - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d] - 1,3 - dioxolane. It should be noted that this process and the resulting product are claimed in the specification of our copending application No. 1280/67 (Serial No. 1074086). The latter compound is then hydrolysed in an inert solvent in the presence of an acidic catalyst to form the corresponding 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - tertiaryaminopropyl) - 5H - dibenzo[a,d]cycloheptene. This process may be illustrated as follows:



In the above process, Hal represents halogen, preferably chlorine or bromine, R' and R'' are as previously defined and R⁴ and R⁵ are hydrogen, alkyl, aryl, or aralkyl.

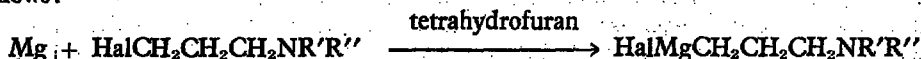
The starting compound in which X and X' are both hydrogen and R⁴ and R⁵ are both methyl, namely 3a,12b - dihydro - 2,2 - dimethyl - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d] - 1,3 - dioxolan - 8 - one, may be prepared in the manner described by G. L. Buchanan and D. B. Jhaveri in J. Org. Chem. 26, 4295-4299 (1961). Those starting compounds in which at least one of X and X' is other than hydrogen, may be prepared from the corresponding nuclearly substituted 5H - dibenzo[a,d]cycloheptadien - 5 - one by 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, pgs. 1489-1499 (1953).

Those starting compounds in which R⁴ and R⁵ are other than methyl may be prepared from the corresponding diol by treatment with an appropriate aldehyde or

ketone by 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 as the R⁴ and R⁵ substituents are removed during the preparation of the end compounds of the 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 R⁴ and R⁵ 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:



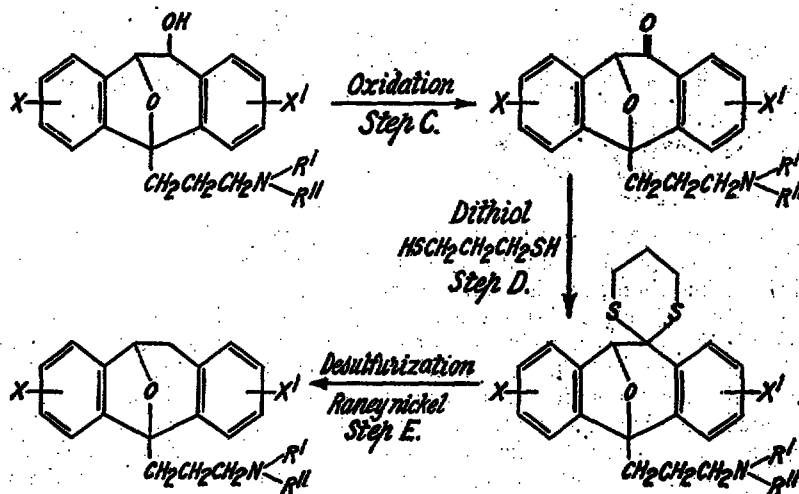
It has been found that the use of tetrahydrofuran as the solvent for the reaction results in a rapid production of the Grignard reagent in high yield.

The reaction with the Grignard reagent is preferably initially carried out at low temperature such as is obtained 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 used.

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 hydrolysed 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 decantation or filtration.

Conversion of the carbinol to the corresponding 5,10 - epoxy - 11 - hydroxy derivative (Step B) is effected by hydrolyzing the former in an inert solvent, preferably at elevated temperatures, in the presence of an acidic catalyst, for example, *p*-toluenesulfonic acid, sulfuric acid, trifluoroacetic acid, or hydrochloric acid. A variety of solvents may be used, but a C₁₋₆ alkanol such as methanol, ethanol, or isopropanol is preferred. Where the product is insoluble in the solvent, it may be recovered (as the salt) by filtration, and further purified by conventional methods. Where the product is soluble in the solvent, it may be recovered (as the base) by evaporation of the solvent, diluting with water, neutralizing any residual acid with sufficient alkali to render the medium basic and collecting the precipitate which forms by filtration.

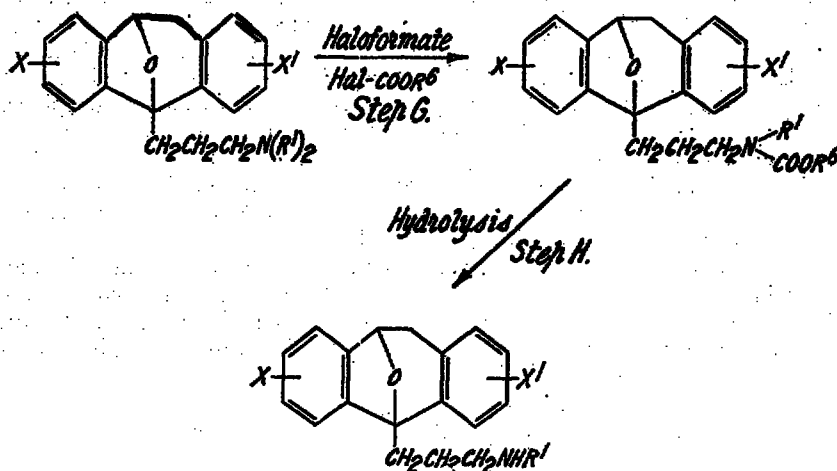
The preparation of those compounds represented by structural formula I, wherein R is hydrogen and X, X', R' and R'' are as defined, may be accomplished from the corresponding 11-hydroxy compound obtained in Step B. This process may be illustrated as follows:



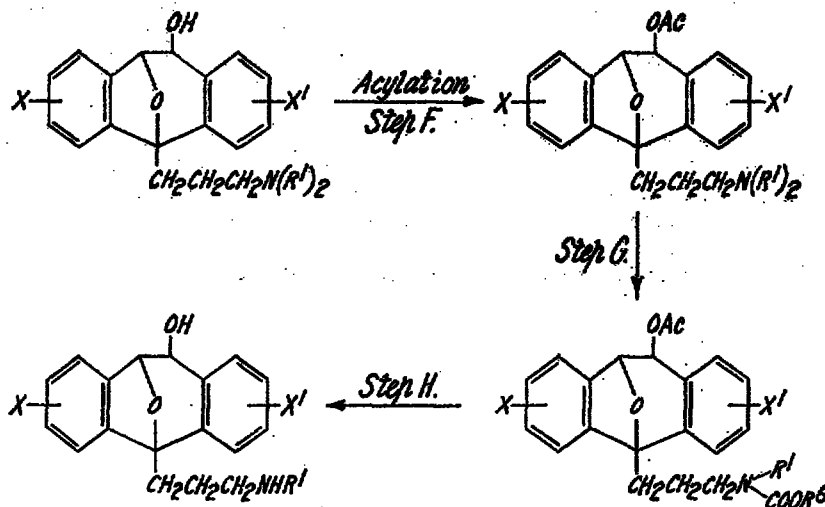
The conversion of the 11-hydroxy compound to the corresponding 11-keto compound can be effected by the standard Oppenauer oxidation reaction. If desired, the product may be isolated in conventional manner. Conversion of the ketone to the

corresponding thioetheral (Step D) is accomplished by contacting the former with a dithiol such as ethylene dithiol or trimethylene dithiol in the presence of a catalyst such as boron trifluoride etherate or zinc chloride-hydrochloric acid. The resulting product which, if desired, can be isolated by conventional methods, is then desulfurized with Raney Nickel in a suitable solvent such as C₁₋₆ alkanol, preferably ethanol. The product may be recovered by evaporation of the solvent.

The preparation of those compounds represented by structural formula II, wherein R is limited to hydrogen, can be readily effected by dealkylation of the corresponding compound of structural formula I, where R' and R'' are both C₁₋₆ alkyl, and preferably are the same. This process may be illustrated as follows, where R⁶ is alkyl, aryl or aralkyl.



Where it is desired to prepare those compounds of structural formula II, in which R is hydroxy, the above dealkylation process may be utilized provided that the hydroxy group is protected during the formation of the urethane intermediate (Step G). This is readily accomplished by acylating the starting 5 - (3 - dialkylaminopropyl) - 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene (Step F), employing any of the common acylating agents. The preferred acylating agents are the acid anhydrides, such as acetic anhydride, since they can serve as both solvent and reagent. Once having obtained the acylated derivative, the dealkylation may proceed as indicated by Steps G and H. This process may be illustrated as follows:



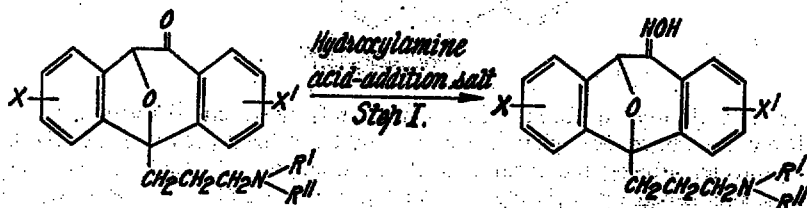
where Ac represents acyl, and X, X', R⁶ and R' are as previously defined. However, it will be readily appreciated by those skilled in the art that as the R' substituent is removed during the dealkylation step, the selection of the particular haloformate will be limited only by its availability and subsequent ease of hydrolysis of the intermediate urethane produced.

Step G 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 use a solvent. Suitable solvents include aromatic hydrocarbons such as benzene and toluene, aliphatic hydrocarbons such as heptane and hexane, and halogenated hydrocarbons such as chloroform and carbon tetrachloride. 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 basic material, by evaporation of the solvent.

The urethane intermediate thus produced then is subjected to hydrolysis (Step H). The hydrolysis preferably is 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.

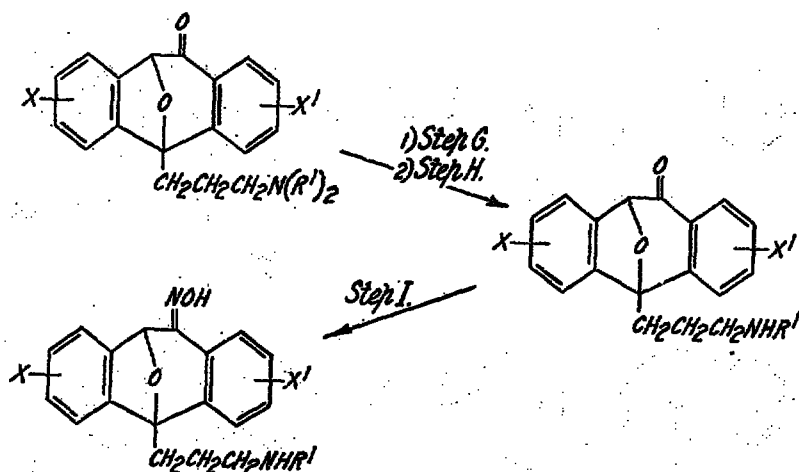
If it is desired, the compounds represented by structural formula II, wherein R is hydrogen, also may be prepared by first dealkylating the 5 - (3 - dialkylaminopropyl) - 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene, in the manner described in Steps F, G and H above, to form the corresponding 5 - (3 - alkylaminopropyl) - 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene and then converting the latter to the corresponding 5 - (3 - alkylaminopropyl) - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene, following the procedure described in Steps C, D and E above.

The preparation of those compounds represented by structural formula I, wherein R is hydroxyimino (=NOH) and R', R'', X and X' are as defined, may be accomplished by treating the 11-keto compound obtained in Step C with an acid-addition salt of hydroxylamine in the presence of an inert solvent. This process may be illustrated as follows:



The conversion of the 11-keto compound to the corresponding 11-hydroxyimino compound is carried out in the presence of an inert suitable solvent and preferably at elevated temperatures, e.g. the reflux temperature of the mixture. Since hydroxylamine base is unstable, an acid addition salt, preferably the hydrochloride, is used. Suitable solvents which may be employed are the C₁₋₆ alkanols and, of these, methanol is preferred. However, other inert organic solvents which are capable of solubilizing the hydroxylamine also may be used. After completion of the reaction, the solvent is removed as by distillation, the residue dissolved in water and the solution rendered alkaline. The precipitated product which forms is readily recovered by filtration.

