

PATENT SPECIFICATION

(11) 1 274 261

1274261

NO DRAWINGS

- (21) Application No. 22175/69 (22) Filed 1 May 1969
 (31) Convention Application No. 6612 (32) Filed 3 May 1968 in
 (33) Switzerland (CH)
 (45) Complete Specification published 17 May 1972
 (51) International Classification C07C 87/28, 97/10; A61K 27/00
 (52) Index at acceptance

C2C 171—178—185 200 226 227 22X 22Y 29X 29Y 304
 30Y 313 31Y 322 323 32Y 334 338 340 34Y 351
 355 3A13A3A3 3A13A3B2 3A13A3H1 43X 440 442
 445 456 45Y 561 577 620 627 650 665 70Y 776
 779 790 79Y HG KA LL LZ NN



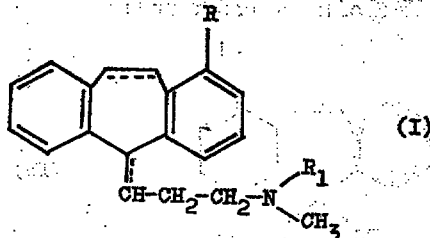
(54) DIBENZOCYCLOHEPTENE DERIVATIVES AND THE MANUFACTURE THEREOF

(71) We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, 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:—

The present invention relates to dibenzocycloheptene derivatives and the manufacture thereof.

5H-Dibenzo[a,d]cycloheptenes and 10,11-dihydro-5H-dibenzo[a,d]cycloheptenes having a basic side-chain in the 5-position are already known as psychopharmaco-ns; for example, 10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene and 10,11-dihydro-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene.

It has now been surprisingly found in accordance with the present invention that dibenzocycloheptene compounds of the general formula



in which R₁ represents a hydrogen atom or a methyl group, R represents a methyl or acetyl group and the dotted bonds can be hydrogenated, as well as N-oxides of such compounds in which R₁ represents a methyl group, geometric and optical isomers and acid addition salts of said compounds and N-oxides, which differ from the known representatives of the group of substances in question by the presence of a methyl or acetyl group in the 1-position, are distinguished by a considerably increased antidepressant action and reduced toxicity. The only slight anticholinergic action is to be mentioned as being particularly advantageous. In addition, the dibenzocycloheptene compounds of formula I are distinguished by various actions on the nervous system. Thus, adrenolytic, antihistamine-like and local anaesthetic actions have been found.

Examples of dibenzocycloheptene compounds of formula I and their corresponding N-oxides are:

- 1-(methyl or acetyl)-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene,
- 1-(methyl or acetyl)-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene,
- 1-(methyl or acetyl)-10,11-dihydro-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene,

1 - (methyl) - 10,11 - dihydro - 5 - (3 - methylaminopropyl) - 5H - dibenzo[*a,d*]cycloheptene,

1-(methyl or acetyl)-5-(3-dimethylaminopropylidene)-5H - dibenzo[*a,d*]cycloheptene,

1-(methyl or acetyl)-5-(3-dimethylaminopropyl)-5H-dibenzo[*a,d*]cycloheptene,

1-(acetyl)-5-(3-methylaminopropylidene)-5H-dibenzo[*a,d*]cycloheptene,

1-(methyl or acetyl)-5-(3-methylaminopropyl)-5H-dibenzo[*a,d*]cycloheptene,

1-(methyl or acetyl)-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[*a,d*]cycloheptene-N-oxide,

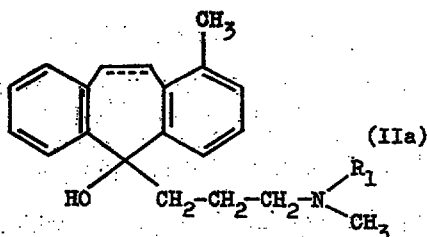
1-(methyl or acetyl)-5-(3-dimethylaminopropylidene)-5H-dibenzo[*a,d*]cycloheptene-N-oxide and

1-(methyl or acetyl)-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[*a,d*]cycloheptene-N-oxide.

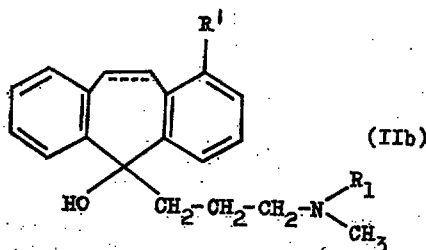
Particularly interesting are 1-methyl-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[*a,d*]cycloheptene, and 1-methyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[*a,d*]cycloheptene-N-oxide.

Thus, the dibenzocycloheptene derivatives provided by the present invention are dibenzocycloheptene compounds of formula I, as well as N-oxides of such compounds in which R_1 represents a methyl group and geometric and optical isomers and acid addition salts of said compounds.

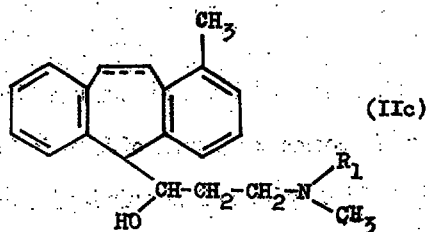
According to the process provided by the invention, the dibenzocycloheptene derivatives aforesaid are manufactured by either (a) reducing a carbinol of the general formula



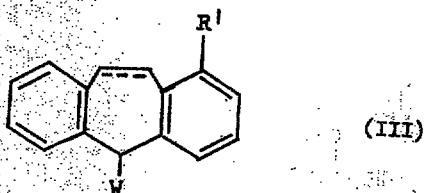
in which R_1 and the dotted bond have the significance given earlier, or (b) dehydrating a carbinol of the general formula



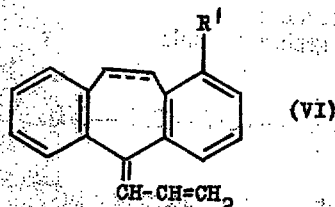
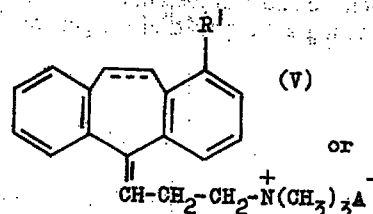
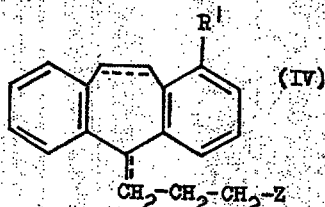
wherein R_1 and the dotted bond have the significance given earlier and R' represents a methyl or ketalised acetyl (as hereinafter defined) group, a carbinol of the general formula



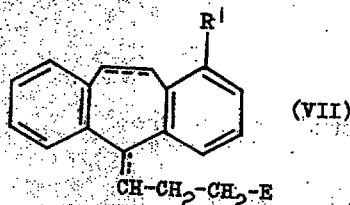
in which R_1 and the dotted bond have the significance given earlier, or an N-oxide of a carbinol of formula IIb or IIc in which R_1 represents a methyl group, or (c) reacting a halide of the general formula



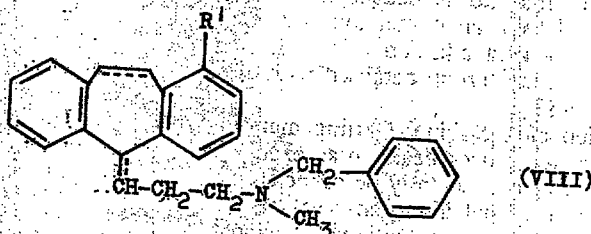
in which R' and the dotted bond have the significance given earlier and W represents a halogen atom,
 with a 3-dimethylaminopropyl magnesium halide,
 or (d) treating a compound of the general formula



