This is a continuation-in-part of my copending application Serial No. 16,660, filed March 22, 1960, now U.S. Patent 3,119,829, and reference is also made to the application entitled Dibenzylocycloheptane Derivatives filed concurrently herewith which is also a continuation-in-part of said copending application Serial No. 16,660.

Reference is also made to my copending application Serial No. 90,153 filed May 2, 1960, now abandoned, and Serial No. 141,590 filed September 29, 1960 with respect to the preparation of the intermediate carbinitols from the corresponding ketones referred to above. Both of these last-named applications are based upon Netherlands application No. 237,663, filed April 1, 1959.

This invention relates to therapeutically active dibenzylocycloheptane derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

According to the present invention there are provided new compounds of the general formula 1.

\[
\text{in which}
\]

\[X \text{ is a radical selected from the group consisting of } -\text{CH}_2-\text{CH}_2- \text{ and } -\text{CH}_3-\text{CH}_2-\]

\[R_4 \text{ and } R_5 \text{ are each selected from the group consisting of a hydrogen atom and a lower alkyl group, preferably an alkyl group having at most 4 carbon atoms, }\]

\[Y \text{ is a member of the group consisting of a lower alkylene group, preferably a saturated straight or branched hydrocarbon chain having at most 6 carbon atoms, and a lower alkylene group interrupted by an oxygen atom, preferably a saturated hydrocarbon chain interrupted by an oxygen atom and having at most 5 carbon atoms, }\]

\[Z \text{ is a member of the group consisting of }\]

\[
\text{wherein } R_3 \text{ is a member of the group consisting of a hydrogen atom and a lower alkyl group, preferably an alkyl group having not more than 6 carbon atoms, and } R_4 \text{ is a member of the group consisting of a lower alkylene group, preferably an alkyl group having not more than 6 carbon atoms,}\]

\[
\text{and }\]

\[
\text{wherein } A \text{ is a member of the group consisting of }\]

\[
\text{and } NR_3-, \text{ wherein } R_3 \text{ represents a lower alkyl group, preferably an alkyl group having not more than 6 carbon atoms, and salts thereof.}\]

Typical compounds of the invention have the following formulae:

The particularly preferred compounds are those of Formula I wherein X represents the \(-\text{CH}_3-\text{CH}_2-\) group, Y is a saturated hydrocarbon chain having two to three carbon atoms (i.e., ethylene, trimethylene-1,3, and propylene-1,2); Z represents a dialkyl amino radical, an N-pyrrolidino radical or an N-morpholinio radical, R3 is in the 3-position and represents hydrogen, chloro, or methyl, ethyl, propyl, isopropyl, and tertiary butyl, and R5 is hydrogen.

The salts of the dibenzylocycloheptane derivatives coming within the purview of this invention include the acid addition salts, more particularly the non-toxic acid addition salts, i.e., salts which are not harmful to the animal organism when used in therapeutic doses. Acids useful for preparing the acid addition salts include, inter alia, inorganic acids, such as the hydrohalic acids (e.g., hydrochloric and hydrobromic acid) and organic acids, such as oxalic, maleic, tartaric, citric, acetic, and succinic acid.

The compounds of this invention are therapeutically active compounds which have utility as antihistaminics, apart from their antihistaminic activity, the compounds also exhibit a remarkably strong anti-acetyl choline activity. Moreover, they have a central activity, as appears, inter alia, from their action on tremors induced by the compound 1,4 - dipropylindobutyne - (2) (tremorine), from the reduction of the "compulsive circling" in guinea pigs caused by the administration of scopolamine (physostigmine), and from the prolongation of the sleeping period of mice after subcutaneous injection.

The toxicity of the compounds according to the invention, expressed in LD50 on mice, is about 40 mg./kg. after intravenous, and about 200 mg./kg. after subcutaneous administration. The novel compounds of this invention can be administered orally or parenterally in conventional dosage forms such as tablets, capsules, injection solutions, or the like, by incorporating the appropriate dose of the compound with carriers according to accepted pharmaceutical practice.