The preparation of those compounds represented by structural formula II, wherein R is hydroxyimino and R', X and X' are as defined, is readily effected by first dealkylating the above 11-keto compound, where R' and R'' are both C₁₋₆ alkyl and preferably are the same, following the procedures of Steps G and H and then treating the corresponding secondary aminopropyl derivative with hydroxylamine hydrochloride as described in Step I. This process may be illustrated as follows:

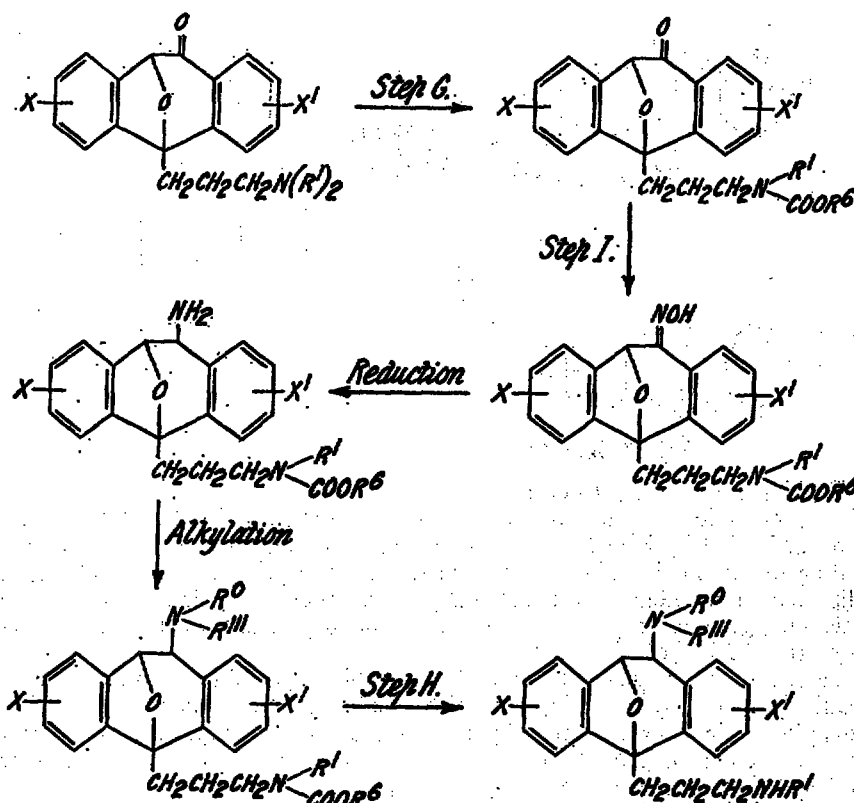


where R', X and X' are as previously defined.

The preparation of those compounds of structural formulae I and II, wherein R is amino and R', R'', X and X' are as defined is accomplished by reducing the corresponding oxime obtained in Step I. The reduction is preferably accomplished using metallic sodium in ethanol, although other conventional reducing agents as well as catalytic hydrogenation may be employed. The desired product may be readily recovered by conventional methods.

The compounds of structural formula I in which R is alkylamino or dialkylamino are readily prepared by alkylating the corresponding amino compound. The alkylation is accomplished in known manner by reductive alkylation employing an appropriate aldehyde or ketone to give the corresponding monoalkylamine, or in the case where formaldehyde is used, the corresponding dimethylamine derivative.

Alternatively, the mono and dialkylamines can be prepared in conventional manner by acylating the primary amine with an acylating agent derived from a C_{2-4} alkanolic acid, for example, acetic anhydride, propionic anhydride or butyric anhydride, to form the corresponding amide, and then reducing the latter to the secondary amine using a suitable reducing agent such as lithium aluminum hydride. The dialkylamines can be obtained from the monoalkylamines by again acylating and then reducing the secondary amide. The preparation of those compounds of structural formula I, wherein R' and R'' are different, can be readily achieved by appropriate selection of the acylating agent, or in the case of the dialkylamines, wherein one of the alkyl radicals is methyl, by subjecting the secondary amine prepared via the acylation and reduction route to reductive alkylation using formaldehyde. The compounds of structural formula II, wherein R is alkylamino or dialkylamino, are prepared by treating the 11-keto compound obtained from Step C (wherein R' and R'' are the same) with a haloformate as described in Step G to form the corresponding 11-keto urethane. The 11-keto urethane is then treated with hydroxylamine as described in Step I to form the corresponding oxime and the oxime reduced to the corresponding primary amine as described hereinabove. The primary amine can then be alkylated using the processes described above and the resulting 11-alkyl or dialkylamino urethane hydrolysed as described in Step H. This overall process may be represented as follows:



The preparation of those compounds of structural formulae I and II, wherein the 11-position contains both hydroxyl and C_{1-6} alkyl substituents, i.e., wherein R is the radical $-\text{C}(\text{OH})(\text{R}''')$, where R' , R'' , R''' , X and X' are as defined may be accomplished

by treating the corresponding tertiary aminopropyl-11-keto compound obtained in Step C with an appropriate Grignard reagent, namely, an alkylmagnesium halide and then hydrolyzing the resulting Grignard adduct following the procedure of Step A. The corresponding secondary aminopropyl can be prepared by dealkylating the tertiary aminopropyl compound following the procedures of Steps G and H or, if desired, the secondary aminopropyl-11-keto compound obtained in Step H can be reacted directly with the Grignard reagent and the Grignard adduct hydrolysed as described above.

The compounds represented by structural formulae I and II hereinabove, where R is hydroxy or amino, exist as geometric isomers. The geometric isomers exist as racemates and resolution into enantiomorphs is possible by conventional techniques, such as fractional crystallization of the salts with optically active acids. Where R is hydroxy, the separate geometric isomers can be obtained by starting with the desired isomer of the ketone in Step A. Such isomers can be obtained by the procedure described in an article by G. L. Buchanan et al., referred to hereinabove. While both isomers possess pharmacological activity, the activity of one isomer may be substantially greater than the other.

When the carbinols obtained in Step A above contain a nuclear substituent, conversion to the 5,10 - epoxy - 11 - hydroxy derivative (Step B) may give either of two compounds depending upon the direction of the ring closure. Thus, when a 6-substituted carbinol is used, the product may be the 3- or 7-substituted-5,10-epoxy-11-hydroxy derivative, and the designation 3(7) is employed, when applicable, in the following Examples, Examples 12—50 of which describe the preparation of representative compounds encompassed within the scope of the present invention. Examples 1—5 and 9—11 are directed to the preparation of various starting materials.

EXAMPLE 1

cis 3a,12b-Dihydro-2-phenyl-8H-dibenzo[3,4:6,7]-
cyclohepta[1,2-d]1,3-dioxolan-8-one

A solution of *cis* 10,11 - dihydro - 10,11 - dihydroxy - 5H - dibenzo[a,d]-
cyclohepten-5-one (2.4 g., 0.01 mole) and *p*-toluenesulfonic acid monohydrate (25 mg.,
0.00013 mole) in 100 ml. of dry benzene is stirred and heated to refluxing. The solvent
is distilled slowly and after approximately 5 ml. of distillate is collected, 5 ml. of
freshly distilled benzaldehyde is added to the mixture. Stirring and slow distillation
are continued for 1 hour. After the addition of 1 ml. of pyridine, the mixture is
evaporated to dryness under reduced pressure. Crystallization of the solid residue from
absolute ethanol gives the product, m.p. 167—175°C., in a yield of 1.3 g. (40%).
An analytical sample melts at 175—176.5°C. after repeated recrystallizations from
absolute ethanol.

Analysis Calc'd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91.

Found: C, 80.38; H, 5.04.

EXAMPLE 2

cis 3a,12b-Dihydro-2,2-dimethyl-8-(3-dimethylamino-
propyl)-8-hydroxy-8H-dibenzo[3,4:6,7]cyclohepta-
[1,2-d]-1,3-dioxolane

3-Dimethylaminopropylmagnesium chloride is prepared from magnesium turnings
(290 mg., 0.012 g. atom) and 3-dimethylaminopropyl chloride (1.47 g., 0.012 mole)
in 12 ml. of dry tetrahydrofuran following the method of U.K. Patent No. 829,763.
In a nitrogen atmosphere, a solution of *cis* 3a,12b - dihydro - 2,2 - dimethyl - 8H -
dibenzo[3,4:6,7]cyclohepta[1,2-d] - 1,3 - dioxolan - 8 - one (1.7 g., 0.0061 mole)
in 13 ml. of dry tetrahydrofuran is added dropwise to the stirred solution of the
Grignard reagent while cooling in an ice-bath. The dark yellow solution is allowed to
come to room temperature and stirred for 2 hours. The bulk of the solvent then is
distilled at room temperature under reduced pressure. The residue is dissolved in 25
ml. of benzene, and water, 6 ml., is added dropwise with stirring and cooling. The
benzene layer is decanted from the gelatinous precipitate which then is extracted with
three 30 ml. portions of boiling benzene. The combined benzene extracts are washed
with water repeatedly. The benzene is evaporated and the residual solid crystallized
from 95% ethanol. *cis* 3a,12b - Dihydro - 2,2 - dimethyl - 8 - (3 - dimethylamino-
propyl) - 8 - hydroxy - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d] - 1,3 - dioxolane
is obtained as white needles, m.p. 181—188°C., in a yield of 1.56 g. (70%). The pure
product from a repeat of this experiment melts at 189—190°C. after recrystallization
from 95% ethanol and from isopropyl alcohol.

Analysis Calc'd for $C_{28}H_{36}O_3N$: C, 75.17; H, 7.95; N, 3.81.

Found: C, 75.12; H, 7.82; N, 4.01.

EXAMPLE 3

cis 3a,12b-Dihydro-8-(3-dimethylaminopropyl)-8-
hydroxy-2-phenyl-8H-dibenzo[3,4:6,7]cyclohepta-
[1,2-d]-1,3-dioxolane

By following the procedure of Example 2, but using an equimolecular quantity of
cis 3a,12b - dihydro - 2 - phenyl - 8H - dibenzo[a,d]cyclohepta[1,2-d] - 1,3 -
dioxolan - 8 - one instead of the *cis* 3a,12b - dihydro - 2,2 - dimethyl - 8H - dibenzo-
[3,4:6,7]cyclohepta[1,2-d] - 1,3 - dioxolan - 8 - one, there is obtained *cis* 3a,12b -
dihydro - 8 - (3 - dimethylaminopropyl) - 8 - hydroxy - 2 - phenyl - 8H - dibenzo-
[3,4:6,7]cyclohepta[1,2-d] - 1,3 - dioxolane as a white crystalline solid, m.p. 155—
161°C., in a yield of 71%. Repeated recrystallizations from 95% ethanol give an
analytical sample, m.p. 166—167°C.

Analysis Calc'd for $C_{27}H_{28}NO_3$: C, 78.04; H, 7.04; N, 3.37.

Found: C, 78.09; H, 7.21; N, 3.42.

EXAMPLE 4

Following the procedure of Example 2, the products enumerated below are ob-
tained using the ketone of Example 2 and the Grignard reagent designated below.

Grignard reagent
3-diethylaminopropylmagnesium
chloride

Product
cis 8-(3-diethylamino-
propyl)-3a,12b-dihydro-
2,2-dimethyl-8-hydroxy-8H-
dibenzo[3,4:6,7]cyclohepta-
[1,2-d]-1,3-dioxolane

*Grignard reagent*3-(1-pyrrolidyl)-propyl-
magnesium chloride*Product**cis* 3a,12b-dihydro-2,2-
dimethyl-8-hydroxy-8-
[3-(1-pyrrolidyl)-propyl]-
8H-dibenzo[3,4:6,7]cyclo-
hepta[1,2-d]-1,3-dioxolane3-(1-piperidyl)-propyl-
magnesium chloride*cis* 3a,12b-dihydro-2,2-
dimethyl-8-hydroxy-8-
[3-(1-piperidyl)-propyl]-
8H-dibenzo[3,4:6,7]cyclo-
hepta[1,2-d]-1,3-dioxolane3-(1-ethyl-4-piperazinyl)-
propylmagnesium chloride*cis* 3a,12b-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-dioxolane3-(4-morpholinyl)-propyl-
magnesium chloride*cis* 3a,12b-dihydro-2,2-
dimethyl-8-hydroxy-8-
[3-(4-morpholinyl)-propyl]-
8H-dibenzo[3,4:6,7]cyclo-
hepta[1,2-d]-1,3-dioxolane3-(N-ethyl-N-methylamino)-
propylmagnesium chloride*cis* 3a,12b-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-
dioxolane

EXAMPLE 5

Following the procedure of Example 2, the products enumerated below are obtained using the Grignard reagent of Example 2 and the ketone designated below.