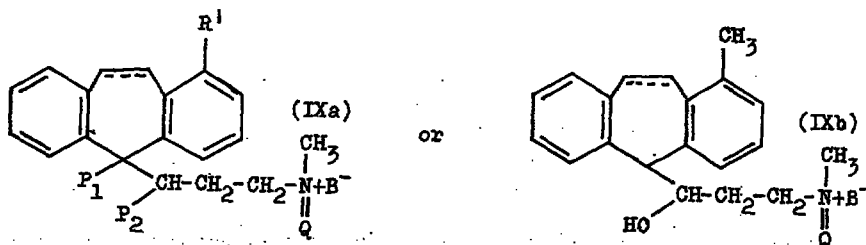
in which R' and the dotted bonds have the significance given earlier, Z represents a halogen atom or a substituted-sulfonyloxy residue and A represents the anion
 with methylamine, dimethylamine or dimethylhydroxylamine,
 or (e) methylating a compound of the general formula



in which R' and the dotted bonds have the significance given earlier and E represents an amino group or an N-hydroxy-N-methylamino group,
 or (f) debenzylating a compound of the general formula

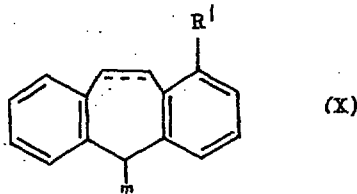


in which R' and the dotted bonds have the significance given earlier,
 or (g) heating a compound of the general formula



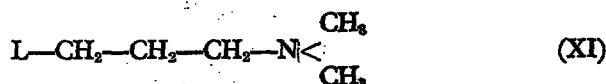
in which R' and the dotted bonds have the significance given earlier, P₁ represents a hydrogen atom or a hydroxyl group, and P₂ represents a hydrogen atom or P₁ and P₂ together represent an additional bond, Q represents the residue of an aldehyde and B represents the anion of an acid,

or (h) reacting a compound of the general formula



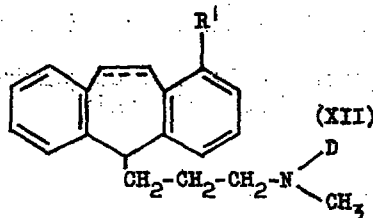
in which R' and the dotted bond have the significance given earlier and T represents an alkali metal atom,

with a compound of the general formula



in which L represents a halogen atom or a substituted sulfonyloxy group,

or (i) hydrolytically cleaving a compound of the general formula



in which R' and the dotted bond have the significance given earlier and D represents an acyl group or an esterified carboxyl group,

whereupon, in any desired sequence and if desired, a resulting compound in which R₁ represents a hydrogen atom is methylated, if desired, a compound in which R₁ represents a methyl group is oxidised or converted into a compound in which R₁ represents a hydrogen atom by demethylation, if desired, an unsaturated product obtained is hydrogenated, if desired, a 10,11-dihydro compound obtained is dehydrogenated, if necessary, a ketal obtained is deketalised, if desired, the geometric and/or optical isomers are isolated from an isomer mixture obtained and, if desired, a base obtained is converted into an acid addition salt. (The term "ketalised acetyl" group is used herein to mean an acetyl group ketalised with an alkanol or alkylene glycol containing up to 7 carbon atoms.)

The reduction of a carbinol starting material of formula IIa in accordance with embodiment (a) of the process leads to an exocyclically saturated compound of formula I. The reduction may conveniently be carried out with catalytically activated hydrogen (e.g. in the presence of palladium-charcoal or platinum oxide). The reduction can be effected in a lower alkanol (e.g. methanol, ethanol or isopropanol) and at a temperature between room temperature and ca 100°C. The reduction can be carried out under pressure, if desired. A carbinol of formula IIa can also be reduced by treatment with zinc in glacial acetic or, preferably, with hydroiodic acid in the presence of red phosphorus. When this reduction technique is employed, it is preferable to work in the presence of a solvent such as acetic acid or acetic acid anhydride and at a temperature

between room temperature and the boiling point of the reduction mixture. By the reduction of a carbinol of formula IIa, compounds of formula I which are saturated in the 10,11-position are chiefly obtained.

The dehydration of a carbinol of formula IIb or IIc or an N-oxide of a carbinol of formula IIb or IIc in which R_1 represents a methyl group in accordance with embodiment (b) of the process leads to an exocyclically unsaturated compound of formula I or an N-oxide thereof depending on whether a carbinol or N-oxide is used. This dehydration is conveniently carried out using a mineral acid such as hydrochloric acid or hydrobromic acid, in which case the dehydration can be carried out in an anhydrous or aqueous medium. The dehydration is preferably carried out in ethanolic hydrochloric acid at a temperature between room temperature and the boiling point of the dehydration mixture. However, the dehydration can also be carried out by heating (for example, at 50°C. up to the reflux temperature, preferably at the reflux temperature), with a high-boiling anhydrous solvent such as dimethyl sulfoxide. Other usual dehydrating agents can also be employed (e.g. acetic acid anhydride or sulfuric acid). The temperature at which this last-mentioned dehydration is carried out conveniently lies at between room temperature and the boiling point of the dehydration mixture.

When an acidic agent is used to bring about the dehydration, a ketalised acetyl group which may be present is deketalised. On the other hand, by employing, for example, dimethyl sulfoxide, the ketal protecting group is retained. This is subsequently split off in the manner described hereinafter.

The carbinol starting materials of formulae IIa, IIb and IIc hereinbefore and the N-oxides of those carbinols in which R_1 represents a methyl group are claimed *per se* in the specification of our copending Application for Letters Patent No. 28705/71 (now Serial No. 1,274,262) and can be prepared as described therein. The preferred starting materials for embodiment (b) of the process are carbinols of formula IIa and N-oxide of such carbinols in which R_1 represents a methyl group.

According to embodiment (c) of the process in accordance with the invention, a halide of formula III is reacted with a 3-dimethylaminopropyl magnesium halide. Exocyclically saturated compounds of formula I are obtained by this reaction. This embodiment is particularly suitable for the manufacture of those exocyclically saturated compounds of formula I which simultaneously carry a double bond in the 10,11-position. According to a preferred aspect, a halide of formula III in which W represents a chlorine atom, either in solid, finely-powdered form or in an inert organic solvent (for example, absolute ether, benzene or tetrahydrofuran) is introduced into a suspension of 3-dimethylaminopropyl magnesium chloride in one of the inert solvents mentioned earlier. The reaction is conveniently carried out at a temperature between room temperature and the boiling point of the reaction mixture.

The halide starting materials of formula III can be prepared according to methods which are known *per se*; for example, by reduction of the corresponding 5H-dibenzo[a,d]cyclohepten-5-one or 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one and subsequent halogenation of the resulting 5-hydroxy compound. Resulting halides which are deketalised in the 1-position can again be ketalised in accordance with methods known *per se*; for example, by treatment with a lower (i.e. C_1-C_6) alkanol or glycol (e.g. methyl alcohol or ethylene glycol).

According to embodiment (d) of the process of this invention, a compound of formula IV, V or VI is treated with methylamine, dimethylamine or dimethylhydroxylamine.

In formula IV, Z preferably represents a chlorine or bromine atom. The substituted sulfonyloxy group denoted by Z is preferably a lower (C_1-C_7) alkylsulfonyloxy group such as mesyloxy (methanesulfonyloxy), a phenylsulfonyloxy group, a (lower (C_1-C_7) alkyl)-phenylsulfonyloxy group such as tosyloxy or a phenyl-(lower (C_1-C_7) alkyl)sulfonyloxy group such as phenyl-mesyloxy (phenyl-methanesulfonyloxy). The anion A is preferably derived from an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, or sulfuric acid.