The compounds of this invention can be prepared from the corresponding ketones having the following formula:

\[
\text{wherein } X, R_1 \text{ and } R_2 \text{ have the meaning hereinbefore}\]
defined, and this ketone first being converted into a carbonyl intermediate of the general formula

\[
\begin{align*}
&\text{(II)} & &\hspace{1cm} &\text{(III)} \\
&\text{R}_1 & &\text{X} & &\text{R}_2 \\
&\text{R}_1 & &\text{Hal} & &\text{Y} \rightarrow & &\text{R}_2 \\
&\text{R}_1 & &\text{O} & &\text{R}_2
\end{align*}
\]

by reduction of the ketone of general Formula II, by treatment with a reducing agent such as sodium borohydride, sodium amalgam, aluminum isopropanoxides and lithium aluminum hydride. The resulting alcohol is then interacted with a basically substituted alkyl halide (preferably chloride) of the formula \(Z-Y\)-halide (IV), the reaction preferably being conducted in the presence of a basic condensation reagent such as sodamide.

This series of reactions is shown by the following equations:

\[
\begin{align*}
&\text{(V)} & &\hspace{1cm} &\text{(I)} \\
&\text{R}_1 & &\text{CH}=\text{CH} & &\text{R}_2 \\
&\text{R}_1 & &\text{COOH} & &\text{R}_2 \\
&\text{R}_1 & &\text{CHO} \\
&\text{R}_1 & &\text{C}=\text{O} & &\text{R}_2
\end{align*}
\]

The starting keto compound is suitably prepared by interacting a phthalic anhydride with a phenylacetic acid to yield a benzylphthalide derivative, which in turn is reacted with phosphorus and hydroiodic acid to yield the corresponding dibenzyl-o-carboxylic acid. The resulting carboxylic acid derivative is then cyclized and condensed by treatment with phosphorus pentoxide at an elevated temperature or by treatment of the acid halide of the carboxylic acid with a Friedel-Crafts catalyst such as aluminum chloride. This series of reactions is shown by the following equations, wherein \(R_1\) and \(R_2\) have the meanings hereinbefore defined:

\[
\begin{align*}
&\text{R}_1 & &\text{O} & &\text{R}_2 \\
&\text{O} & &\text{CH}=\text{COOH} \\
&\text{R}_1 & &\text{C}=\text{O} \\
&\text{R}_1 & &\text{C}=\text{O} & &\text{R}_2
\end{align*}
\]

Compounds of Formula II, wherein \(X\) represents a \(-\text{CH}=\text{CH}=-\) group, are preferably obtained by conversion of the \(-\text{CH}_2-\text{CH}_2-\) group into the \(-\text{CH}=\text{CH}-\) group by conventional methods such as bromination followed by removal of \(\text{HBr}\).

It is also possible, though not preferred, first to prepare compounds of the formula

\[
\begin{align*}
&\text{R}_1 & &\text{CH}=\text{CH} & &\text{R}_2 \\
&\text{R}_1 & &\text{COOH} & &\text{R}_2 \\
&\text{R}_1 & &\text{CHO} \\
&\text{R}_1 & &\text{C}=\text{O} & &\text{R}_2
\end{align*}
\]

by reacting a compound of the formula

\[
\begin{align*}
&\text{R}_1 & &\text{H} & &\text{C} & &\text{R}_2 \\
&\text{R}_1 & &\text{CH}=\text{COOH} & &\text{R}_2
\end{align*}
\]

with a compound of the formula

\[
\begin{align*}
&\text{R}_1 & &\text{C}=\text{O} & &\text{R}_2 \\
&\text{R}_1 & &\text{C}=\text{O} & &\text{R}_2
\end{align*}
\]

wherein \(R_1\) and \(R_2\) are as hereinbefore defined, and thereafter effecting cyclization by treatment with phosphorus pentoxide at an elevated temperature.

If a substituted phthalic anhydride is used as a reactant in the above series of reactions, the position of the substituent on the resulting benzophthalide will depend on the position of the substituent on the phthalic anhydride. Thus, when ortho-substituted phthalic anhydride is condensed with phenylacetic acid, a mixture of 3- and 7-substituted 3-benzophthalides is obtained. These products are then separated by fractional crystallization and the separated products treated with phosphorus and hydroiodic acid, followed by phosphorous pentoxide, to yield a 4-substituted dibenzo(a,d)-1,4-cycloheptadienone-(5) and a 4-substituted dibenzo(a,d)-1,4-cycloheptadienone-(5), respectively. Where a meta-substituted phthalic anhydride is used, a mixture of 5- and 6-substituted 3-benzophthalides is obtained. These products are then separated by fractional crystallization and then treated with phosphorus and hydroiodic acid followed by phosphorous pentoxide, to yield 2-substituted dibenzo(a,d)-1,4-cycloheptadienone-(5) and 3-substituted dibenzo(a,d)-1,4-cycloheptadienone-(5), respectively.