*Ketone**cis* 3a,12b-dihydro-8H-dibenzo-
[3,4:6,7]cyclohepta[1,2-d]-1,3-
dioxolan-8-one*Product**cis* 3a,12b-dihydro-8-(3-
dimethylaminopropyl)-8-
hydroxy-8H-dibenzo-
[3,4:6,7]cyclohepta[1,2-d]-
1,3-dioxolane*cis* 3a,12b-dihydro-2-methyl-
8H-dibenzo[3,4:6,7]cyclo-
hepta[1,2-d]-1,3-
dioxolan-8-one*cis* 3a,12b-dihydro-8-(3-
dimethylaminopropyl)-8-
hydroxy-2-methyl-8H-
dibenzo[3,4:6,7]cyclo-
hepta[1,2-d]-1,3-dioxolane*cis* 2-benzyl-3a,12b-dihydro-
8H-dibenzo[3,4:6,7]cyclo-
hepta[1,2-d]-1,3-dioxolan-
8-one*cis* 2-benzyl-3a,12b-
dihydro-8-(3-dimethyl-
aminopropyl)-8-hydroxy-
8H-dibenzo[3,4:6,7]cyclo-
hepta[1,2-d]-1,3-dioxolane*cis* 3a,12b-dihydro-2-ethyl-
2-methyl-8H-dibenzo[3,4:6,7]-
cyclohepta[1,2-d]-1,3-
dioxolan-8-one*cis* 3a,12b-dihydro-8-
(3-dimethylaminopropyl)-
2-ethyl-8-hydroxy-2-
methyl-8H-dibenzo-
[3,4:6,7]cyclohepta[1,2-d]-
1,3-dioxolane

	<i>Ketone</i>	<i>Product</i>	
5	<i>cis</i> 3a,12b-dihydro-2,2-dimethyl-6-methylsulfonyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolan-8-one	<i>cis</i> 3a,12b-dihydro-2,2-dimethyl-8-(3-dimethylaminopropyl)-8-hydroxy-6-methylsulfonyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane	5
10	<i>cis</i> 6-chloro-3a,12b-dihydro-2,2-dimethyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolan-8-one	<i>cis</i> 6-chloro-3a,12b-dihydro-2,2-dimethyl-8-(3-dimethylaminopropyl)-8-hydroxy-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane	10
15	<i>cis</i> 3a,12b-dihydro-2,2-dimethyl-6-dimethylsulfamoyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolan-8-one	<i>cis</i> 3a,12b-dihydro-2,2-dimethyl-8-(3-dimethylaminopropyl)-6-dimethylsulfamoyl-8-hydroxy-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane	15

EXAMPLE 6

cis 10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hydroxy-5H-dibenzo[a,d]cycloheptene

A solution of *cis* 3a,12b - dihydro - 2,2 - dimethyl - 8 - (3 - dimethylaminopropyl) - 8 - hydroxy - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane (2.95 g., 0.008 mole) and *p*-toluenesulfonic acid monohydrate (3.0 g., 0.0158 mole) in 300 ml. of absolute methanol is heated to refluxing for 4 hours. The solution is neutralized with 16 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, dried by filtration through paper, and then evaporated to dryness under reduced pressure. Crystallization of the residual solid from 50% ethanol gives the product, m.p. 145—152°C., in a yield of 1.9 g. (81%). An analytical sample melts at 151—153°C. after repeated crystallizations from cyclohexane.

Analysis Calc'd for C₂₀H₂₃NO₃: C, 77.64; H, 7.49; N, 4.53.

Found: C, 77.67; H, 7.70; N, 4.52.

EXAMPLE 7

cis 10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hydroxy-5H-dibenzo[a,d]cycloheptene

A solution of *cis* 3a,12b - dihydro - 8 - (3 - dimethylaminopropyl) - 8 - hydroxy - 2 - phenyl - 8H - dibenzo[a,d]cyclohepta[1,2-d] - 1,3 - dioxolane (415 mg., 0.001 mole) and *p*-toluenesulfonic acid monohydrate (380 mg., 0.002 mole) in 40 ml. of absolute methanol is heated to refluxing for 8 hours. The cooled solution is made basic with 5 ml. of 1 M. potassium hydroxide in methanol and the solvent is distilled under reduced pressure. The residue is partitioned between benzene and water and after re-extraction of the aqueous phase with benzene, the combined benzene extracts are washed with water and dried by filtration through anhydrous sodium sulfate. Evaporation of the benzene under reduced pressure leaves an oily residue which solidifies upon trituration with ether, yielding 200 mg. (65%), m.p. 137—144°C. A purified sample is identical in melting point (149—152°C.), mixture melting point and infrared spectrum to *cis* 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene, prepared as in Example 6.

EXAMPLE 8

Employing the procedure of Example 6, the products enumerated below are obtained using the products enumerated in Examples 4 and 5 in place of the dioxole used in Example 6.

cis 5 - (3 - diethylaminopropyl) - 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene
cis 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - [3 - (1 - pyrrolidyl) - propyl] - 5H - dibenzo[a,d]cycloheptene

- cis* 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - [3 - (1 - piperidyl) - propyl] - 5H - dibenzo[a,d]cycloheptene
- cis* 10,11 - dihydro - 5,10 - epoxy - 5 - [3 - (1 - ethyl - 4 - piperazinyl) - propyl] - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene
- cis* 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - [3 - (4 - morpholinyl) - propyl] - 5H - dibenzo[a,d]cycloheptene
- cis* 10,11 - dihydro - 5,10 - epoxy - 5 - [3 - (N - ethyl - N - methylamino) - propyl] - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene
- cis* 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hydroxy - 3(7) - methylsulfonyl - 5H - dibenzo[a,d]cycloheptene.
- cis* 3(7) - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene
- cis* 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 3(7) - dimethylsulfonyl - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene

EXAMPLE 9

trans 3a,12b-Dihydro-2,2-dimethyl-8-(3-dimethylamino-propyl)-8-hydroxy-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane

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.K. Patent No. 829,763. In a nitrogen atmosphere, a solution of *trans* 3a,12b - dihydro - 2,2 - dimethyl - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d] - 1,3 - dioxolane - 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 then is distilled off 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 benzene 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 benzene 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* 3a,12b - dihydro - 2,2 - dimethyl - 8 - (3 - dimethylaminopropyl) - 8 - hydroxy - 8H - dibenzo[3,4:6,7]cyclohepta[1,2-d] - 1,3 - dioxolane 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 C₂₃H₂₉NO₃·C₂H₂O₄: C, 65.62; H, 6.83. Found: C, 65.08; H, 6.72.

EXAMPLE 10

Following the procedure of Example 9, the products enumerated below are obtained using the ketone of Example 9 and the Grignard reagent designated below.

Grignard reagent
3-diethylaminopropylmagnesium chloride

Product
trans 8-(3-diethylamino-propyl)-3a,12b-dihydro-2,2-dimethyl-8-hydroxy-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane

3-(1-pyrrolidyl)-propylmagnesium chloride

trans 3a,12b-dihydro-2,2-dimethyl-8-hydroxy-8-[3-(1-pyrrolidyl)-propyl]-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane

	<i>Grignard reagent</i>	<i>Product</i>	
5	3-(1-piperidyl)-propyl-magnesium chloride	<i>trans</i> 3a,12b-dihydro-2,2-dimethyl-8-hydroxy-8-[3-(1-piperidyl)-propyl]-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane	5
10	3-(1-ethyl-4-piperazinyl)-propylmagnesium chloride	<i>trans</i> 3a,12b-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-dioxolane	10
15	3-(4-morpholinyl)-propyl-magnesium chloride	<i>trans</i> 3a,12b-dihydro-2,2-dimethyl-8-hydroxy-8-[3-(4-morpholinyl)-propyl]-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane	15
20	3-(N-ethyl-N-methylamino)-propylmagnesium chloride	<i>trans</i> 3a,12b-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-dioxolane	20
25	EXAMPLE 11 Following the procedure of Example 9, the products enumerated below are obtained using the Grignard reagent of Example 9 and the ketone designated below.		25
30	<i>Ketone</i> <i>trans</i> 3a,12b-dihydro-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolan-8-one	<i>Product</i> <i>trans</i> 3a,12b-dihydro-8-(3-dimethylaminopropyl)-8-hydroxy-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane	30
35	<i>trans</i> 3a,12b-dihydro-2-phenyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolan-8-one	<i>trans</i> 3a,12b-dihydro-8-(3-dimethylaminopropyl)-8-hydroxy-2-phenyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane	35
40	<i>trans</i> 3a,12b-dihydro-2-methyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolan-8-one	<i>trans</i> 3a,12b-dihydro-8-(3-dimethylaminopropyl)-8-hydroxy-2-methyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane	40
45	<i>trans</i> 2-benzyl-3a,12b-dihydro-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolan-8-one	<i>trans</i> 2-benzyl-3a,12b-dihydro-8-(3-dimethylaminopropyl)-8-hydroxy-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane	45
50	<i>trans</i> 3a,12b-dihydro-2-ethyl-2-methyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolan-8-one	<i>trans</i> 3a,12b-dihydro-8-(3-dimethylaminopropyl)-2-ethyl-8-hydroxy-2-methyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane	50

Ketone

trans 3a,12b-dihydro-2,2-dimethyl-6-methylsulfonyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolan-8-one.

trans 6-chloro-3a,12b-dihydro-2,2-dimethyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolan-8-one.

trans 3a,12b-dihydro-2,2-dimethyl-6-dimethylsulfamoyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolan-8-one.

Product

trans 3a,12b-dihydro-2,2-dimethyl-8-(3-dimethylaminopropyl)-8-hydroxy-6-methylsulfonyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane.

trans 6-chloro-3a,12b-dihydro-2,2-dimethyl-8-(3-dimethylaminopropyl)-8-hydroxy-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane.

trans 3a,12b-dihydro-2,2-dimethyl-8-(3-dimethylaminopropyl)-6-dimethylsulfamoyl-8-hydroxy-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane.

EXAMPLE 12

trans 10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hydroxy-5H-dibenzo[a,d]cycloheptene

A solution of *trans* 3a,12b-dihydro-2,2-dimethyl-8-(3-dimethylaminopropyl)-8-hydroxy-6-methylsulfonyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-d]-1,3-dioxolane (29.4 g., 0.08 mole) and *p*-toluenesulfonic acid monohydrate (30.5 g., 0.16 mole) in 2.3 l. of absolute methanol is heated to refluxing for 4 hours. The cooled solution is neutralized with 150 ml. of 1 M. potassium hydroxide in methanol and the solvent then is distilled under reduced pressure. The residue is partitioned between benzene and 5% aqueous sodium hydroxide and water and the aqueous layer is re-extracted with three portions of benzene. The combined benzene extracts are washed with water, dried by filtration through anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. Crystallization of the residual solid from a mixture of benzene and cyclohexane affords the white crystalline product, m.p. 156—160°C., in a yield of 18 g. (73%). The pure product melts at 157—158°C. after recrystallization from benzene and sublimation at 140°C. and 0.01 mm. Analysis Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.73; H, 7.71; N, 4.73.