The treatment of a compound of formula IV, V or VI with methylamine, dimethylamine or dimethylhydroxylamine is conveniently effected in a closed vessel at an elevated temperature (for example, at 50°-175°C.). The treatment can be effected in an inert organic solvent such as methanol, ethanol, benzene or toluene. It is preferable to carry out the treatment in the presence of an excess of methylamine, dimethylamine or dimethylhydroxylamine. Where a compound of formula IV is used, this excess serves as an acid-binding agent. Other acid-binding agents (e.g. anhydrous potassium carbonate) can, however, also be employed. A compound of formula VI

is preferably treated in the presence of a metal-organic compound (e.g. phenyl lithium or a GRIGNARD compound). The use of a GRIGNARD compound is particularly advantageous.

Where a compound of formula IV, V or VI in which R' represents a methyl group is treated with dimethylhydroxylamine, there is obtained an N-oxide of a compound of formula I in which R₁ represents a methyl group.

A ketalised 1-acetyl group which may be present is retained after the treatment with dimethylhydroxylamine and must subsequently be deketalised as hereinafter described, to form the corresponding N-oxide of a compound of formula I in which R₁ represents a methyl group.

The starting materials of formulae IV and V are claimed *per se* in the specification of our copending Application for Letters Patent No. 28706/71 (now Serial No. 1,274,263) and can be prepared as described therein. The starting materials of formula VI are claimed *per se* in the specification of our copending Application for Letters Patent No. 28707/71 (now Serial No. 1,274,264) and can be prepared as described therein.

According to embodiment (e) of the process provided by the invention, a compound of formula VII is methylated. The methylation can be carried out by treatment with a usual methylating agent such as, for example, methyl iodide, methyl tosylate or dimethyl sulfate, preferably at a temperature of ca 15°—75°C. According to another procedure, a mixture of formaldehyde and formic acid, preferably in excess and at elevated temperature (e.g. between ca 50°C. and the boiling point of the mixture), is reacted with a compound of formula VII in which E represents an amino group. A ketalised acetyl group present is deketalised by this procedure. A preferred aspect for the manufacture of compounds of formula I in which R₁ represents a hydrogen atom consists in reacting a compound of formula VII in which E represents an amino group with a haloformic acid ester (e.g. chloro- or bromoformic ethyl ester) to yield a carbamate and subsequently reducing this with a metal hydride such as lithium aluminium hydride or diisobutyl aluminium hydride. Both the reaction and the reduction are preferably carried out in an inert solvent (e.g. ether or tetrahydrofuran) and at a temperature between room temperature and the reflux temperature of the mixture (especially at the reflux temperature). According to another method for the manufacture of compounds of formula I in which R₁ represents a hydrogen atom, a compound of formula VII in which E represents an amino group is reacted with chloral, preferably in inert solvent such as chloroform or benzene and at elevated temperature (e.g. between ca 50°C. and the boiling point of the reaction mixture). The resulting formylamino compound is subsequently reduced to the desired compound of formula I with a metal hydride (e.g. lithium aluminium hydride in anhydrous ether). A further method for the manufacture of compounds of formula I in which R₁ represents a hydrogen atom consists in reacting a compound of formula VII in which E represents an amino group with formaldehyde, preferably in an inert solvent such as benzene or toluene and at a temperature between room temperature and the boiling point of the reaction mixture. The resulting SCHIFF's base is subsequently converted into the desired compound of formula I by reduction. This reduction is conveniently effected with catalytically activated hydrogen (for example, with hydrogen in the presence of palladium-charcoal, nickel or platinum dioxide) or, especially where double bonds present as well as a ketalised 1-acetyl group present are to be retained, with a metal hydride such as sodium borohydride or lithium aluminium hydride in anhydrous ether or dioxan.

When a N-hydroxy-N-methylamino compound of formula VII is used, it is chiefly reacted with one of the usual methylating agents mentioned earlier (e.g. methyl iodide, methyl tosylate or dimethyl sulfate) to yield an N-oxide of a compound of formula I in which R₁ represents a methyl group. A ketalised acetyl group R' which may be present in the starting material is retained by this reaction and must subsequently be deketalised in the manner described hereinafter.

The starting materials of formula VII hereinafore are claimed *per se* in the specification of our copending Application for Letters Patent No. 28708/71 (now Serial No. 1,274,265) and can be prepared as described therein.

According to embodiment (f) of the present process, a compound of formula VIII is debenzylated. By the debenzylation, the benzyl group attached to the nitrogen atom is replaced by a hydrogen atom and there is obtained a compound of formula I in which R₁ represents a hydrogen atom. This debenzylation is conveniently carried out by reduction with an alkali metal (i.e. sodium or lithium) in liquid ammonia. According to this procedure, double bonds which are present are substantially retained. The

debenzylolation can also be carried out by treating a compound of the formula VIII with a haloformic acid ester and hydrolysing the resulting carbamate. The alcoholic portion of the haloformic acid ester is preferably derived from a lower alkanol (e.g. methanol, ethanol or isopropanol), phenol or a phenyl-(lower (C_1-C_7) alkanol) (e.g. benzyl alcohol). The halogen atom is conveniently a chlorine atom. The treatment with the haloformic acid ester is conveniently effected in a high-boiling inert solvent such as xylene or toluene and at a temperature between *ca* 50°C. and the reflux temperature of the mixture, preferably at the reflux temperature. The subsequent hydrolysis can be carried out under alkaline or acidic conditions (for example, with the aid of potassium hydroxide in butanol or hydrogen bromide in glacial acetic acid) and at a temperature between *ca* 50°C. and the boiling point of the mixture.

The starting materials of formula VIII are claimed *per se* in the specification of our copending Application for Letters Patent No. 28708/71 (now Serial no 1,274,265) and can be prepared as described therein.

According to embodiment (g) of the foregoing process, a compound of formula IXa or IXb is heated. If desired, the heating can be effected in the presence of aqueous acid such as sulfuric acid. Carbinol starting materials of formula IXa or IXb are dehydrated and ketalized 1-acetyl groups present are deketalised. The substituent Q is simultaneously removed and the corresponding compounds of formula I in which R_1 represents a hydrogen atom are formed.

In formulae IXa and IXb, Q represents, for example, a grouping of the formula $R_2CH=$ in which R_2 represents an alkyl, phenyl, phenalkyl, alkylphenyl or alkoxyphenyl group; the alkyl and alkoxy groups containing from 1 to 7 carbon atoms. Q preferably represents the benzylidene group.

B preferably represents the anion of a strong inorganic or organic acid; for example, the anion of hydrochloric acid, sulfuric acid, methanesulfonic acid, benzenesulfonic acid or, preferably, the anion of toluenesulfonic acid.

According to a preferred aspect of this embodiment, a compound of formula IXa in which P_1 represents a hydroxy group and P_2 represents a hydrogen atom is heated at a temperature in the approximate range of from 50°C. to 150°C.

The starting materials of formulae IXa and IXb are claimed *per se* in the specification of our copending Application for Letters Patent No. 28709/71 (now Serial No. 1,274,266) and can be prepared as described therein. The compounds of formulae IXa and IXb can be used in the present process without further purification. Often it is even recommended not to isolate them, but to immediately allow the mixture in which they are prepared to react with aqueous acid at an elevated temperature in the manner described earlier.

According to embodiment (h) of the present process, a compound of formula X is reacted with a compound of formula XI to yield an exocyclically saturated compound of formula I. In formula X, T preferably represents a sodium, potassium or lithium atom. L in formula XI preferably represents a chlorine atom. When L in formula XI represents a substituted sulfonyloxy group, this is preferably a lower (C_1-C_7) alkylsulfonyloxy group such as mesyloxy, a lower (C_1-C_7) cycloalkylsulfonyloxy group such as cyclopropylsulfonyloxy, the phenylsulfonyloxy group, a (lower alkyl)-phenylsulfonyloxy group such as tosyloxy or a phenyl-(lower alkyl)-sulfonyloxy group such as phenylmesyloxy. The reaction is conveniently carried out in an inert solvent such as benzene, toluene, hexane, heptane or ether at a temperature between room temperature and the boiling point of the reaction mixture.