If a substituted phenylacetic acid is used as a reactant in the above series of reactions, the position of the substituent on the resulting benzophthalide will depend on the position of the substituent on the phenylacetic acid. Thus, if an ortho-substituted phenylacetic acid is condensed with phthalic anhydride and the remaining steps of the process are carried out, a 1-substituted dibenzo(a,d)-1,4-cycloheptadienone-5 is obtained. If a meta-substituted phenylacetic acid is used, a mixture of 2-substituted and 4-substituted dibenzo(a,d)-1,4-cycloheptadienones-5 is prepared, which can be separated by fractional crystallization.

If a para-substituted phenylacetic acid is used, a 3-substituted dibenzo(a,d)-1,4-cycloheptadienone-5 is obtained.

Among the suitable phthalic anhydrides utilizable as initial reagents in these reactions may be mentioned:

phthalic anhydride, halophthalic anhydrides, such as 3- and 4-chlorophthalic anhydride, 3- and 4-bromophthalic anhydride, and 3- and 4-fluorophthalic anhydride, alkylphthalic anhydrides, such as 3- and 4-methyl phthalic anhydride, 3- and 4-ethylphthalic anhydride, 3- and 4-isopropylphthalic anhydride, and 3- and 4-tertiary butylphthalic anhydride.

Among the suitable phenylacetic acids utilizable as initial reagents in these reactions may be mentioned: phenylacetic acid, halo-phenylacetic acids, such as 2-, 3-, and 4-chlorophenylacetic acid, 2-, 3- and 4-bromophenylacetic
acid, and 2-, 3-, 4-fluorophenylacetic acid, alkyl phenylacetic acids, such as 2-, 3-, and 4-methyl phenylacetic acid, 2-, 3- and 4-ethylphenylacetic acid, 2-, 3- and 4-isopropylphenylacetic acid, and 2-, 3-, and 4-tertiary butylphenyl acetic acid.

According to another feature of the invention, a compound having the formula

is reacted with a compound of the general formula Br—Y—Z wherein A and B are different and each represents a halogen (preferably chlorine) atom or the group —OM, in which M is an alkali metal atom, or A represents a halogen atom or a hydroxyl group and B represents a hydroxyl group, and R1, R2, X, Y, and Z, are as hereinbefore defined. The reaction can be carried out in the presence or absence of an inert organic solvent. When A represents a halogen atom and B an OH— group, the reaction can be carried out while using an excess of the amino alcohol or with the addition of another acid-binding substance. Preferably, the chloride of the tricyclic alcohol is reacted with an excess of the aminocalcohol at a temperature of about 140–160 °C, whereby the hydrochloride of the aminocalcohol and the free base of the desired compound are formed.

When A and B both represent an OH— group, both reaction components are preferably heated, either dry or in solution, in the presence of an organic sulfonic acid, e.g., paratoluene sulphonic acid.

When A represents an O-alkali metal group or a halogen atom, the compounds can be produced from the corresponding alcohols in a manner known per se.

The preparation of the acid addition salts from the base suitably takes place by methods known per se, for example, by mixing equivalent quantities of base and acid in an inert organic solvent followed by filtration of the salt.

Typical compounds of the Formula II which may be used for the manufacture of the compounds according to the invention, e.g., dibenzoyl(3,4), 1,4-cycloheptadienone-5 (boiling at 203–204 °C (7 mm Hg) and dibenzyl(90,13), 5-cycloheptatrienone-5 (melting point 90–91 °C) are known from the literature. The first mentioned compound has been described by W. Treibs and H. J. Klinkhammer, Ber. 83, 567–371 (1950), the latter by E. D. Bergmann et al., Bull. Soc. Chim. Fr., 18 684–692 (1951). While the compounds of this invention are produced directly from compounds of the Formula III, these latter compounds are, in effect, intermediates in producing the compounds of the invention from the corresponding ketones of the Formula II.

The terms "methods known per se" as used in the specification means methods heretofore employed or described in the chemical literature.

The following examples illustrate the invention (all temperatures being in centigrade). The first ten examples are directed to the preparation of the ketones of the Formula II and the remaining examples are directed to the preparation of the carbinol intermediates and the final compounds of this invention.