EXAMPLE 13

Employing the procedure of Example 12, the products enumerated below are obtained using the products enumerated in Examples 10 and 11 in place of the dioxole used in Example 12.

trans 5-(3-diethylaminopropyl)-10,11-dihydro-5,10-epoxy-11-hydroxy-5H-dibenzo[a,d]cycloheptene

trans 10,11-dihydro-5,10-epoxy-11-hydroxy-5-[3-(1-pyrrolidyl)-propyl]-5H-dibenzo[a,d]cycloheptene

trans 10,11-dihydro-5,10-epoxy-11-hydroxy-5-[3-(1-piperidyl)-propyl]-5H-dibenzo[a,d]cycloheptene

trans 10,11-dihydro-5,10-epoxy-5-[3-(1-ethyl-4-piperazinyl)-propyl]-11-hydroxy-5H-dibenzo[a,d]cycloheptene

trans 10,11-dihydro-5,10-epoxy-11-hydroxy-5-[3-(4-morpholinyl)-propyl]-5H-dibenzo[a,d]cycloheptene

trans 10,11-dihydro-5,10-epoxy-5-[3-(N-ethyl-N-methylamino)-propyl]-11-hydroxy-5H-dibenzo[a,d]cycloheptene

trans 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hydroxy-3(7)-methylsulfonyl-5H-dibenzo[a,d]cycloheptene

trans 3(7)-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hydroxy-5H-dibenzo[a,d]cycloheptene

trans 10,11-dihydro-5-(3-dimethylaminopropyl)-3(7)-dimethylsulfamoyl-5,10-epoxy-11-hydroxy-5H-dibenzo[a,d]cycloheptene

EXAMPLE 14

cis 11-Acetoxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[a,d]cycloheptene

A solution of *cis* 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene (630 mg., 0.00204 mole) in 12 ml. of acetic anhydride is heated to refluxing for 4-1/2 hours. The dark yellow solution is evaporated to dryness under reduced pressure and the oily residue dissolved in 20 ml. of water containing 1 ml. of 6 N. hydrochloric acid. After one extraction with benzene, the aqueous solution 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, 600 mg. (84%).

The base may be converted to the hydrogen oxalate salt by treating a solution in isopropyl alcohol with a solution of oxalic acid (10% excess) in isopropyl alcohol. *cis* 11 - Acetoxy - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene hydrogen oxalate is obtained as a white crystalline solid, m.p. 171—173°C., dec. Repeated recrystallizations from isopropyl alcohol and from mixtures of absolute ethanol and absolute ether to give the product, m.p. 173—175°C., dec.

Analysis Calc'd for $C_{22}H_{25}NO_3 \cdot C_2H_2O_4$: C, 65.29; H, 6.16; N, 3.17.

Found: C, 65.27; H, 6.40; N, 3.06.

EXAMPLE 15

Following the procedure of Example 14, the products enumerated below are obtained employing the acylating agents designated below in place of acetic anhydride used in Example 14.

25	Acylating agent propionic anhydride	Product <i>cis</i> 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-propionyloxy-5H-dibenzo[a,d]cycloheptene	25
30	butyryl chloride/pyridine	<i>cis</i> 11-butyryloxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[a,d]cycloheptene	30
35	benzoyl chloride/pyridine	<i>cis</i> 11-benzoyloxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[a,d]cycloheptene	35
40	caproyl chloride/pyridine	<i>cis</i> 11-caproyloxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[a,d]cycloheptene	40

EXAMPLE 16

Following the procedure of Example 14, the products enumerated below are obtained employing, in place of *cis* 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene, the reactants designated below.

50	Reactant <i>cis</i> 5-(3-diethylaminopropyl)-10,11-dihydro-5,10-epoxy-11-hydroxy-5H-dibenzo[a,d]cycloheptene	Product <i>cis</i> 11-acetoxy-5-(3-diethylaminopropyl)-10,11-dihydro-5,10-epoxy-5H-dibenzo[a,d]cycloheptene	50
55	<i>cis</i> 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hydroxy-3(7)-methylsulfonyl-5H-dibenzo[a,d]cycloheptene	<i>cis</i> 11-acetoxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-3(7)-methylsulfonyl-5H-dibenzo[a,d]cycloheptene	55

Reactant	Product
5 <i>cis</i> 3(7)-chloro-10,11-dihydro-5-(3-dimethylamino-propyl)-5,10-epoxy-11-hydroxy-5H-dibenzo[a,d]-cycloheptene	5 <i>cis</i> 11-acetoxy-3(7)-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[a,d]-cycloheptene
10 <i>cis</i> 10,11-dihydro-5-(3-dimethylaminopropyl)-3(7)-dimethylsulfamoyl-5,10-epoxy-11-hydroxy-5H-dibenzo[a,d]cycloheptene	10 <i>cis</i> 11-acetoxy-10,11-dihydro-5-(3-dimethylaminopropyl)-3(7)-dimethylsulfamoyl-5,10-epoxy-5H-dibenzo[a,d]cycloheptene

EXAMPLE 17

15	<i>cis</i> 11-Acetoxy-5-[3-(N-carbethoxy-N-methylamino)-propyl]-10,11-dihydro-5,10-epoxy-5H-dibenzo[a,d]cycloheptene	15
20	A solution of <i>cis</i> 11 - acetoxy - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene (600 mg., 0.00172 mole) in 3 ml. of dry benzene is added dropwise to a stirred solution of 0.7 ml. of ethyl chloroformate in 2 ml. of dry benzene. A yellow gum separates, but dissolves upon warming the mixture. After stirring for 1 hour at reflux, the mixture is cooled, diluted with benzene, and washed with 2 N, hydrochloric acid, then with water. Evaporation of the benzene under reduced pressure leaves the product as an oily residue weighing, typically, 650 mg. (92.5%).	20

EXAMPLE 18

25	Following the procedure of Example 17, the products enumerated below are obtained using the products enumerated in Examples 15 and 16 in place of the dibenzocycloheptene compound used in Example 17.	25
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	<i>cis</i> 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 11 - propionyloxy - 5H - dibenzo[a,d]cycloheptene	
30	<i>cis</i> 11 - butyryloxy - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene	30
	<i>cis</i> 11 - benzoyloxy - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene	
	<i>cis</i> 11 - acetoxy - 5 - [3 - (N - carbethoxy - N - ethylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene	
35	<i>cis</i> 11 - acetoxy - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 3(7) - methylsulfonyl - 5H - dibenzo[a,d]cycloheptene	35
	<i>cis</i> 11 - acetoxy - 3(7) - chloro - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene.	
40	<i>cis</i> 11 - acetoxy - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 3(7) - dimethylsulfamoyl - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene	40
	<i>cis</i> 11 - caproyloxy - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene.	

EXAMPLE 19

45	Following the procedure of Example 17, the products enumerated below are obtained employing the haloformate designated below.	45
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Haloformate	Product
50 benzyl chloroformate	50 <i>cis</i> 11-acetoxy-5-[3-(N-carbobenzoyloxy-N-methylamino)-propyl]-10,11-dihydro-5,10-epoxy-5H-dibenzo[a,d]cycloheptene
phenyl chloroformate	<i>cis</i> 11-acetoxy-5-[3-(N-carbophenoxy-N-methylamino)-propyl]-10,11-dihydro-5,10-epoxy-5H-dibenzo[a,d]cycloheptene
55 propyl chloroformate	55 <i>cis</i> 11-acetoxy-5-[3-(N-carbopropoxy-N-methylamino)-propyl]-10,11-dihydro-5,10-epoxy-5H-dibenzo[a,d]cycloheptene.

EXAMPLE 20

cis 10,11-Dihydro-5,10-epoxy-11-hydroxy-5-(3-methylaminopropyl)-5H-dibenzo[a,d]cycloheptene

A solution of the crude urethane obtained in Example 17 (650 mg., 0.00159 mole) and potassium hydroxide (500 mg., 0.0089 mole) in 10 ml. of n-butyl alcohol is stirred and heated to refluxing in a nitrogen atmosphere for 7 hours. The solvent is evaporated under reduced pressure and the residue partitioned between benzene and water. After two re-extractions 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 benzene layer then is washed with water. Evaporation of the solvent under reduced pressure leaves the neutral material, *cis* 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene, as an oily residue weighing, typically, 300 mg. The citric acid extract is rendered alkaline with sodium hydroxide and the oily base extracted into benzene. The washed benzene extract is evaporated to dryness under reduced pressure. Crystallization of the residue from absolute ether gives the product as a white crystalline solid, m.p. 128—130°C., in a yield of 110 mg.

A solution of the neutral material and potassium hydroxide (250 mg., 0.0045 mole) in 4 ml. of n-butyl alcohol is stirred and heated to refluxing in a nitrogen atmosphere for 10 hours. The reaction mixture is worked up as described above and the basic material crystallized from absolute ether to obtain additional product, m.p. 126—128°C., in a yield of 70 mg. The combined products (180 mg., 35%) are purified by recrystallization from absolute ether and sublimation at reduced pressure gives an analytical sample which melts at 138—139°C.

Analysis Calc'd for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.17; N, 4.74.
Found: C, 77.07; H, 6.95; N, 4.91.

EXAMPLE 21

Following the procedure of Example 20, the products enumerated below are obtained employing the products enumerated in Examples 18 and 19 in place of the urethane used in Example 20.

cis 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - methylaminopropyl) - 5H - dibenzo[a,d]cycloheptene

cis 10,11 - dihydro - 5,10 - epoxy - 5 - (3 - ethylaminopropyl) - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene

cis 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - methylaminopropyl) - 3(7) - methylsulfonyl - 5H - dibenzo[a,d]cycloheptene

cis 3(7) - chloro - 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - methylaminopropyl) - 5H - dibenzo[a,d]cycloheptene

cis 10,11 - dihydro - 3(7) - dimethylsulfonyl - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - methylaminopropyl) - 5H - dibenzo[a,d]cycloheptene

EXAMPLE 22

trans 11-Acetoxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[a,d]cycloheptene

By replacing the *cis* 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene used in Example 14 with an equimolecular amount of the *trans* isomer and following substantially the same procedure described in Example 14, there is obtained *trans* 11 - acetoxy - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene. The yield of white crystalline base, m.p. 116.5—120°C., is 79%. An analytical sample melts at 125—126°C. after recrystallization from petroleum ether.

Analysis Calc'd for $C_{22}H_{25}NO_3$: C, 75.18; H, 7.17; N, 3.99.
Found: C, 74.93; H, 7.04; N, 3.94.

EXAMPLE 23

Following the procedure of Example 22, the products enumerated below are obtained employing the acylating agents enumerated in Example 15.

trans 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - propionyloxy - 5H - dibenzo[a,d]cycloheptene

trans 11 - butyryloxy - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene

trans 11 - benzoyloxy - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene
trans 11 - caprolyoxy - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene

EXAMPLE 24

Following the procedure of Example 22, the products enumerated below are obtained employing in place of *trans* 10,11 - dihydro - 5 - (3 - dimethylamino - propyl) - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene, the reactants designated below.

Reactant	Product
<i>trans</i> 5-(3-diethylamino-propyl)-10,11-dihydro-5,10-epoxy-11-hydroxy-5H-dibenzo[a,d]cycloheptene	<i>trans</i> 11-acetoxy-5-(3-diethylaminopropyl)-10,11-dihydro-5,10-epoxy-5H-dibenzo[a,d]cycloheptene
<i>trans</i> 10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hydroxy-3(7)-methylsulfonyl-5H-dibenzo[a,d]cycloheptene	<i>trans</i> 11-acetoxy-10,11-dihydro-5(3-dimethylaminopropyl)-5,10-epoxy-3(7)-methylsulfonyl-5H-dibenzo[a,d]cycloheptene
<i>trans</i> 3(7)-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hydroxy-5H-dibenzo[a,d]cycloheptene	<i>trans</i> 11-acetoxy-3(7)-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[a,d]cycloheptene
<i>trans</i> 10,11-dihydro-5-(3-dimethylaminopropyl)-3(7)-dimethylsulfamoyl-5,10-epoxy-11-hydroxy-5H-dibenzo[a,d]cycloheptene	<i>trans</i> 11-acetoxy-10,11-dihydro-5-(3-dimethylaminopropyl)-3(7)-dimethylsulfamoyl-5,10-epoxy-5H-dibenzo[a,d]cycloheptene

EXAMPLE 25

trans 11-Acetoxy-5-[3-(N-carbethoxy-N-methylamino)-propyl]-10,11-dihydro-5,10-epoxy-5H-dibenzo[a,d]cycloheptene
trans 11 - Acetoxy - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene, 5.5 g. (0.0157 mole), is added in small portions with stirring to 150 ml. of ethyl chloroformate cooled in an ice-bath. The mixture is stirred in the cold for 1-1/2 hours, then heated to refluxing for 16 hours. Excess ethyl chloroformate is distilled under reduced pressure and the oily residue treated with benzene and the mixture evaporated to dryness under reduced pressure. This treatment is repeated and the residue finally is partitioned between benzene and water. The benzene layer is washed with water, 0.5 M. citric acid, and water, dried by filtration through anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. Crystallization of the oily residue from ether-petroleum ether gives the product, m.p. 75—76°C., in a yield of 2.4 g. A second crop of 2.0 g., m.p. 72—73°C., is obtained from the mother liquor. A purified sample melts at 77—78°C. after recrystallization from a mixture of absolute ether and petroleum ether.
 Analysis Calc'd for $C_{24}H_{27}NO_6$: C, 70.40; H, 6.65.
 Found: C, 69.78; H, 6.80.