The starting materials of formula X can be prepared, for example, by treating the corresponding 5-ketone or 5-hydroxy compound (after previous ketalisation of a 1-acetyl group which may be present) with aluminium isopropoxide and subsequently reacting the product with an alkali metal amide or hydride. A suitable method for the preparation of the starting materials of formula X in which R' represents a ketalised acetyl group comprises the following: 1-carboxy-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-one prepared as in Example 5 of Application 28705/71 (Serial No. 1,274,262) is converted into the corresponding 5-hydroxy compound with sodium borohydride in dioxane and the 5-hydroxy compound is transformed into the 5-unsubstituted compound with hydroiodic acid and red phosphorus. The 5-unsubstituted compound obtained is converted into the corresponding 1-chlorocarbonyl compound. The latter compound is treated with a salt of a malonic acid ester (e.g. the magnesium salt). By decomposition of the product obtained with aqueous hydrochloric acid, 1-acetyl-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene is obtained and this is ketalised in the usual manner. The resulting product is converted with the aid of an alkali metal amide or hydride into the corresponding starting material of formula X.

According to embodiment (i) of the foregoing process, a compound of formula XII is hydrolytically cleaved to yield a compound of formula I in which R_1 represents a hydrogen atom. In formula XII D can, for example, represent an acyl group such as a lower (C_1-C_7) alkanoyl group (e.g. formyl or acetyl), a phenyl-(lower (C_1-C_7) alkanoyl) group (e.g. benzoyl), a lower (C_1-C_7) alkylsulfonyl group (e.g. mesyl), the phenylsulfonyl group, a (lower alkyl)-phenylsulfonyl group (e.g. tosyl) or a phenyl-(lower alkyl) sulfonyl group (e.g. phenylmesyl). When D represents an esterified carboxy group this is preferably a lower carbalkoxy group such as carbomethoxy, carbethoxy or carboisopropoxy, the carbophenoxy group or a lower carbophenylalkoxy group such as carbobenzoxo. Where a starting material of formula XII in which D represents a group which does not contain sulfur is used, the hydrolytic cleavage proceeds under the conditions which are usual for acidic or alkaline hydrolysis (e.g. with heating at a temperature between *ca* 50°C. and the boiling point of the mixture) in the presence of an ethanolic solution of hydrochloric acid, acetic acid, sodium hydroxide or potassium hydroxide. The alkaline hydrolysis is preferred. Where a starting material of formula XII in which D represents a sulfur-containing group is used, it is recommended to carry out the hydrolytic cleavage by treatment, for example, with hydrobromic acid in acetic acid in the presence of phenol or with an alkali metal and a high-boiling alcohol (e.g. sodium and butanol). Such procedures are conveniently effected with heating (i.e. at a temperature between *ca* 50°C. and the boiling point of the mixture). Another method for the hydrolytic cleavage of sulfur-containing groups D consists in treatment with liquid ammonia and an alkali metal (e.g. sodium). In the case of alkaline hydrolytic cleavage, ketalised 1-acetyl groups must subsequently be deketalised in the manner described hereinafter.

The starting materials of formula XII are claimed *per se* in the specification of our copending Application for Letters Patent No. 28708/71 (now Serial No. 1,274,265) and can be prepared as described therein.

The compounds of formula I manufactured in the manner described earlier can, if desired, be subjected to further transformations:

The resulting compound of formula I in which R_1 represents a hydrogen atom or a corresponding compound containing a ketalised 1-acetyl group can be transformed into a compound in which R_1 represents a methyl group according to methods known *per se*, for example, by treatment with a methylating agent such as methyl iodide, methyl mesylate, methyl tosylate or dimethyl sulfate, preferably at a temperature of *ca* 15°–75°C. According to another procedure, a mixture of formaldehyde and formic acid, preferably in excess and at elevated temperature (e.g. between *ca* 50°C. and the boiling point of the mixture), is reacted with a compound of formula I in which R_1 represents a hydrogen atom. It is also possible, where R represents a methyl group, to obtain a corresponding compound of formula I in which R_1 represents a methyl group by reacting a compound of formula I in which R_1 represents a hydrogen atom with formaldehyde and hydrogen at room temperature in the presence of a catalyst such as palladium-charcoal, RANEY-nickel or platinum dioxide.

Resulting compounds of formula I in which R_1 represents a methyl group or corresponding compounds containing a ketalised 1-acetyl group can be transformed into the corresponding compounds in which R_1 represents a hydrogen atom. A particularly suitable embodiment of this transformation consists in reacting a compound of formula I in which R_1 represents a methyl group with a cyanogen halide, preferably with cyanogen bromide. The reaction is conveniently carried out in an inert solvent such as, for example, benzene, ether, tetrahydrofuran or methylene chloride and at a temperature between room temperature and the boiling point of the mixture. The resulting N-cyano-N-methyl-amino compound is subsequently hydrolysed in a manner known *per se* in alkaline or acidic medium, a compound of formula I in which R_1 represents a hydrogen atom being formed as the base or as an acid addition salt depending upon the hydrolysis medium used.

According to another embodiment for the demethylation of compounds of formula I in which R_1 represents a methyl group or of corresponding compounds containing a ketalised 1-acetyl group, these compounds are treated with a haloformic acid ester and the resulting carbamate is hydrolysed. The alcoholic portion of the haloformic acid ester is preferably derived from a lower alkanol (e.g. methanol, ethanol or *iso*-propanol), phenol or a lower phenylalkanol (e.g. benzyl alcohol). The halogen atom is conveniently a chlorine atom. The treatment with the haloformic acid ester is conveniently effected in a high-boiling inert solvent such as xylene or toluene and at a temperature between *ca* 50°C. and the reflux temperature of the mixture, preferably at the reflux temperature. The subsequent hydrolysis can be carried out under alkaline

or acidic conditions (for example, with the aid of potassium hydroxide in butanol or hydrogen bromide in glacial acetic acid) and at a temperature between *ca* 50°C. and the boiling point of the mixture.

By oxidation of a compound of formula I in which R₁ represents a methyl group or a corresponding compound containing a ketalised 1-acetyl group, a corresponding N-oxide is obtained. Various compounds which readily release oxygen can be used as the oxidising agent; for example, organic peroxides such as monosubstituted organic peroxides (e.g. alkyl hydroperoxides containing up to 4 carbon atoms such as *tert*butyl hydroperoxide as well as phenyl-substituted derivatives of alkyl hydroperoxides containing up to 4 carbon atoms such as cumyl hydroperoxide). If desired, the phenyl substituent can carry a further substituent (for example, an alkyl or alkoxy group containing up to 4 carbon atoms or a halogen atom). As the oxidising agent there can also be used various inorganic oxidising agents; for example, hydrogen peroxide, ozone, hypochlorites such as sodium, potassium or ammonium hypochlorite, peroxymonodisulfuric acid and peroxydisulfuric acid. The use of hydrogen peroxide is preferred. The oxidation is advantageously effected in a solvent such as, for example, methanol, ethanol, ether, benzene or chloroform and at a temperature between about minus 50°C. and 100°C. After working up in the usual manner, with the removal of the excess oxidising agent, there is obtained the corresponding N-oxide. The latter is conveniently recovered in the form of an acid addition salt.