EXAMPLE 1

Dibenzo(a,d)-1,4-cycloheptadienone-5

(e) PREPARATION OF 3-BENZALPHALDIALDE

In a 500 cc. round bottom flask are placed 100 grams of phthalic anhydride, 110 grams of phenylacetic acid and 2.6 grams of fused sodium acetate.

The reaction mixture is heated rapidly in an oil-bath until the internal temperature reaches 230°. During the next three hours the internal temperature is slowly raised to 240°, during which the water formed in the reaction is allowed to distill out. The mixture is then cooled to 90° and the product dissolved in 400 ml. of boiling alcohol, the solution being filtered to separate a small amount of insoluble material and allowed to cool. The benzaldehyde is filtered and washed with cold alcohol. It is sufficiently pure for use in the next step.

(b) PREPARATION OF DIBENZYL-6-CARBONIC ACID

A mixture of 289 g. of benzaldehyde, 113.3 g. of hydrogen iodide (sp. gravity 1.7) and 113.3 g. of red phosphorus is refluxed with stirring for ten hours and the resulting mixture poured into ice water. A red crystalline mass is obtained which is filtered off and dried. The dried solid is extracted with one liter of boiling acetone and filtered while hot. The acetone filtrate is concentrated to about 300 cc. and cooled. One liter of water is added and the mixture is again cooled. The solid which crystallizes is filtered to yield about 243 g. of product, melting at about 115–118°. Recrystallization from aqueous acetone gives the pure product of a constant melting point of about 121–122°.

(c) PREPARATION OF DIBENZO(a,d)-1,4-

CYCLOHEPTADIONONE-5

To 260 cc. of 85% phosphoric acid at 80° is added 377 g. of phosphorus pentoxide. The temperature is kept at 80–90° by slowly adding the phosphorus pentoxide. At the end of the addition, the reaction is kept at 100° for one hour, then heated to 170° C., and 118 g. of dibenzyl-o-carboxylic acid is added portionwise. The mixture is heated at 170° for 2½ hours and then poured with stirring into four liters of ice water and allowed to stand overnight. The dark oil is extracted with 3 x 700 cc. of ether. The ether is washed with sodium bicarbonate and dried over magnesium sulfate. After removal of the ether, the residue is distilled to yield about 81 g. of product, boiling at about 175–180°/3.5 mm., nD30=1.6315.

EXAMPLE 2

1- and 4-chlorodibenz(o,d)-1,4-cycloheptadienone-5

Following the procedure of Example 1, but substituting an equivalent amount of 3-chlorophthalic anhydride for the phthalic anhydride in step a, there is obtained a mixture of 4-chloro-3-benzaldehyde, which yields 1-chloro-

dibenzo(a,d)-1,4-cycloheptadien-5-one and 7-chloro-3-benzaldehyde, which yields 4-chlorodibenzo(a,d)-1,4-cycloheptadien-5-one.

EXAMPLE 3

3-chloro dibenzo(a,d)-1,4-cycloheptadienone-5

Following the procedure of Example 1, but substituting an equivalent amount of 4-chlorophenyl acetic acid for the phenyl acetic acid in step a, 3-chlorodibenzo(a,d)-1,4-cycloheptadienone-5, melting point 55°–57° is obtained. The melting point can be increased to 62.5–63.5° by further crystallization from petroleum ether.

EXAMPLE 4

3-methyl dibenzo(a,d)-1,4-cycloheptadienone-5

Following the procedure of Example 1, but substituting an equivalent amount of 4-methylphenylacetic acid for the phenyl acetic acid in step a, 3-methyl dibenzo(a,d)-1,4-cycloheptadienone-5, boiling point 165–167°/2 mm. is obtained in 81% yield.

EXAMPLE 5

3-bromodibenzo(a,d)-1,4-cycloheptadienone-5

Following the procedure of Example 1, but substituting an equivalent amount of 4-bromophenacylacetic acid for the phenyl acetic acid in step a, 3-bromodibenzo(a,d)-1,4-

cycloheptadienone-5 is obtained in 53% yield. It has a melting point of 80–81° after crystallization from petroleum ether (boiling range 60–80°).
EXAMPLE 6
3-tertiary butyl dibenzo(a,d)-1,4-cycloheptadienone-5
Following the procedure of Example 1, but substituting an equivalent amount of 4-tertiary butylphenylacetic acid for the phenylacetic acid in step a, 3-tertiary butyl dibenzo(a,d)-1,4-cycloheptadienone-5 is obtained in 83% yield, boiling point 160°–162°/1 mm.