EXAMPLE 26

Following the procedure of Example 25, the products enumerated below are obtained employing the products enumerated in Examples 23 and 24 in place of the dibenzocycloheptene compound used in Example 25.

trans 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 11 - propionyloxy - 5H - dibenzo[a,d]cycloheptene
trans 11 - butyryloxy - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene
trans 11 - benzoyloxy - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene

	<i>trans</i> 11 - acetoxy - 5 - [3 - (N - carbethoxy - N - ethylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene	
	<i>trans</i> 11 - acetoxy - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 3(7) - methylsulfonyl - 5H - dibenzo[a,d]cycloheptene	
5	<i>trans</i> 11 - acetoxy - 3(7) - chloro - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene	5
	<i>trans</i> 11 - acetoxy - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 3(7) - dimethylsulfamoyl - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene	
10	<i>trans</i> 11 - caproyloxy - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene.	10

EXAMPLE 27

Following the procedure of Example 25, the products enumerated below are obtained employing the haloformate enumerated in Example 19.

Haloformate	Product	
15 benzyl chloroformate	<i>trans</i> 11-acetoxy-5-[3-(N-carbobenzoxy-N-methylamino)-propyl]-10,11-dihydro-5,10-epoxy-5H-dibenzo[a,d]cycloheptene	15
20 phenyl chloroformate	<i>trans</i> 11-acetoxy-5-[3-(N-carbophenoxy-N-methylamino)-propyl]-10,11-dihydro-5,10-epoxy-5H-dibenzo[a,d]cycloheptene	20
25 propyl chloroformate	<i>trans</i> 11-acetoxy-5-[3-(N-carbopropoxy-N-methylamino)-propyl]-10,11-dihydro-5,10-epoxy-5H-dibenzo[a,d]cycloheptene	25

EXAMPLE 28

trans 10,11-Dihydro-5,10-epoxy-11-hydroxy-5-(3-methylaminopropyl)-5H-dibenzo[a,d]cycloheptene

35	A solution of <i>trans</i> 11 - acetoxy - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene (4.1 g., 0.01 mole) and potassium hydroxide (20 g., 0.358 mole) in 100 ml. of <i>n</i> -butyl alcohol is stirred and heated to refluxing in a nitrogen atmosphere for 11 hours. The solvent is evaporated under reduced pressure and the residue partitioned between benzene and water. After two re-extractions of the aqueous phase, the combined benzene extracts are washed with water and then extracted with three 100 ml. portions of 0.5 M. citric acid. The citric acid extract is rendered alkaline with sodium hydroxide and the oily base extracted into benzene. The washed benzene extract is dried by filtration through anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Crystallization of the oily residue from a mixture of absolute ether and petroleum ether gives the product as a white crystalline solid, m.p. 128—129°C., in a yield of 1.5 g. (51%). An analytical sample melts at 129—130°C. after sublimation at 115°C. and 0.1 mm.	35
40		40
45		45

Analysis Calc'd for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.17; N, 4.74.

Found: C, 77.33; H, 7.20; N, 4.94.

EXAMPLE 29

50	Following the procedure of Example 28, the products enumerated below are obtained employing the products enumerated in Examples 26 and 27 in place of the urethane used in Example 28.	50
55	<i>trans</i> 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - methylaminopropyl) - 5H - dibenzo[a,d]cycloheptene	55
	<i>trans</i> 10,11 - dihydro - 5,10 - epoxy - 5 - (3 - ethylaminopropyl) - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene	
	<i>trans</i> 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - methylaminopropyl) - 3(7) - methylsulfonyl - 5H - dibenzo[a,d]cycloheptene	
60	<i>trans</i> 3(7) - chloro - 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - methylaminopropyl) - 5H - dibenzo[a,d]cycloheptene	60

trans 10,11 - dihydro - 3(7) - dimethylsulfamoyl - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - methylaminopropyl) - 5H - dibenzo[a,d]cycloheptene.

EXAMPLE 30

10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-keto-5H-dibenzo[a,d]cycloheptene

A solution of *trans* 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene (6.18 g., 0.02 mole) and 60 ml. of freshly distilled cyclohexanone in 600 ml. of dry toluene is heated to boiling and 250 ml. of toluene is distilled. Slow distillation is continued while a solution of aluminum isopropoxide (8.0 g., 0.039 mole) in 400 ml. of dry toluene is added dropwise over a 1 hour period and for an additional 30 minutes. The mixture is cooled in ice and hydrolysed by the addition of 100 ml. of a saturated aqueous solution of Rochelle salt. The aqueous layer is separated and re-extracted twice with benzene. After washing with water, the combined organic layers are extracted with 200 ml. of 0.5 M. citric acid. The citric acid extract is cooled in an ice-bath, rendered alkaline with sodium hydroxide and the oily base extracted into benzene. The washed and dried benzene extract is evaporated under reduced pressure to give the product as a crystalline residue, m.p. 67—69°C., in a yield of 6.05 g. (98.5%). An analytical sample melts at 76—78°C. after repeated recrystallizations from hexane.

Analysis Calc'd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56.
Found: C, 78.22; H, 6.99; N, 4.49.

EXAMPLE 31

Following the procedure of Example 30, the products enumerated below are obtained employing the products enumerated in Example 13 in place of the dibenzocycloheptene used in Example 30.

10,11 - dihydro - 5 - (3 - diethylaminopropyl) - 5,10 - epoxy - 11 - keto - 5H - dibenzo[a,d]cycloheptene
10,11 - dihydro - 5,10 - epoxy - 11 - keto - 5 - [3 - (1 - pyrrolidyl) - propyl] - 5H - dibenzo[a,d]cycloheptene
10,11 - dihydro - 5,10 - epoxy - 11 - keto - 5 - [3 - (1 - piperidyl) - propyl] - 5H - dibenzo[a,d]cycloheptene
10,11 - dihydro - 5,10 - epoxy - 5 - [3 - (1 - ethyl - 4 - piperazinyl) - propyl] - 11 - keto - 5H - dibenzo[a,d]cycloheptene
10,11 - dihydro - 5,10 - epoxy - 11 - keto - 5 - [3 - (4 - morpholinyl) - propyl] - 5H - dibenzo[a,d]cycloheptene
10,11 - dihydro - 5,10 - epoxy - 5 - [3 - (N - ethyl - N - methylamino) - propyl] - 11 - keto - 5H - dibenzo[a,d]cycloheptene
10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - keto - 3(7) - methylsulfonyl - 5H - dibenzo[a,d]cycloheptene
3(7) - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - keto - 5H - dibenzo[a,d]cycloheptene
10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 3(7) - dimethylsulfamoyl - 5,10 - epoxy - 11 - keto - 5H - dibenzo[a,d]cycloheptene.

EXAMPLE 32

Spiro[10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[a,d]cycloheptene]-11,2'-m-dithiane

A solution of 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - keto - 5H - dibenzo[a,d]cycloheptene (900 mg., 0.003 mole) and 1 ml. of trimethylene dithiol in 20 ml. of glacial acetic acid is stirred and treated with 2 ml. of redistilled boron trifluoride etherate. After stirring 1-1/2 hours at room temperature, the clear yellow solution is allowed to stand overnight. The solution then is poured into 300 ml. of ice-cold 5% aqueous sodium hydroxide. The precipitate is collected, washed with water, air-dried and dissolved in 150 ml. of absolute ether. After removing the insoluble material by filtration, the ether is distilled under reduced pressure. The white crystalline solid residue weighs 1.1 g. (92.5%), m.p. 122—126°C. The pure product melts at 130.5—132°C. after repeated crystallizations from mixtures of ethanol and water and from isopropyl alcohol.

Analysis Calc'd for $C_{29}H_{27}NOS_2$: C, 69.47; H, 6.85; N, 3.52.
Found: C, 69.19; H, 6.82; N, 3.40.

EXAMPLE 33

Following the procedure of Example 32, the products enumerated below are obtained employing the products enumerated in Example 31 in place of the 11-keto compound used in Example 32.

- 5 Spiro[10,11 - dihydro - 5 - (3 - diethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo- 5
[a,d]cycloheptene] - 11,2' - *m* - dithiane
Spiro[10,11 - dihydro - 5,10 - epoxy - 5 - (3 - (1 - pyrrolidyl) - propyl) - 5H -
dibenzo[a,d]cycloheptene] - 11,2' - *m* - dithiane
10 Spiro[10,11 - dihydro - 5,10 - epoxy - 5 - (3 - (1 - piperidyl) - propyl) - 5H - 10
dibenzo[a,d]cycloheptene] - 11,2' - *m* - dithiane
Spiro[10,11 - dihydro - 5,10 - epoxy - 5 - (3 - (1 - ethyl - 4 - piperazinyl) - propyl) -
5H - dibenzo[a,d]cycloheptene] - 11,2' - *m* - dithiane
Spiro[10,11 - dihydro - 5,10 - epoxy - 5 - (3 - (4 - morpholinyl) - propyl) - 5H -
dibenzo[a,d]cycloheptene] - 11,2' - *m* - dithiane
15 Spiro[10,11 - dihydro - 5,10 - epoxy - 5 - (3 - (N - ethyl - N - methylamino) - 15
propyl) - 5H - dibenzo[a,d]cycloheptene] - 11,2' - *m* - dithiane
Spiro[10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 3(7) -
methylsulfonyl - 5H - dibenzo[a,d]cycloheptene] - 11,2' - *m* - dithiane
20 Spiro[3(7) - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 20
5H - dibenzo[a,d]cycloheptene] - 11,2' - *m* - dithiane
Spiro[10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 3(7) - dimethylsulfamoyl -
5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene] - 11,2' - *m* - dithiane.

EXAMPLE 34

Following the procedure of Example 32, the products enumerated below are obtained employing the compounds enumerated in Example 31 and ethylene dithiol in place of the 11-keto compound and trimethylene dithiol used in Example 32.

- 25 Spiro[10,11 - dihydro - 5 - (3 - diethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo- 25
[a,d]cycloheptene] - 11,2' - 1',3' - dithiolane
Spiro[10,11 - dihydro - 5,10 - epoxy - 5 - (3 - (1 - pyrrolidyl) - propyl) - 5H -
dibenzo[a,d]cycloheptene] - 11,2' - 1',3' - dithiolane
30 Spiro[10,11 - dihydro - 5,10 - epoxy - 5 - (3 - (1 - piperidyl) - propyl) - 5H - di- 30
benzo[a,d]cycloheptene] - 11,2' - 1',3' - dithiolane
Spiro[10,11 - dihydro - 5,10 - epoxy - 5 - (3 - (1 - ethyl - 4 - piperazinyl) - propyl)-
5H - dibenzo[a,d]cycloheptene] - 11,2' - 1',3' - dithiolane
35 Spiro[10,11 - dihydro - 5,10 - epoxy - 5 - (3 - (4 - morpholinyl) - propyl) - 5H - 35
dibenzo[a,d]cycloheptene] - 11,2' - 1',3' - dithiolane
Spiro[10,11 - dihydro - 5,10 - epoxy - 5 - (3 - (N - ethyl - N - methylamino) -
propyl) - 5H - dibenzo[a,d]cycloheptene] - 11,2' - 1',3' - dithiolane
40 Spiro[10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 3(7) - 40
methylsulfonyl - 5H - dibenzo[a,d]cycloheptene] - 11,2' - 1',3' - dithiolane
Spiro[3(7) - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy-
5H - dibenzo[a,d]cycloheptene] - 11,2' - 1',3' - dithiolane
Spiro[10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 3(7) - dimethylsulfamoyl -
5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene] - 11,2' - 1',3' - dithiolane.