Compounds of formula I in which R represents a methyl group and which carry an exocyclic double-bond in the 5-position and/or a double bond in the 10,11-position can be hydrogenated to yield the correspondingly saturated compounds of formula I. The double-bond in the 10,11-position is more readily hydrogenated than the exocyclic double-bond in the 5-position so that, insofar as both are simultaneously present, the hydrogenation can be carried out selectively on the double-bond in the 10,11-position. The hydrogenation can be carried out, for example, at room temperature with the aid of hydrogen in the presence of a catalyst such as RANEY-nickel, palladium-charcoal or platinum oxide.

Compounds of formula I which contain a single-bond in the 10,11-position or corresponding compounds containing a ketalised 1-acetyl group can be dehydrogenated in the 10,11-position. This is conveniently effected by heating (e.g. to 150°—250°C.) with a catalyst such as palladium-charcoal, RANEY-nickel or platinum dioxide, conveniently in an inert solvent such as, for example, tetrahydronaphthalene or diethyleneglycol monomethyl ether.

According to another procedure for the dehydrogenation of compounds of formula I which contain a single bond in the 10,11-position and a methyl group R or corresponding compounds containing a ketalised 1-acetyl group, after the introduction of a protecting group into any compound in which R₁ represents a hydrogen atom, a halogen atom is introduced into the 10- or 11-position by halogenation. The halogen atom can be split off in the manner described hereinafter with the formation of a 10,11-double-bond. After splitting off any protecting group which may be present, there is obtained a compound of formula I which contains a double-bond in the 10,11-position or a corresponding compound containing a ketalised 1-acetyl group.

Examples of suitable protecting groups which can be used in the procedure described in the preceding paragraph are the cyano group or an esterified carboxy group such as carbomethoxy, carbethoxy, carboisopropoxy, carbophenoxy and carbo-benzoyl. The cyano group is conveniently introduced by reaction with a cyanogen halide (preferably cyanogen bromide), for example, in an inert solvent such as benzene, ether, tetrahydrofuran or methylene chloride and at a temperature between room temperature and the boiling point of the reaction mixture. The introduction of an esterified carboxy group is effected, for example, by reaction with a corresponding haloformic acid ester such as a chloroformic acid ester. This reaction is preferably effected in an inert solvent (e.g. chloroform, xylene or toluene) and at between room temperature and the boiling point of the reaction mixture. If the cyano group or an esterified carboxyl group is to be introduced into a compound of formula I in which R₁ represents a hydrogen atom, it is recommended to add an acid-binding agent (e.g. triethylamine or pyridine). The reaction then proceeds particularly rapidly, often already at room temperature.

A further protecting group which is suitable for introduction into a compound of formula I in which R₁ represents a hydrogen atom is an acyl group derived from a lower (C₁—C₇) carboxylic acid (e.g. an acetyl, isobutyryl, benzoyl or phenylacetyl group). The introduction of such a protecting group is effected, for example, by reacting a compound of formula I in which R₁ represents a hydrogen atom with acetyl chloride

or acetic anhydride, conveniently in the presence of an acid-binding agent (e.g. triethylamine or pyridine). The reaction can be effected at a temperature between about room temperature and the reflux temperature of the reaction mixture, although room temperature is often sufficient.

The resulting compound, which may be protected at the nitrogen atom is subsequently treated with a halogenating agent such as N-bromosuccinimide, N-chlorosuccinimide, bromine, chlorine or sulphuryl chloride, whereby a halogen atom is introduced into the 10- or 11-position. This treatment is preferably effected in an inert solvent such as carbon tetrachloride, benzene, heptane, chloroform or tetrahydrofuran and at elevated temperature (e.g. at 50°C. up to the boiling point of the mixture). It is very advantageous to add a small amount of a promoter (e.g. azo-bis-butyronitrile or dibenzoyl peroxide) as well as a hydrogen halide acceptor (e.g. pyridine, triethylamine, collidine, allyl chloride or an epoxide). The resulting 10,11-dihydro compound, which is halogenated in the 10- or 11-position, is subsequently treated with a basic agent (e.g. sodium hydroxide, potassium carbonate or triethylamine) at a temperature between room temperature and the boiling point of the mixture, whereby a 10,11-double bond is formed with the splitting off of hydrogen halide. Any protecting group present on the nitrogen atom is then hydrolytically split off in the manner described earlier, and there results a compound of formula I in which a double-bond is present in the 10,11-position or a corresponding compound containing a ketalised 1-acetyl group.

The deketalisation of a ketalised 1-acetyl group is conveniently effected by treatment with a dilute acid such as hydrochloric acid or sulfuric acid at a temperature between room temperature and the boiling point of the mixture. The treatment may be carried out in the presence of a lower (C_1-C_7) alkanol such as, for example, methanol or ethanol.

Resulting compounds of formula I in which an exocyclic double-bond is present in the 5-position and their salts can be separated into their geometric isomers, i.e. α - or β -isomers. The methods of separation are known *per se*. The geometric isomers are preferably separated by fractional crystallization of the acid addition salts from a solvent (e.g. acetone) or from a solvent mixture (e.g. a mixture of methanol and diethyl ether).

The resulting compounds of formula I in which an exocyclic single-bond is present in the 5-position and their salts exist as racemates. A racemate can be separated into its optical isomers in a manner known *per se*; for example, by reaction with optically active acids such as tartaric acid or camphorsulfonic acid and subsequent crystallisation.

The separation of the geometric and/or optical isomers can be undertaken at a stage in the process so that, in this manner, the process in accordance with the invention is carried out using geometrically and/or optically uniform starting materials.

The compounds of formula I and the N-oxides of those compounds in which R_1 represents a methyl group are basic in character and can be converted into their acid addition salts. Such salts are, for example, those with organic acids such as oxalic acid, citric acid, acetic acid, lactic acid, maleic acid and tartaric acid or with inorganic acids such as hydrochloric acid, hydrobromic acid or sulfuric acid. The acid addition salts are crystalline solid substances which are soluble in water, somewhat less soluble in polar solvents such as methanol and ethanol and relatively insoluble in non-polar solvents such as benzene, ether and petroleum ether.

As mentioned earlier, the dibenzocycloheptene derivatives provided by the invention possess an excellent antidepressant action. To demonstrate this, a number of such derivatives were administered to groups each comprising 5 rats in three doses of 50 mg/kg *p.o.*, twice on the day before and once on the day of the experiment. Six hours after the last application, the rats received 20 mg/kg of 2-hydroxy-2-ethyl-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[a]quinolizine hydrochloride injected subcutaneously. The same dosage was administered to a control group of 5 non-pretreated rats. The ratings include central and peripheral symptoms which are characteristic for tricyclic antidepressants [See Ann. N.Y. Acad. Sci. 96, 279 (1962)]. Motility (climbing), sensitivity to stimulus, seeking behaviour and suppression of ptosis were observed for the purpose of determining antidepressant action. These changes were recorded according to a rating scheme which utilized numbers.

The derivatives set forth in Table I hereinafter demonstrated in this test a strong antidepressive action which manifested itself in strongly increased characteristic motility, sensitivity to stimulus, seeking behaviour as well as complete suppression of ptosis. The stated percentages are compared with the values for amitriptyline [10,11 - dihydro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene; amitriptyline=100%].

TABLE I

Test Derivative	Activity in % compared with amitriptyline
1-Methyl-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride	220
1-Methyl-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene hydrochloride	180
1-Methyl-10,11-dihydro-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride	140
1-Methyl-10,11-dihydro-5-(3-methylaminopropyl)-5H-dibenzo[a,d]cycloheptene hydrochloride	180
1-Methyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride	130
1-Methyl-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride	230
1-Methyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride	140

The low toxicity of the dibenzocycloheptene derivatives provided by this invention can be illustrated by the acute toxicity of 1-methyl-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene hydrochloride in mice (24-hour values):

LD₅₀ i.v. = 25—50 mg/kg
LD₅₀ p.o. = 300—600 mg/kg

The low anticholinergic action can be shown by the lack of salivation inhibition in rabbits. The salivation in rabbits under light urethane narcosis was increased by pilocarpine injection (5 mg/kg s.c.) and the amount of saliva was measured at intervals of 5 minutes. The inhibition of salivation is expressed as a percentage based upon the salivation of animals which only received pilocarpine.