4-tertiary butylphenylacetic acid of melting point 79.5°–80.5° is prepared by converting tertiary butyl benzene into 4-tertiary butylbenzyl chloride. This compound in turn is converted into the corresponding cyanide as described by Skinner et al., J. Am. Chem. Soc. 73, 2230 (1951). The nitrite is saponified by treatment under reflux with potassium hydroxide in an aqueous ethanol solution.

EXAMPLE 7
1-methyl dibenzo(a,d)-1,4-cycloheptadienone-5
Following the procedure of Example 1, but substituting an equivalent amount of 2-phenylbenzylacetic acid for the phenylacetic acid in step a, 1-methyl dibenzo(a,d)-1,4-cycloheptadienone-5, of melting point 67°–68°, is obtained in 83% yield.

EXAMPLE 8
3-methyl dibenzo(a,e)-1,3,5-cycloheptatrienone-5
In a 100 ml. flask a mixture of 6.7 g. of 3-methyl dibenzo(a,d)-1,4-cycloheptadienone-5, 5.3 g. of N-bromo-succinimide and 0.1 g. of benzyldiethylperoxide is boiled for 2 hours in 25 ml. of carbon tetrachloride under reflux cooling. After cooling, the succinimide is removed by filtration, whereupon the solvents are removed by evaporation. The resulting monobromo compound can be recrystallized from petroleum ether (boiling range 60°–80°). 6.4 g. of the brominated product are heated with 20 ml. of pyridine and the mixture is poured into 250 ml. of 2 N hydrochloric acid. The precipitate is filtered and crystallized from petroleum ether (boiling range 60°–80°). There is obtained 3-methyl dibenzo(a,e)-1,3,5-cycloheptatrienone-5, melting point 80°–81°, in 78% yield.

EXAMPLE 9
3-bromodibenzo(a,e)-1,3,5-cycloheptatrienone-5
Following the procedure of Example 8, but substituting an equivalent amount of 3-bromodibenzo(a,d)-1,4-cycloheptadienone-5 for the 3-methyl dibenzo(a,d)-1,4-cycloheptadienone - 5, 3 - bromodibenzo(a,e), 1,3,5-cycloheptatrienone - 5, melting point 111°–112°, is obtained in 74% yield.

EXAMPLE 10
Dibenzo(a,e)-1,3,5-cycloheptatrienone-5
Following the procedure of Example 8, but substituting an equivalent amount of dibenzo(a,d)-1,4-cycloheptadienone-5 for the 3-methyl dibenzo(a,d)-1,4-cycloheptadienone - 5, dibenzo(a,e), 1,3,5-cycloheptatrienone - 5, melting point 89°, is obtained.

EXAMPLE 11
Dibenzo(a,d)-1,4-cycloheptadienol-5
To a solution of 50 g. of dibenzo(a,d)-1,4-cycloheptadienone-5 in 500 ml. of methanol is added a solution of 9.1 g. of sodium borohydride in 100 ml. of water at room temperature. The temperature is not controlled and rises to 46°. The resulting solution is refluxed for one hour. The pH adjusted to 4.0 with acetic acid and then the methanol is distilled off. A light yellow oil precipitates which is extracted with ether, the ether is dried over magnesium sulphate, filtered and allowed to evaporate at room temperature. The residue is triturated with a small amount of hexane to yield about 43 g. of a product melting at about 80°–85°. Recrystallization from hexane yields a pure compound, of constant melting point of about 89°–90°.

EXAMPLE 12
3-chlorodibenzo(a,d)-1,4-cycloheptadienol-5
1.21 g. of 3-chlorodibenzo(a,d) - 1,4 - cycloheptadienone-5 are dissolved in 190 ml. of ethanol (96%). The solution is boiled under reflux for 20 hours with 2.2 kg. of 0.5% sodium amalgam, and is then poured into ice-water-acidified with 3 N HCl acid. The precipitate formed is filtered off, dried and crystallized from benzene. 9.1 g. of 3-chlorodibenzo(a,d)-1,4-cycloheptadienol-5 are obtained. The melting point is 117°–118° and the yield 75%.