EXAMPLE 35

10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-
5H-dibenzo[a,d]cycloheptene

A solution of Spiro[10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 -
epoxy - 5H - dibenzo[a,d]cycloheptene] - 11,2' - *m* - dithiane (600 mg., 0.0015 mole)
50 in 75 ml. of absolute ethanol is stirred and heated to refluxing with 7 g. of Raney 50
nickel for 24 hours. The nickel is removed by filtration through a mat of diatomaceous
earth and washed with absolute ethanol. The alcoholic filtrate is evaporated under
reduced pressure, the residual oil dissolved in benzene and the solution again evaporated
under reduced pressure, leaving the product as a colorless oily residue weighing
55 200 mg. 55

The base may be converted to the hydrogen maleate salt by treating an ethanolic
solution with a solution of maleic acid (10% excess) in absolute ether. Further
dilution with absolute ether precipitates 10,11 - dihydro - 5 - (3 - dimethylamino-
propyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene hydrogen maleate as a white
60 crystalline solid, m.p. 135—138°C. An analytical sample melts at 141.5—143.5°C. 60
after repeated crystallizations from mixtures of isopropyl alcohol and absolute ether.

Analysis Calc'd for $C_{20}H_{23}NO \cdot C_4H_4O_4$: C, 70.41; H, 6.65; N, 3.42.
 Found: C, 70.61; H, 6.75; N, 3.45.

EXAMPLE 36

Following the procedure of Example 35, the products enumerated below are obtained employing the products enumerated in Examples 33 and 34 in place of the dithiane used in Example 35.

- 10,11 - dihydro - 5 - (3 - diethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]-cycloheptene
- 10,11 - dihydro - 5,10 - epoxy - 5 - [3 - (1 - pyrrolidyl) - propyl] - 5H - dibenzo[a,d]cycloheptene
- 10,11 - dihydro - 5,10 - epoxy - 5 - [3 - (1 - piperidyl) - propyl] - 5H - dibenzo[a,d]cycloheptene
- 10,11 - dihydro - 5,10 - epoxy - 5 - [3 - (1 - ethyl - 4 - piperaziny] - propyl] - 5H - dibenzo[a,d]cycloheptene
- 10,11 - dihydro - 5,10 - epoxy - 5 - [3 - (4 - morpholinyl) - propyl] - 5H - dibenzo[a,d]cycloheptene
- 10,11 - dihydro - 5,10 - epoxy - 5 - [3 - (N - ethyl - N - methylamino) - propyl] - 5H - dibenzo[a,d]cycloheptene
- 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 3(7) - methylsulfonyl - 5H - dibenzo[a,d]cycloheptene
- 3(7) - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene
- 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 3(7) - dimethylsulfamoyl - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene.

EXAMPLE 37

trans 10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hexanoyloxy-5H-dibenzo[a,d]cycloheptene

A solution of *trans* 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hydroxy - 5H - dibenzo[a,d]cycloheptene, 310 mg. (0.001 mole), in 2 ml. of hexanoic anhydride is heated on the steam-bath for 18 hours. The solution is stirred with 75 ml. of water for 4 hours, then cooled in ice and made strongly basic with aqueous sodium hydroxide. The oily base is extracted into benzene and isolated by evaporation of the washed and dried benzene extract under reduced pressure. The residual oil is dissolved in absolute ether and treated with a 10% excess of maleic acid in absolute ethanol. The crystalline hydrogen maleate salt, m.p. 108—110°C., is obtained in a yield of 350 mg. (67%). Recrystallizations from ethanol-ether and isopropyl alcohol-ether afford an analytical sample, m.p. 109—110°C.
 Analysis, Calcd. for $C_{26}H_{33}NO_5 \cdot C_4H_4O_4$: C, 68.81; H, 7.12; N, 2.68.
 Found: C, 68.61; H, 7.07; N, 2.62.

EXAMPLE 38

10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hydroxyimino-5H-dibenzo[a,d]cycloheptene

10,11 - Dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - keto - 5H - dibenzo[a,d]cycloheptene, 310 mg. (0.001 mole), together with 80 mg. (0.00115 mole) of hydroxylamine hydrochloride, 100 mg. (0.0012 mole) of sodium acetate, 1 ml. of water, and 9 ml. of methanol is heated to refluxing for 2 hours. Methanol is distilled under reduced pressure and the residue dissolved in water. The solution is rendered alkaline and the precipitate collected, washed with water, and dried *in vacuo*. The yield of product, m.p. 197—204°C., is 300 mg. (93%). A sample purified by repeated crystallizations from 95% ethanol melts at 206—210°C.
 Analysis, Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69.
 Found: C, 74.37; H, 7.12; N, 8.56.

EXAMPLE 39

11-Amino-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[a,d]cycloheptene

10,11 - Dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hydroxyimino - 5H - dibenzo[a,d]cycloheptene, 400 mg. (0.00124 mole), is dissolved in 18 ml. of hot absolute ethanol and the solution is concentrated by distillation of 12 ml. of ethanol. To the refluxing mixture, sodium spheres, 460 mg. (0.02 g., atom), are

added as rapidly as possible over a 4 minute period. After another 15 minutes at reflux, 2 ml. of absolute ethanol are added and refluxing is continued until dissolution of the sodium is complete. The cooled mixture is diluted with an equal volume of water and ethanol is evaporated under reduced pressure. The oily product that separates from the residue is extracted into benzene. After washing with water, the benzene extract is evaporated to dryness under reduced pressure, leaving the oily base as the residue in a yield of 275 mg. (72%).

The base may be converted to the dihydrogen maleate salt by treating an ethanolic solution with two equivalents of maleic acid dissolved in absolute ethanol. Dilution with absolute ether precipitates 11 - amino - 10,11 dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene dihydrogen maleate that melts at 163—167°C., dec., after recrystallization from a mixture of absolute ethanol and absolute ether. Further purification affords a sample melting at 169—172°C., dec.

Analysis, Calcd. for $C_{20}H_{24}N_2O \cdot 2C_4H_4O_4$: C, 62.21; H, 5.97; N, 5.18.
Found: C, 61.90; H, 6.33; N, 5.46.

EXAMPLE 40

10,11-Dihydro-11-dimethylamino-5-(3-dimethylaminopropyl)-
5,10-epoxy-5H-dibenzo[a,d]cycloheptene

A mixture of 11 - amino - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene, 308 mg. (0.001 mole), 37% formaldehyde, 180 mg. (0.0022 mole), and 98—100% formic acid, 250 mg. (0.005 mole), is heated on a steam-bath for 8 hours. The solution is cooled, diluted with 10 ml. of 6 N. hydrochloric acid and the excess formic acid and formaldehyde removed by distillation under reduced pressure. The 10,11 - dihydro - 11 - dimethylamino - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene is obtained when the residual aqueous acid solution is rendered alkaline.

EXAMPLE 41

11-Acetamido-10,11-dihydro-5-(3-dimethylaminopropyl)-
5,10-epoxy-5H-dibenzo[a,d]cycloheptene

11 - Amino - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene, 308 mg. (0.001 mole), is dissolved in 3 ml. of dry pyridine, 0.5 ml. of acetic anhydride added, and the solution heated to refluxing for 30 minutes. After cooling, the solution is poured into 50 ml. of water and the mixture extracted with benzene. Evaporation of the washed and dried benzene extract leaves the product as the residue.

EXAMPLE 42

Following the procedure of Example 41, the products enumerated below are obtained employing the anhydride designated below in place of the acetic anhydride used in Example 41.

	Product	
propionic anhydride	10,11-dihydro-5-(3-dimethylamino-propyl)-5,10-epoxy-11-propionamido-5H-dibenzo[a,d]cycloheptene	
butyric anhydride	11-butyramido-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[a,d]cycloheptene	

EXAMPLE 43

10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-
11-ethylamino-5H-dibenzo[a,d]cycloheptene

A solution of 11 - acetamido - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene, 350 mg. (0.001 mole), in 10 ml. of absolute ether is added dropwise to a stirred suspension of 85 mg. (0.0022 mole) of lithium aluminum hydride in 5 ml. of absolute ether at room temperature and in an atmosphere of nitrogen. After stirring at reflux for 6 hours, the mixture is cooled in ice and hydrolyzed by the successive dropwise addition of 0.1 ml. of water, 0.1 ml. of 20% aqueous sodium hydroxide and 0.3 ml. of water. The ether solution is filtered from the granular precipitate, washed with water, and dried over anhydrous sodium

sulfate. Evaporation of the ether leaves 10,11 - dihydro - 5 - (3 - dimethylamino-propyl) - 11 - ethylamino - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene as the residue.

EXAMPLE 44

Following the procedure of Example 43, the products enumerated below are obtained employing the dibenzocycloheptene designated below in place of the 11° acetamido - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene used in Example 43.

		Product	
10	10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-propionamido-5H-dibenzo[a,d]-cycloheptene	10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-propylamino-5H-dibenzo[a,d]-cycloheptene	10
15	11-butyramido-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[a,d]cycloheptene	11-butyramino-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[a,d]-cycloheptene	15

EXAMPLE 45

5-[3-(N-carbethoxy-N-methylamino)-propyl]-10,11-dihydro-5,10-epoxy-11-keto-5H-dibenzo[a,d]cycloheptene

A solution of 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - keto - 5H - dibenzo[a,d]cycloheptene, 620 mg. (0.002 mole), in 3 ml. of dry benzene is added dropwise to a stirred solution of 1.0 ml. of ethyl chloroformate in 3 ml. of dry benzene. After stirring for 1 hour at reflux, the mixture is cooled, diluted with benzene, and washed with 2 N. hydrochloric acid, then with water. Evaporation of the benzene under reduced pressure leaves the product as the residue.

EXAMPLE 46

5-[3-(N-carbethoxy-N-methylamino)-propyl]-10,11-dihydro-5,10-epoxy-11-hydroxyimino-5H-dibenzo[a,d]cycloheptene

5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 11 - keto - 5H - dibenzo[a,d]cycloheptene, 370 mg. (0.001 mole), together with 80 mg. (0.00115 mole) of hydroxylamine hydrochloride, 100 mg. (0.0012 mole) of sodium acetate, 1 ml. of water and 9 ml. of methanol, is heated to refluxing for 2 hours. Methanol is distilled under reduced pressure and the residue triturated with water. The product is obtained as the precipitate.

EXAMPLE 47

11-Amino-5-[3-(N-carbethoxy-N-methylamino)-propyl]-10,11-dihydro-5,10-epoxy-5H-dibenzo[a,d]cycloheptene

The oxime obtained in Example 46, 385 mg. (0.001 mole), is dissolved in 6 ml. of hot absolute ethanol. To the refluxing mixture, sodium spheres, 460 mg. (0.02 g., atom), are added as rapidly as possible. After another 15 minutes at reflux, 2 ml. of absolute ethanol are added and refluxing is continued until dissolution of the sodium is complete. The cooled mixture is diluted with an equal volume of water and ethanol is evaporated under reduced pressure. The residual mixture is extracted with benzene and the product obtained by evaporation of the washed and dried benzene extract.

EXAMPLE 48

5-[3-(N-carbethoxy-N-methylamino)-propyl]-10,11-dihydro-11-dimethylamino-5,10-epoxy-5H-dibenzo[a,d]cycloheptene

11 - Amino - 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene, 365 mg. (0.001 mole), 37% formaldehyde, 180 mg. (0.0022 mole), and 98—100% formic acid, 250 mg. (0.005 mole), are heated on a steam-bath for 8 hours. After cooling, the solution is diluted with 100 ml. of 6 N. hydrochloric acid and the excess formic acid and formaldehyde removed by distillation under reduced pressure. The product is obtained when the residual aqueous acid solution is rendered alkaline.