The derivatives as set forth in Table II hereinafter demonstrated in this test a low salivation inhibition, (amitriptyline=96% inhibition of salivation).

TABLE II

Test Derivative (3 mg/kg <i>iv.</i>)	% Inhibition of Salivation
1-Methyl-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride	50
1-Methyl-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene hydrochloride	50
1-Methyl-10,11-dihydro-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride	50
1-Methyl-10,11-dihydro-5-(3-methylaminopropyl)-5H-dibenzo[a,d]cycloheptene hydrochloride	40
1-Methyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride	60
1-Methyl-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride	60
1-Methyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride	14

The compounds of formula I, N-oxides of such compounds in which R₁ represents a methyl group, geometric and optical isomers of such compounds and N-oxides and pharmaceutically acceptable acid addition salts of said compounds, N-oxides and isomers can be used as medicaments: for example, in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier. This carrier can be an organic or inorganic carrier which is suitable for enteral (e.g. oral) or parenteral application. Examples of such carriers are water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, gum arabic and polyalkylene glycols. The pharmaceutical preparations can be made up in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). The pharmaceutical preparations may be sterilized and/or may contain additives such as preserving, stabilizing, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They can also contain other therapeutically valuable substances.

Convenient pharmaceutical dosage forms contain 1 to 200 mg of a compound of formula I. Convenient oral dosages are in the range of from 0.1 mg/kg per day to 5 mg/kg per day. Convenient parenteral dosages are in the range of from 0.01 mg/kg per day to 0.5 mg/kg per day. However, these ranges can be extended upwards or downwards depending upon individual requirements.

The following Examples illustrate the process provided by the invention:

EXAMPLE 1

18 g of 1-methyl-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene [prepared as described in the specification of our copending Application No. 28705/71 (now Serial No. 1,274,262)] and 180 ml of 3% ethanolic hydrochloric acid are heated on a steam-bath under reflux for 2 hours and subsequently evaporated to dryness. The residual 1-methyl-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride (mixture of the α - and β -isomers) melts at 216°—220°C. after recrystallization from ethanol/ether.

EXAMPLE 2

39.5 g of 1-methyl-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene are dissolved in 400 ml of glacial acetic acid and hydrogenated at room temperature and under normal pressure in the presence of 3 g of platinum oxide. When the uptake of hydrogen has ceased, the solution is filtered from the catalyst, evaporated and the residue distilled, 1-methyl-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene passing over at 140°C./0.01 mmHg. The hydrochloride melts at 181°—183°C. after recrystallization from ethanol/ether.

EXAMPLE 3

9.1 g of 1-methyl-10,11-dihydro-5-(3-methylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene [prepared as described in the specification of our copending Application No. 28705/71 (now Serial No. 1,274,262)] and 100 ml of 3% ethanolic hydrochloric acid are heated on a steam-bath under reflux for 3 hours and subsequently evaporated to dryness. The residual 1-methyl-10,11-dihydro-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride (mixture of α - and β -isomers) melts at 210°—228°C. after recrystallization from ethanol/ether.

EXAMPLE 4

12.2 g of 1-methyl-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene dissolved in 180 ml of dry benzene are added dropwise to a mixture of 13.6 g of chloroformic acid ethyl ester and 50 ml of dry benzene and the whole is boiled and stirred under reflux for 20 hours. After cooling, the benzene solution is washed with dilute hydrochloric acid and with water and evaporated. The residual 1-methyl-10,11-dihydro-5-(3-methylcarbethoxyaminopropyl)-5H-dibenzo[a,d]cycloheptene, which is claimed in our Application No. 28708/71 (Serial No. 1,274,265) distils at 180°C./0.01 mmHg. 10.6 g of 1-methyl-10,11-dihydro-(3-methylcarbethoxyaminopropyl)-5H-dibenzo[a,d]cycloheptene, 12.6 g of potassium hydroxide and 110 ml of *n*-butanol are boiled at reflux for 20 hours under nitrogen and with strong stirring. The butanol is distilled off under reduced pressure, the residue taken up in ether and the ethereal solution shaken with dilute hydrochloric acid. By treatment of the aqueous acidic phase with excess potassium carbonate, 1-methyl-10,11-dihydro-5-(3-methylaminopropyl)-5H-dibenzo[a,d]cycloheptene separates out as an oil which distils at 150°C./0.01 mm Hg. After recrystallization from ethanol/ether, the hydrochloride melts at 173°—175°C.

EXAMPLE 5

10 g of 1-methyl-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene [prepared as described in the specification of our copending Application No. 28705/71 (now Serial No. 1,274,262)] and 100 ml of 3% ethanolic hydrochloric acid are heated under reflux for 3 hours and subsequently evaporated to dryness. The residual 1-methyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride (mixture of the α - and β -isomers) melts at 185°—195°C. after recrystallization from methanol/ether. The free base boils at 158°C./0.01 mmHg.

EXAMPLE 6

6.2 g of 1-methyl-5-(3-methylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene [prepared as described in the specification of our copending Application No. 28705/71 (now Serial No. 1,274,262)] and 60 ml of 3% ethanolic hydrochloric acid are heated under reflux for 3 hours and evaporated to dryness. The residual 1-methyl-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride (mixture of the α - and β -isomers) is recrystallized from ethanol/ether and melts at 170°—180°C. The free base boils at 150°C./0.01 mmHg.

EXAMPLE 7

1.9 g of 1-methyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene (isomer mixture 1:1) are dissolved in 20 ml of methanol at 0°C. and treated with 2.25 g of 30% aqueous hydrogen peroxide solution. The mixture is subsequently stirred at 50°C. for a further 16 hours. The excess hydrogen peroxide is decomposed by the addition of platinum black. After filtration, the solution is adjusted to pH 2 with methanolic hydrochloric acid and dried for 30 minutes at 20°C. under strongly reduced pressure. The residue is crystallized from methanol/ether. 1-Methyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride of melting point 179°—180°C. is obtained.

benzene are heated with 45 ml of thionyl chloride for 2 hours under reflux. The mixture is subsequently evaporated under reduced pressure. The resulting white crystalline residue is recrystallized from carbon tetrachloride. 5-Chloro-1-methyl-5H-dibenzo-[a,d]cycloheptene melting at 158°—160°C. is obtained.

B) The process:

A GRIGNARD reagent is prepared in the usual manner from 7 g of GILMAN alloy in 20 ml of absolute ether and 33.6 g of 3-dimethylaminopropyl chloride in 50 ml of absolute tetrahydrofuran. The solvent is distilled off in an argon atmosphere and replaced by 150 ml of absolute benzene. A solution of 20 g of 5-chloro-1-methyl-5H-dibenzo[a,d]cycloheptene in 250 ml of absolute benzene is added dropwise at room temperature. The mixture is heated for 15 minutes under reflux, hydrolysed with 50 ml of water, filtered, washed three times with chloroform and evaporated under reduced pressure. After working up in the usual manner, oily 1-methyl-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene (mixture of the diastereomers in the proportion of ca 1:1) is obtained. The corresponding maleate (mixture of the diastereomers in the proportion of ca 1:1) is a crystalline compound which melts at 130°—131°C.

EXAMPLE 17

10 g of 1-methyl-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene (mixture of the diastereomers in the proportion of ca 1:1) are heated in 100 ml of methanol with 7.8 g of 30% aqueous hydrogen peroxide solution for 20 hours at 50°C. Working up is effected in the manner described in Example 13. 1-Methyl-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene-N-oxide melting at 180°—181°C. is obtained.