EXAMPLE 13
3-methyl dibenzo(a,e)-1,3,5-cycloheptatrienol-5
An ethereal solution of 11.5 g. of 3-methyl dibenzo(a,e) 1,3,5-cycloheptatrienone-5 is added to a solution of 1.0 g. of lithiumaluminumhydride in 200 ml. of ether. The mixture is then refluxed for 4 hours, after which it is decomposed by addition of moist ether and aqueous acetic acid. The ethereal layer is washed with water, dilute sodium hydroxide solution, and again with water, and subsequently dried on sodium sulphate. Evaporation of the solvent yields 8.5 g. of 3-methyl dibenzo(a,e)-1,3,5-cycloheptatrienol-5, melting at 118°–119.5° after crystallization from ligroin (boiling range 60°–80°).

EXAMPLE 14
3-methyl dibenzo(a,d)-1,4-cycloheptadienol-5
Following the procedure of Example 12, but substituting an equivalent amount of 3-methyl dibenzo(a,d) - 1,4 - cycloheptadienone - 5 for the 3-chlorodibenzo(a,d) - 1,4 - cycloheptadienone - 5, 3 - methyl dibenzo(a,d) - 1,4 - cycloheptadienol - 5, melting point 124°–125.5°, is obtained in 87% yield.

EXAMPLE 15
Dibenzo(a,e)-1,3,5-cycloheptatrienol-5
Following the procedure of Example 11, but substituting an equivalent amount of dibenzo(a,e)-1,3,5-cycloheptatrienone - 5 for the dibenzo(a,d) - 1,4 - cycloheptadienone - 5, dibenzo(a,e)-1,3,5-cycloheptatrienol-5, melting point 119°–120°, is obtained.

EXAMPLE 16
1-methyl dibenzo(a,d)-1,4-cycloheptadienol-5
Following the procedure of Example 13, but substituting an equivalent amount of 1-methyl dibenzo(a,d)-1,4-cycloheptadienone-5 for the 3-methyl dibenzo(a,e)-1,3,5-cycloheptatrienone-5, 1-methyl dibenzo(a,d)-1,4-cycloheptadienol-5, melting point 97°–100°, is obtained in 90% yield.

Similarly, by substituting an equivalent amount of each of the following substituted dibenzo(a,d)-1,4-cycloheptadienone-5 compounds for the 1-methyl dibenzo(a,d)-1,4-cycloheptadienone-5 in Example 16, the indicated substituted dibenzo(a,d)-1,4-cycloheptadienol-5 is formed.

Substituted dibenzo(a,d)-1,4-
cycloheptadienol-5:

<table>
<thead>
<tr>
<th>Product</th>
<th>3-tertiary butyl</th>
<th>3-tertiary butyl</th>
<th>1-chloro</th>
<th>1-chloro</th>
</tr>
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<td>3-bromo</td>
<td>3-bromo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-chloro</td>
<td>1-chloro</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EXAMPLE 17
2-(dibenzo(a,d)-1,4-cycloheptadien-5-yl) N,N-di-methylglycine, salt with maleic acid
PREPARATION OF 2-(DIBENZO(a,d)-1,4-CYCLOHEPTADIEN-5-YL)OXY)-N,N-DIMETHYL ETHYLAMINE, SALT WITH MALEIC ACID
(a) 63.1 g. of dibenzo(a,d)-1,4-cycloheptadienol-5 is dissolved in benzene and hydrogen chloride is then passed through the solution for half an hour.
The solution is dried with calcium chloride and, after filtration, evaporated to dryness to remove all hydrogen chloride.

The residue is dissolved in 350 ml of xylene and added to a boiling solution of 33.4 g of dimethylaminoethanol in 180 ml of xylene. The reaction mixture is refluxed for 3 hours, cooled, and the separated dimethylaminoethanol hydrochloride filtered off. The filtrate is washed with water, dried and the solvent evaporated to yield crude 2-(dibenz[a,d]-1,4-cycloheptadien-5-yl oxy)-N,N-dimethylamine, which is purified by distillation under high vacuum.

**PREPARATION OF THE MALEIC ACID SALT**

(b) The maleinate is prepared by solution of the base in ether and addition of maleic acid in ether until no further precipitate is formed. Melting point of the maleinate: 118–120°. Yield 65%.

**EXAMPLE 18**

3-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N,N-dimethylpropylamine, salt with oxalic acid

Following the procedure of Example 17, but substituting an equivalent amount of 3-dimethylaminopropanol for the dimethylaminoethanol in step a, 3-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N,N-dimethylpropylamine is prepared. The oxalic acid salt, melting at 135–136.5°, is obtained in 50% yield by following the procedure of Example 17, step b but substituting oxalic acid for the maleic acid.