EXAMPLE 49

10,11-Dihydro-11-dimethylamino-5,10-epoxy-5-(3-methylaminopropyl)-5H-dibenzo[a,d]cycloheptene

A solution of 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 11 - dimethylamino - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene, 395 mg. (0.001 mole), and potassium hydroxide, 300 mg. (0.00535 mole), in 6 ml. of n-butyl alcohol is stirred and heated to refluxing in a nitrogen atmosphere for 8 hours. The solvent is evaporated under reduced pressure and the residue partitioned between benzene and water. Evaporation of the washed and dried benzene extract leaves the product as the residue.

EXAMPLE 50

10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hydroxy-11-methyl-5H-dibenzo[a,d]cycloheptene

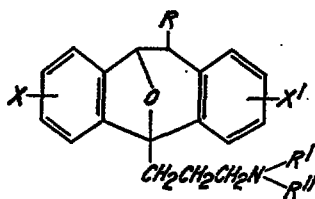
Magnesium turnings, 145 mg. (0.06 g., atom), a crystal of iodine, and 25 ml. of tetrahydrofuran are placed in a 50 ml. reaction flask fitted with a stirrer, reflux condenser and gas inlet tube. The apparatus is flushed with dry nitrogen and protected from atmospheric moisture by means of a drying tube. The reaction is initiated with a drop of methyl iodide and then methyl chloride is introduced below the surface of the stirred mixture at room temperature. Passage of the gas is continued until all of the magnesium dissolves. The solution of the Grignard reagent then is added dropwise to a stirred solution of 900 mg. (0.0029 mole) of 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - keto - 5H - dibenzo[a,d]cycloheptene in 25 ml. of tetrahydrofuran maintained in a nitrogen atmosphere and cooled in an ice-bath. The mixture is stirred at room temperature for 45 minutes and the bulk of the tetrahydrofuran is evaporated below 50°C. under reduced pressure. The residue is dissolved in benzene and hydrolyzed by the dropwise addition of 10 ml. of water. The benzene layer is separated by decantation and the gelatinous precipitate washed with several portions of benzene. After washing with water, the combined benzene solutions are extracted with three 25 ml. portions of 0.5 M. citric acid. The acid extract is rendered alkaline and the oily base extracted into benzene. The washed and dried benzene extract is evaporated under reduced pressure, leaving the product as an oily residue that solidifies on trituration with absolute ether. The yield of product melting at 108—110°C. is 700 mg. (75%). The base may be converted to the hydrogen maleate salt by treating an ethanolic solution with a 10% excess of maleic acid dissolved in absolute ethanol. Dilution with absolute ether precipitates 10,11 - dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hydroxy-11-methyl-5H-dibenzo[a,d]cycloheptene hydrogen maleate, m.p. 182—184°C. The melting point is unchanged by further recrystallization.

Analysis, Calcd. for $C_{21}H_{25}NO_2 \cdot C_4H_4O_4$: C, 68.32; H, 6.65; N, 3.19.

Found: C, 67.89; H, 6.62; N, 3.30.

WHAT WE CLAIM IS:—

1. A compound of the formula:



in which R is a hydrogen atom, a hydroxy, oxo, hydroxy imino, amino, C_{1-6} alkylamino, or di(C_{1-6} alkyl)amino radical, or R represents a hydroxy and a C_{1-6} alkyl radical attached to the same carbon atom; $NR'R''$ is a C_{1-6} alkylamino, or di(C_{1-6} alkyl)amino radical, or a saturated heterocyclic amino radical containing five or six atoms in the ring and in which any hetero atoms apart from the N shown are nitrogen (either unsubstituted or C_{1-4} alkylated) or oxygen; and each of X and X' is a hydrogen or halogen atom or a C_{1-6} alkyl, C_{2-6} alkenyl, trifluoromethyl, hydroxyl, C_{1-4} alkoxy, mercapto, C_{1-4} alkylthio, C_{1-4} alkylsulfonyl, sulfamoyl, C_{1-4} alkylsulfamoyl or di(C_{1-4} alkyl)sulfamoyl radical, more than one substituent being optionally present on each benzene ring.

EXAMPLE 49

10,11-Dihydro-11-dimethylamino-5,10-epoxy-5-(3-methylaminopropyl)-5H-dibenzo[a,d]cycloheptene

A solution of 5 - [3 - (N - carbethoxy - N - methylamino) - propyl] - 10,11 - dihydro - 11 - dimethylamino - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene, 395 mg. (0.001 mole), and potassium hydroxide, 300 mg. (0.00535 mole), in 6 ml. of n-butyl alcohol is stirred and heated to refluxing in a nitrogen atmosphere for 8 hours. The solvent is evaporated under reduced pressure and the residue partitioned between benzene and water. Evaporation of the washed and dried benzene extract leaves the product as the residue.

EXAMPLE 50

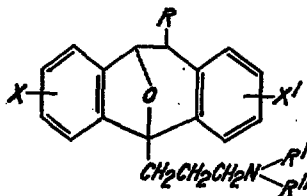
10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-hydroxy-11-methyl-5H-dibenzo[a,d]cycloheptene

Magnesium turnings, 145 mg. (0.06 g., atom), a crystal of iodine, and 25 ml. of tetrahydrofuran are placed in a 50 ml. reaction flask fitted with a stirrer, reflux condenser and gas inlet tube. The apparatus is flushed with dry nitrogen and protected from atmospheric moisture by means of a drying tube. The reaction is initiated with a drop of methyl iodide and then methyl chloride is introduced below the surface of the stirred mixture at room temperature. Passage of the gas is continued until all of the magnesium dissolves. The solution of the Grignard reagent then is added dropwise to a stirred solution of 900 mg. (0.0029 mole) of 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - keto - 5H - dibenzo[a,d]cycloheptene in 25 ml. of tetrahydrofuran maintained in a nitrogen atmosphere and cooled in an ice-bath. The mixture is stirred at room temperature for 45 minutes and the bulk of the tetrahydrofuran is evaporated below 50°C. under reduced pressure. The residue is dissolved in benzene and hydrolyzed by the dropwise addition of 10 ml. of water. The benzene layer is separated by decantation and the gelatinous precipitate washed with several portions of benzene. After washing with water, the combined benzene solutions are extracted with three 25 ml. portions of 0.5 M. citric acid. The acid extract is rendered alkaline and the oily base extracted into benzene. The washed and dried benzene extract is evaporated under reduced pressure, leaving the product as an oily residue that solidifies on trituration with absolute ether. The yield of product melting at 108—110°C. is 700 mg. (75%). The base may be converted to the hydrogen maleate salt by treating an ethanolic solution with a 10% excess of maleic acid dissolved in absolute ethanol. Dilution with absolute ether precipitates 10,11 - dihydro-5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hydroxy - 11 - methyl - 5H - dibenzo[a,d]cycloheptene hydrogen maleate, m.p. 182—184°C. The melting point is unchanged by further recrystallization.

Analysis, Calcd. for $C_{21}H_{28}NO_2 \cdot C_4H_4O_4$: C, 68.32; H, 6.65; N, 3.19. Found: C, 67.89; H, 6.62; N, 3.30.

WHAT WE CLAIM IS:—

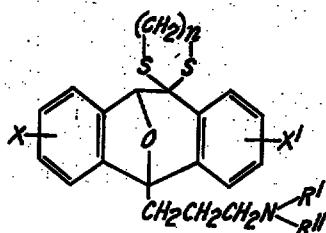
I. A compound of the formula:



in which R is a hydrogen atom, a hydroxy, oxo, hydroxy imino, amino, C_{1-6} alkylamino, or di(C_{1-6} alkyl)amino radical, or R represents a hydroxy and a C_{1-6} alkyl radical attached to the same carbon atom; $NR'R''$ is a C_{1-6} alkylamino, or di(C_{1-6} alkyl)amino radical, or a saturated heterocyclic amino radical containing five or six atoms in the ring and in which any hetero atoms apart from the N shown are nitrogen (either unsubstituted or C_{1-4} alkylated) or oxygen; and each of X and X' is a hydrogen or halogen atom or a C_{1-6} alkyl, C_{2-6} alkenyl, trifluoromethyl, hydroxyl, C_{1-4} alkoxy, mercapto, C_{1-4} alkylthio, C_{1-4} alkylsulfonyl, sulfamoyl, C_{1-4} alkylsulfamoyl or di(C_{1-4} alkyl)sulfamoyl radical, more than one substituent being optionally present on each benzene ring.

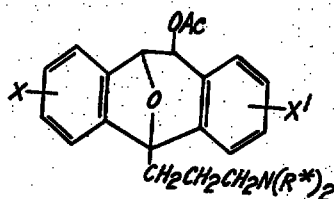


2. Non-toxic acid-addition salts of the compounds claimed in claim 1.
3. A compound of the formula:



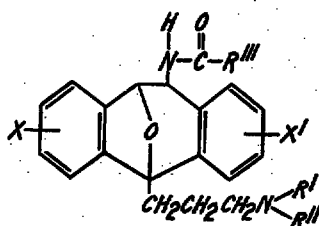
in which $NR'R''$, X and Y are as defined in claim 1 and n is 2 or 3.

4. A compound of the formula:



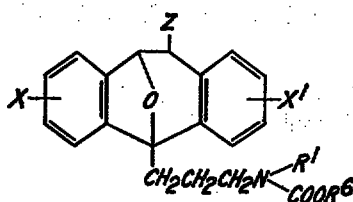
in which R^* is a C_{1-6} alkyl radical, Ac is an acyl radical, and X and X' are as defined in claim 1.

5. A compound of the formula:



in which each of R' and R'' is a C_{1-6} alkyl radical, R''' is a C_{1-6} alkyl radical and X and X' are as defined in claim 1.

6. A compound of the formula:



in which R' is a C_{1-6} alkyl radical, R^6 is an alkyl, aralkyl, or aryl radical, Z is a hydrogen atom or an amino, dialkylamino, oxo, acyloxy, C_{2-6} alkanoylamino, or hydroxyimino radical, and X and X' are as defined in claim 1.

7. 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hexanoyloxy - 5H - dibenzo[a,d]cycloheptene.

8. 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - hydroxyimino - 5H - dibenzo[a,d]cycloheptene.

9. 11 - amino - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene.

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

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

12. 10,11 - dihydro - 5,10 - epoxy - 11 - hydroxy - 5 - (3 - methylaminopropyl) - 5H - dibenzo[a,d]cycloheptene.



13. 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene.

14. 11 - Acetoxy - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene.

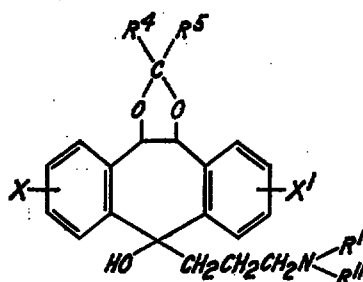
15. 11 - Acetoxy - 5 - [3 - (N - carbethoxy - N - methylamino)propyl] - 10,11 - dihydro - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene.

16. 10,11 - Dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 11 - keto - 5H - dibenzo[a,d]cycloheptene.

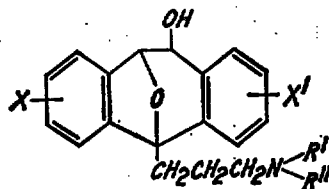
17. Spiro{10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene} - 11,2' - m - dithiane.

18. Each and every 10,11 - dihydro - 5 - [3 - (amino or substituted amino)propyl] - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene compound hereinbefore individually specified with the exception of those claimed in claims 7-17.

19. The process that comprises hydrolysing a compound of the formula:

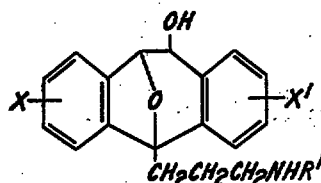


in which NR'R'', X and X' are as defined in claim 1 except that NR'R'' is not C₁₋₆ alkylamino, and each of R⁴ and R⁵ is a hydrogen atom or an alkyl, aryl or aralkyl radical in an inert solvent in the presence of an acidic catalyst to produce a compound of the formula:

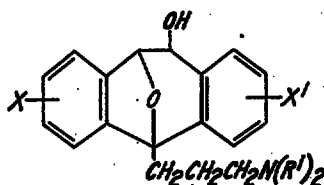


20. A process as claimed in claim 19, including the step of preparing the starting material by a process as claimed in the specification of our copending application No. 1280/67, Serial No. 1074086.