The following Example illustrates a typical pharmaceutical preparation containing one of the dibenzocycloheptene derivatives provided by the invention:

EXAMPLE A

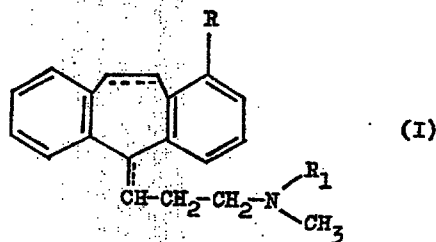
Tablets are prepared, each tablet weighing 200.00 mg and containing the following ingredients:

1-Methyl-10,11-dihydro-5-(3-methylaminopropyl)-5H-dibenzo-[a,d]cycloheptene hydrochloride	28.05 mg.
Lactose	110.00 mg.
Corn Starch	57.95 mg.
Talc	3.40 mg.
Magnesium Stearate	0.60 mg.
	200.00 mg.

The foregoing ingredients are intimately mixed with one another and pressed into 200 mg tablets which are subsequently coated with ethyl cellulose and CARBOWAX [Registered Trade Mark].

WHAT WE CLAIM IS:—

1) Compounds of the general formula



in which R₁ represents a hydrogen atom or a methyl group, R represents a methyl or acetyl group and the dotted bonds can be hydrogenated, N-oxides of compounds of formula I in which R₁ represents a methyl group, geometric and optical isomers of said compounds, and N-oxides and acid addition salts of said compounds, N-oxides and isomers; with the exception of 1-methyl-5-(3-methylaminopropylidene)-5H-dibenzo-[a,d]-cycloheptene and 1-acetyl-5-(3-methylaminopropyl)-5H-dibenzo[a,d]-10,11-dihydrocycloheptene.

benzene are heated with 45 ml of thionyl chloride for 2 hours under reflux. The mixture is subsequently evaporated under reduced pressure. The resulting white crystalline residue is recrystallized from carbon tetrachloride. 5-Chloro-1-methyl-5H-dibenzo-[a,d]cycloheptene melting at 158°—160°C. is obtained.

B) *The process:*

A GRIGNARD reagent is prepared in the usual manner from 7 g of GILMAN alloy in 20 ml of absolute ether and 33.6 g of 3-dimethylaminopropyl chloride in 50 ml of absolute tetrahydrofuran. The solvent is distilled off in an argon atmosphere and replaced by 150 ml of absolute benzene. A solution of 20 g of 5-chloro-1-methyl-5H-dibenzo[a,d]cycloheptene in 250 ml of absolute benzene is added dropwise at room temperature. The mixture is heated for 15 minutes under reflux, hydrolysed with 50 ml of water, filtered, washed three times with chloroform and evaporated under reduced pressure. After working up in the usual manner, oily 1-methyl-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene (mixture of the diastereomers in the proportion of *ca* 1:1) is obtained. The corresponding maleate (mixture of the diastereomers in the proportion of *ca* 1:1) is a crystalline compound which melts at 130°—131°C.

EXAMPLE 17

10 g of 1-methyl-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene (mixture of the diastereomers in the proportion of *ca* 1:1) are heated in 100 ml of methanol with 7.8 g of 30% aqueous hydrogen peroxide solution for 20 hours at 50°C. Working up is effected in the manner described in Example 13. 1-Methyl-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene-N-oxide melting at 180°—181°C. is obtained.

The following Example illustrates a typical pharmaceutical preparation containing one of the dibenzocycloheptene derivatives provided by the invention:

EXAMPLE A

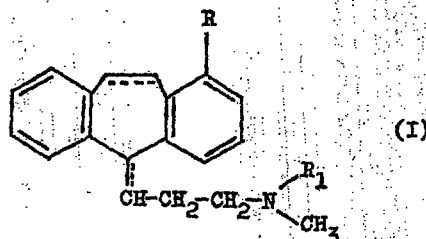
Tablets are prepared, each tablet weighing 200.00 mg and containing the following ingredients:

1-Methyl-10,11-dihydro-5-(3-methylaminopropyl)-5H-dibenzo-[a,d]cycloheptene hydrochloride	28.05 mg.
Lactose	110.00 mg.
Corn Starch	57.95 mg.
Talc	3.40 mg.
Magnesium Stearate	0.60 mg.
	200.00 mg.

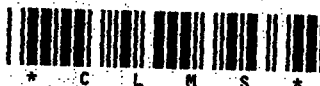
The foregoing ingredients are intimately mixed with one another and pressed into 200 mg tablets which are subsequently coated with ethyl cellulose and CARBOWAX [Registered Trade Mark].

WHAT WE CLAIM IS:—

1) Compounds of the general formula



in which R₁ represents a hydrogen atom or a methyl group, R represents a methyl or acetyl group and the dotted bonds can be hydrogenated, N-oxides of compounds of formula I in which R₁ represents a methyl group, geometric and optical isomers of said compounds, and N-oxides and acid addition salts of said compounds, N-oxides and isomers; with the exception of 1-methyl-5-(3-methylaminopropylidene)-5H-dibenzo-[a,d]-cycloheptene and 1-acetyl-5-(3-methylaminopropyl)-5H-dibenzo[a,d]-10,11-dihydrocycloheptene.



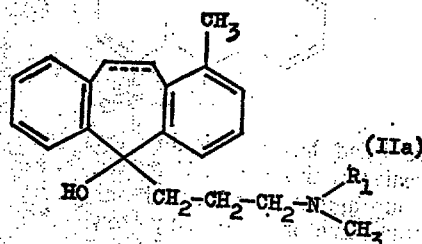
2) 1 - Methyl - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene, optical isomers thereof and acid addition salts of said compound and isomers.

3) 1 - Methyl - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene, geometric isomers thereof and acid addition salts of said compound and isomers.

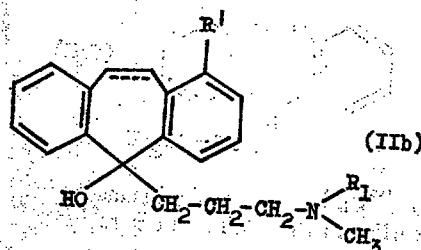
4) 1 - Methyl - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene-N-oxide, geometric isomers thereof and acid addition salts of said N-oxide and isomers.

5) A pharmaceutical preparation comprising a compound as claimed in claim 1 in association with a compatible pharmaceutical carrier.

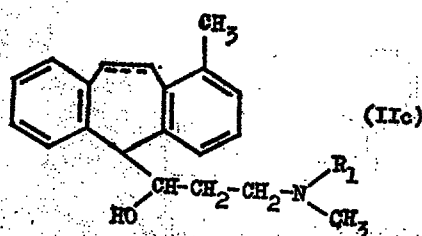
6) A process for the manufacture of the dibenzocycloheptene derivatives claimed in claim 1, which process comprises either (a) reducing a carbinol of the general formula



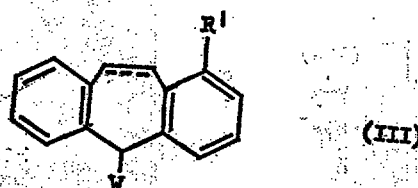
in which R_1 and the dotted bond have the significance given in claim 1, or (b) dehydrating a carbinol of the general formula



in which R_1 and the dotted bond have the significance given in claim 1 and R' represents a methyl or ketalised acetyl (as hereinbefore defined) group, a carbinol of the general formula