**EXAMPLE 19**

4-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N,N-dimethylpentylamine, salt with oxalic acid

Following the procedure of Example 17, but substituting an equivalent amount of 5-diethylaminopentan-2-ol for the dimethylaminoethanol in step a, 4-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-NN-dimethylpentylamine is prepared. The oxalic acid salt, melting at 148–149°, is obtained in 43% yield by following the procedure of Example 17, step b, but substituting oxalic acid for the maleic acid.

**EXAMPLE 20**

5-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N,N-dimethyl-3-oxapentylamine, salt with oxalic acid

Following the procedure of Example 17, but substituting an equivalent amount of dimethylaminooxethanol for the dimethylaminoethanol in step a, 5-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-NN-dimethyl-3-oxapentylamine is prepared. The oxalic acid salt, melting at 123–124°, is obtained in 69% yield by following the procedure of Example 17, step b, but substituting oxalic acid for the maleic acid.

**EXAMPLE 21**

2-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N-pyrrolidinylethylamine, salt with oxalic acid

Following the procedure of Example 17, but substituting an equivalent amount of N,N-dihydroxethylpyrrolidine for the dimethylaminoethanol in step a, 2-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N-pyrrolidinylethylamine is prepared. The oxalic acid salt, melting at 137–139°, is obtained in 45% yield by following the procedure of Example 17, step b, but substituting oxalic acid for the maleic acid.

**EXAMPLE 22**

2-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N-morpholinylethylamine salt with oxalic acid

Following the procedure of Example 17, but substituting an equivalent amount of N,N-dihydroxethylmorpholine for the dimethylaminoethanol in step a, 2-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N-morpholinylethylamine is prepared. The oxalic acid salt, melting at 142–143°, is obtained in 55% yield by following the procedure of Example 17, step b, but substituting oxalic acid for the maleic acid.

**EXAMPLE 23**

2-(dibenzo[a,e]-1,3,5-cycloheptatrien-5-yl oxy)-N,N-dimethylamylamine, salt with maleic acid

Following the procedure of Example 17, but substituting an equivalent amount of dibenzo[a,e]-1,3,5-cycloheptatrien-5-yl oxy)-N,N-dimethylamylamine, melting point 125–128°, is prepared in 57% yield.

**EXAMPLE 24**

2-(3-methyl dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N,N-dimethylamylamine, salt with maleic acid

Following the procedure of Example 17, but substituting an equivalent amount of 3-methyl dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N,N-dimethylamylamine, melting point 124–125°, is obtained in 38% yield.

**EXAMPLE 25**

2-(3-chlorodibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N,N-dimethylamylamine, salt with maleic acid

Following the procedure of Example 17, but substituting an equivalent amount of 3-chlorodibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N,N-dimethylamylamine, melting point 131–132°, is obtained in 42% yield.

**EXAMPLE 26**

5-(3-chlorodibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N,N-dimethyl-3-oxapentylamine, salt with oxalic acid

Following the procedure of Example 17, but substituting an equivalent amount of 3-chlorodibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N,N-dimethyl-3-oxapentylamine is prepared. The oxalic acid salt, melting at 124–126°, is obtained in 20% yield by following the procedure of Example 17, step b, but substituting oxalic acid for the maleic acid.

**EXAMPLE 27**

2-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N-monooxyethylamine

Following the procedure of Example 17, but substituting an equivalent amount of monooxyethylamine for the dimethylaminooxethanol in step a, 2-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N-monooxyethylamine is prepared.

**EXAMPLE 28**

3-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N-piperidinopropylamine, salt with hydrochloric acid

Following the procedure of Example 17, but substituting an equivalent amount of N,N-piperidinopropylamine for the dimethylaminooxethanol in step a and an equivalent amount of hydrochloric acid for the maleic acid in step b, 3-(dibenzo[a,d]-1,4-cycloheptadien-5-yl oxy)-N-piperidinopropylamine, hydrochloric acid salt, is formed.
EXAMPLE 29

$N_1(3\text{-imidazo(a,d)}-1,4\text{-cycloheptadien}-5\text{-yloxy})\text{-propyl}-N^4\text{-methylpiperazine, salt with hydrochloric acid}

(a) PREPARATION OF $N_1(3\text{-imidazo(a,d)}-1,4\text{-cycloheptadien}-5\text{-yloxy})\text{-propyl}-N^4\text{-methylpiperazine}

To a suspension of 4 g. of sodamide in 300 ml. of dry toluene is added 21 g. of dibenzo(a,d)-1,4-cycloheptadien-5-yl esters. The mixture is warmed gently on a steam bath for two hours. It is then cooled to 20° and a solution of 20 g. of 3-(N^4-methylpiperazine)-propyl chloride in 100 ml. of dry toluene is added dropwise with vigorous stirring. The reaction mixture is then heated to gentle reflux for five hours and allowed to cool to room temperature.