21. A process for the preparation of a compound of the formula



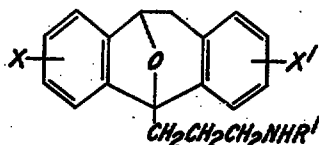
where R' is a C₁₋₆ alkyl radical and X and X' are as defined in claim 1 which comprises acylating a compound of the formula:



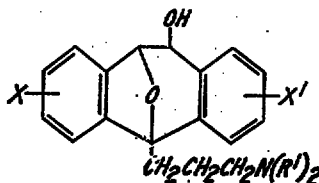
to form the corresponding 11-acyloxy derivative dealkylating the acyloxy derivative, by reaction with a haloformate ester followed by hydrolysis and removing the 11-o-acyl group to produce the desired product.



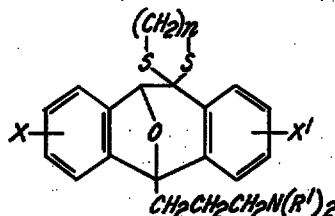
22. A process for the preparation of compounds of the formula:



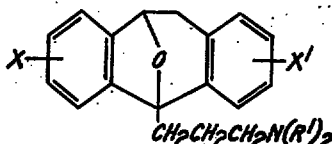
wherein R' is a C₁₋₆ alkyl radical and X and X' are as defined in claim 1 which comprises converting a compound of the formula:



by the Oppenauer selective oxidation reaction to the corresponding 11-keto derivative, treating the latter with a dithiol to form a thioketal of the formula:

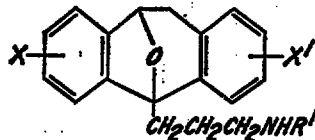


n being 2 or 3, desulfurizing the thioketal to form a compound of the formula:

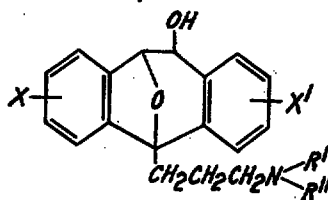


and dealkylating the latter compound by reaction with a haloformate ester followed by hydrolysis to produce the desired product.

23. A process for the preparation of compounds of formula:



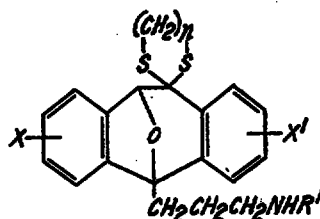
where R' is a C₁₋₆ alkyl radical and X and X' are as defined in claim 1 which comprises acylating a compound of the formula:



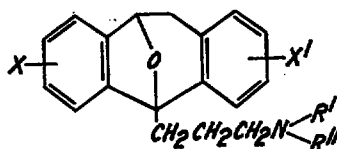
where X and X' are as defined in claim 1, and NR'R'' is di(C₁₋₆ alkyl)amino, to



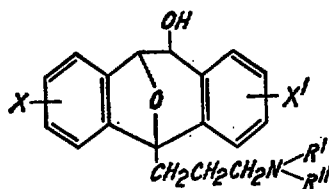
- 5 protect the 11-hydroxy group and form the corresponding 11-acyloxy derivative, de-alkylating the acyloxy derivative by reaction with a haloformate ester followed by hydrolysis to form the corresponding 10,11 - dihydro - 5,10 - epoxy - 5 - (3 - alkyl-aminopropyl) derivative, removing the 11-acyloxy group to regenerate the 11-hydroxy derivative, converting the latter by the Oppenauer selective oxidation reaction to the corresponding 11-keto derivative, and treating the 11-keto derivative with a dithiol to form a thioketal of the formula:



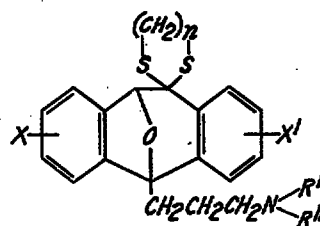
- 10 *n* being 2 or 3, and desulfurizing the thioketal to produce the desired product.
24. A process for the preparation of compounds of the formula:



where X and X', R' and R'' are as defined in claim 1, except that NR'R'' is not C₁₋₈ alkylamino, which comprises converting a compound of the formula:



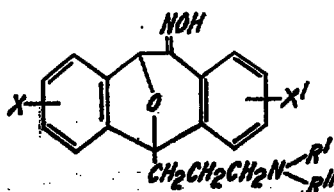
- 15 by the Oppenauer selective oxidation reaction to the corresponding 11-keto derivative, then treating the latter with a dithiol to form a thioketal of the formula:



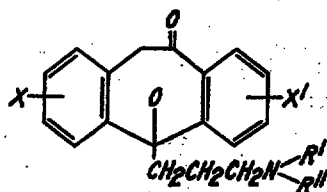
- 20 wherein R', R'', X and X' are as defined and *n* is 2 or 3, and then desulfurizing said thioketal to produce the desired product.

25. A process as claimed in any one of claims 21-24, including the step of preparing the starting material by a process as claimed in claim 19 or 20.

26. A process for the preparation of compounds of the formula:

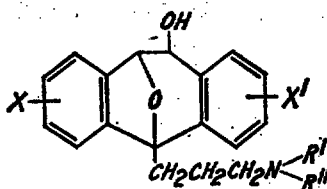


where X, X' and NR'R'' as defined in claim 1 that comprises treating a compound of the formula:



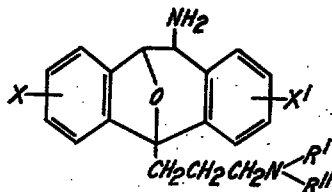
- 5 with an acid-addition salt of hydroxylamine in the presence of an inert solvent to produce the desired product. 5

27. A process as claimed in claim 26, including the step of preparing the starting material by the Oppenauer selective oxidation of the corresponding 11-hydroxy compound of the formula:

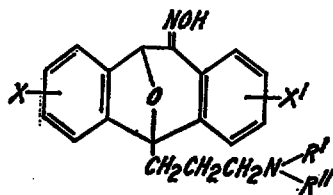


- 10 28. A process as claimed in claim 27, including the step of preparing the 11-hydroxy compound by a process as claimed in claim 19, 20 or 21. 10

29. A process for the preparation of compounds of the formula:



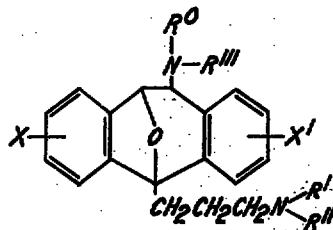
- 15 where X, X' and NR'R'' are as defined in claim 1 that comprises reducing a compound of the formula 15



to produce the desired product.

- 20 30. A process as claimed in claim 29, including the step of preparing the starting material by a process as claimed in claim 26, 27 or 28. 20

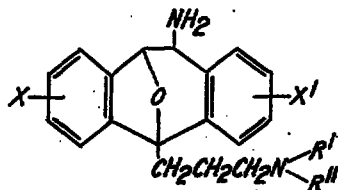
31. A process for the preparation of compounds of the formula:



where X, X' and NR'R'' are as defined in claim 1, except that NR'R'' is not C₁₋₄.



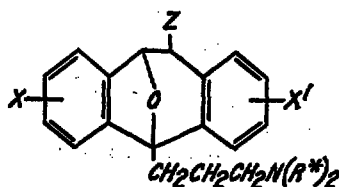
alkylamino, R^0 is a hydrogen atom or a C_{1-6} alkyl radical; and R''' is a C_{1-6} alkyl radical; which comprises alkylating a compound of the formula:



to produce the desired product.

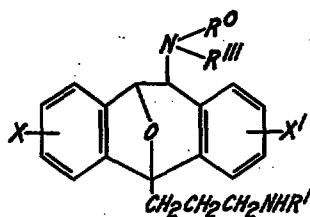
- 5 32. A process as claimed in claim 31, including the step of preparing the starting material by a process as claimed in claim 29 or 30. 5

33. A process for preparing a compound as claimed in claim 6, that comprises reacting a compound of formula:

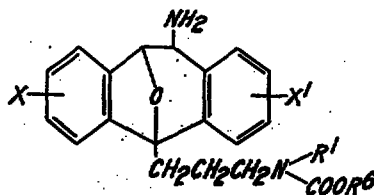


- 10 where X and X' are as defined in claim 1, Z is as defined in claim 6 and each R^* is a C_{1-6} alkyl radical, with a haloformate of formula $Hal.COOR^6$, where Hal is a halogen atom and R^6 is an alkyl, aryl or aralkyl radical, to produce the desired product. 10

34. A process for the preparation of compounds of the formula:



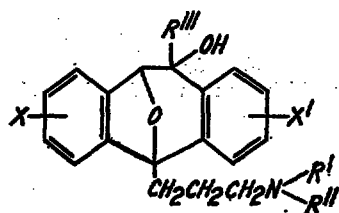
- 15 where R' is a C_{1-6} alkyl radical; R^0 is a hydrogen atom or a C_{1-6} alkyl radical; R''' is a C_{1-6} alkyl radical; and X and X' are as defined in claim 1, which comprises alkylating a compound of the formula: 15



- 20 where R^6 is an alkyl, aralkyl or aryl radical, and hydrolysing the resulting compound to produce the desired product. 20

35. A process as claimed in claim 34, including the step of preparing the starting material by a process as claimed in claim 33, in which Z in the formula represents amino.

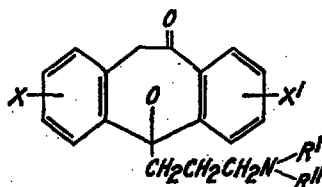
36. A process for the preparation of compounds of the formula



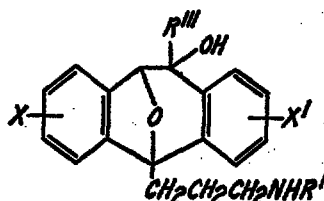
- 25 25



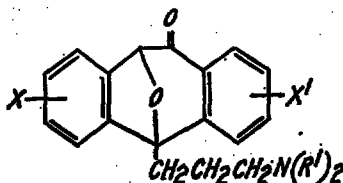
where X, X' and NR'R'' are as defined in claim 1; and R''' is a C₁₋₆ alkyl radical, that comprises treating a compound of the formula:



- 5 with a Grignard reagent of the formula HalMgR''' where Hal represents a halogen atom, and hydrolysing the resulting Grignard adduct to produce the desired product. 5
37. A process for the preparation of compounds of the formula:



where each of R' and R''' is a C₁₋₆ alkyl radical and X and X' are as defined in claim 1 that comprises treating a compound of the formula:



10

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with a Grignard reagent of the formula HalMgR''' where Hal represents a halogen atom, hydrolysing the resulting Grignard adduct and then dealkylating the latter by reaction with a haloformate ester followed by hydrolysis to produce the desired product.

15

15

38. A process for preparing a compound as claimed in any one of claims 1-18, substantially as set forth in the descriptive part of the specification.

39. A process for preparing a 10,11 - dihydro - 5 - [3 - (amino or substituted amino)propyl] - 5,10 - epoxy - 5H - dibenzo[a,d]cycloheptene compound substantially as hereinbefore described in any one of the foregoing Examples 12-50.

20

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40. A compound as claimed in claim 1 or 2, when prepared by a process as claimed in any appropriate preceding process claim or its obvious chemical equivalent.

41. A compound as claimed in any one of claims 3-6, when prepared by a process as claimed in any appropriate preceding process claim or its obvious chemical equivalent.

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42. A pharmaceutical composition comprising a compound as claimed in any one of claims 1-5, 7-13 and 40, together with an inert diluent or carrier.

43. A composition as claimed in claim 42, in the form of a tablet, powder, or sustained-release pellet or an orally or parenterally administrable aqueous solution or suspension.

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