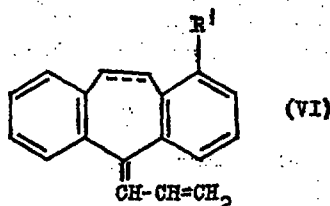
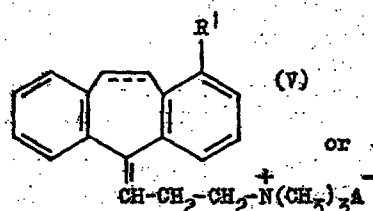
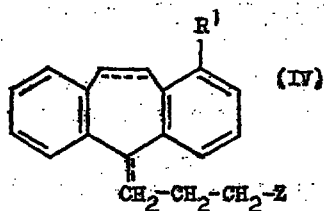


in which R_1 and the dotted bond have the significance given in claim 1, or an N-oxide of a carbinol of formula IIb or IIc in which R_1 represents a methyl group, or (c) reacting a halide of the general formula

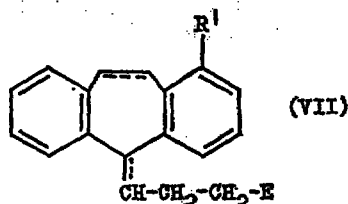


in which the dotted bond has the significance given in claim 1, R' has the significance given earlier in this claim and W represents a halogen atom, with a 3-dimethylaminopropyl magnesium halide, or (d) treating a compound of the general formula

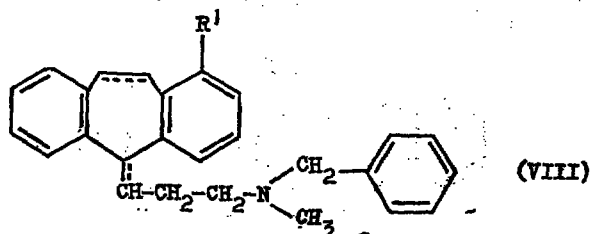




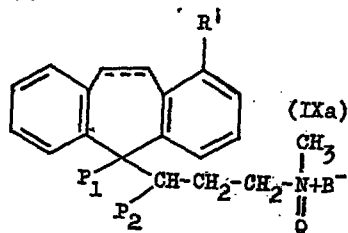
in which the dotted bond has the significance given in claim 1, R' has the significance given earlier in this claim, Z represents a halogen atom or a substituted sulfonyloxy group and A represents the anion of an acid, with methylamine, dimethylamine or dimethylhydroxylamine, or (e) methylating a primary amine of the general formula



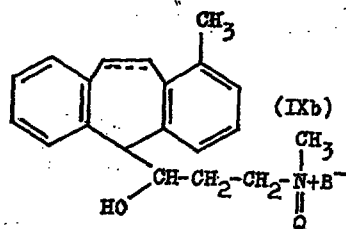
in which the dotted bond has the significance given in claim 1, R' has the significance given earlier in this claim and E represents an amino group or an N-hydroxy-N-methyl group. or (f) debenzylating a compound of the general formula



in which the dotted bonds have the significance given in claim 1 and R' has the significance given earlier in this claim, or (g) heating a compound of the general formula



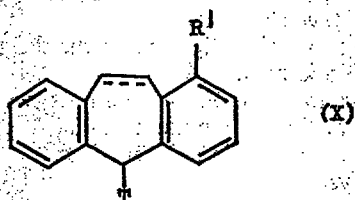
or



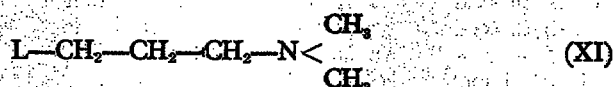
in which the dotted bonds have the significance given in claim 1, R' has the significance given earlier in this claim, P₁ represents a hydrogen atom or a hydroxyl group and P₂ represents a hydrogen atom or P₁ and P₂ together



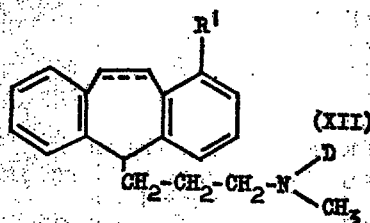
represent an additional bond, Q represents the residue of an aldehyde and B represents the anion of an acid,
or (h) reacting a compound of the general formula



in which the dotted bond has the significance given in claim 1, R' has the significance given earlier in this claim and T represents an alkali metal atom, with a compound of the general formula



in which L represents a halogen atom or a substituted sulfonyloxy group,
or (i) hydrolytically cleaving a compound of the general formula



in which the dotted bond has the significance given in claim 1, R' has the significance given earlier in this claim and D represents an acyl group or an esterified carboxyl group,

whereupon, in any desired sequence and if desired, a resulting compound in which R₁ represents a hydrogen atom is methylated, if desired, a compound in which R₁ represents a methyl group is oxidised or converted into a compound in which R₁ represents a hydrogen atom by demethylation, if desired, an unsaturated product obtained is hydrogenated, if desired, a 10,11-dihydro compound obtained is dehydrogenated, if necessary, a ketal obtained is deketalised, if desired, the geometric and/or optical isomers are isolated from an isomer mixture obtained and, if desired, a base obtained is converted into an acid addition salt.

7) A process according to claim 6, wherein a starting compound of one of formulae II—X and XII is employed in which R' and R₁ each represent a methyl group and the dotted bond in the 10,11-position is hydrogenated, whereafter a 3-dimethylaminopropylidene compound, if obtained, is reduced to the corresponding 3-dimethylaminopropyl compound.

8) A process according to claim 7, wherein 1-methyl-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene is dehydrated and the resulting 1-methyl-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene is reduced to 1-methyl-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene.

9) A process according to claim 8, wherein the dehydration is carried out with the aid of ethanolic hydrochloric acid.

10) A process according to claim 8 or claim 9, wherein the reduction is carried out with the aid of platinum dioxide in glacial acetic acid.

11) A process according to claim 6, wherein a starting compound of one of formulae IIB and IV—IX is employed in which R' represents a methyl group, the dotted bonds are not hydrogenated and P₁ represents a hydroxyl group or P₁ and P₂ together represent an additional bond, whereafter any dimethylaminopropylidene compound obtained is demethylated to the corresponding methylaminopropylidene compound.



- 12) A process according to claim 11, wherein 1-methyl-5-(3-dimethylamino-propyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene is dehydrated and the resulting 1-methyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene is demethylated via the corresponding carbamate to 1-methyl-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]cycloheptene. 5
- 13) A process according to claim 12, wherein the dehydration is carried out with the aid of ethanolic hydrochloric acid.
- 14) A process according to claim 12 or claim 13, wherein the demethylation is carried out by treating the 1-methyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene obtained with chloroformic acid ethyl ester and subjecting the resulting carbamate to alkaline hydrolysis. 10
- 15) A process according to claim 6, wherein a starting compound of one of formulae IIb and IV—IX is employed wherein R' and R₁ both represent a methyl group, the dotted bonds are not hydrogenated and P₁ represents a hydroxyl group or P₁ and P₂ together represent an additional bond, whereafter any dimethylamino-propylidene compound obtained is oxidised to the corresponding N-oxide. 15
- 16) A process according to claim 15, wherein 1-methyl-5-(3-dimethylamino-propyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene is dehydrated and the resulting 1-methyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene is oxidised to 1-methyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide. 20
- 17) A process according to claim 16, wherein the dehydration is carried out with the aid of ethanolic hydrochloric acid.
- 18) A process according to claim 16 or claim 17, wherein the oxidation is carried out by treatment with aqueous hydrogen peroxide. 25
- 19) A process according to claim 6 for the manufacture of the dibenzocycloheptene derivatives claimed in claim 1, substantially as hereinbefore described with reference to Examples 1 to 17.
- 20) Dibenzocycloheptene derivatives as claimed in claim 1, when manufactured by the process claimed in any one of claims 6 to 19 inclusive. 30

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1972.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