The precipitated sodium chloride is removed by filtration and the is then removed by distillation under reduced pressure leaving a residue of N_1(3-dibenz(a,d)-1,4-cycloheptadien-5-yl)-propyl-N^4-methylpiperazine.

(b) PREPARATION OF THE DIHYDROCHLORIDE SALT

To a solution of 3.5 g. of N_1(3-dibenz(a,d)-1,4-cycloheptadien-5-yl)-propyl-N^4-methylpiperazine in 20 ml. of alcohol there is added an ethereal solution of hydrogen chloride to a pH of 2.

Anhydrous ether is added to complete the precipitation of the dihydrochloride. The solid is recovered by filtration and crystallized from a mixture of acetone and ether.

Similarly, by substituting piperazine for the N-methylpiperazine in Example 29, N(3-(dibenz(a,d)-1,4-cycloheptadien-5-yl)-propyl)-piperazine, hydrochloric acid salt, is formed.

EXAMPLE 30

5 grams of 3-chlorodibenzo(a,d)-1,4-cycloheptadien-5-yl are dissolved in 20 mls. of benzene, whereupon dry hydrochloric acid gas is introduced. The initial turbidity due to the formation of water disappears when the reaction is completed. The water formed is removed by drying with anhydrous calcium chloride and filtration over a dry filter and the excess of dissolved hydrochloric acid gas is expelled with a stream of dry air. After evaporation of the benzene the corresponding chloride remains.

A mixture of 1 mol of this chloride is heated with 2 mols of dimethylamino ethanol to 140-160° C., the hydrochloride of the amino alcohol and the free amino alkyl ether base being produced.

After cooling the hydrochloride is separated in the 3,827,716

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bottom and the base being taken up in ether. The base if necessary after intermediate purification by fractionated distillation is treated in an ether solution with an alcohol ether solution of an acid, e.g. maleic acid. Yield 40%. Melting point of the maleinate 131-132° C.

The following table lists some of the compounds prepared in accordance with the foregoing examples.

<table>
<thead>
<tr>
<th>R_1</th>
<th>R_2</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Yield, percent</th>
<th>Salt</th>
<th>Melting point of salt, °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>CH₂CH₃</td>
<td>CH₂CH₃</td>
<td>N(CH₃)₂</td>
<td>61</td>
<td>Maleinate</td>
<td>118-120</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>H</td>
<td>CH₂CH₃</td>
<td>CH₂CH₃</td>
<td>N(CH₃)₂</td>
<td>61</td>
<td>Maleinate</td>
<td>124-125</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>CH₂CH₃</td>
<td>CH₂CH₂CH₃</td>
<td>N(CH₃)₂</td>
<td>60</td>
<td>Oxidate</td>
<td>125-124</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>CH₂CH₃</td>
<td>CH₂CH₂CH₃</td>
<td>N(CH₃)₂</td>
<td>67</td>
<td>Maleinate</td>
<td>129-129</td>
</tr>
</tbody>
</table>

As previously indicated, the product compounds of this invention are administered in conventional manner, either orally or parenterally, in suitable dosage quantities.

In general, a typical dosage unit contains 5 to 25 mg. of the active compound and 95 to 125 mg. of a pharmaceutically-acceptable inert carrier. The following is a typical example of compositions containing the product compounds of the invention.

EXAMPLE 31

A mixture of the following composition is prepared:

<table>
<thead>
<tr>
<th>G.</th>
<th>Lactose</th>
<th>Oxidized starch</th>
<th>Talcum</th>
<th>Magnesium stearate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>(dibenzo(a,d)-1,4-cycloheptadien-5-yloxy)-N,N-dimethylamino maleinate</td>
<td>10</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

This mixture is made into tablets of 100 mg. If desired, the tablet may be provided with a coating, in conventional manner.

I claim:

1. 2-(dibenzo(a,d)-1,4-cycloheptadien-5-yloxy)-N,N-dimethylamino maleinate.
2. A non-toxic acid addition salt of 2-(dibenzo(a,d)-1,4-cycloheptadien-5-yloxy)-N,N-dimethylamino maleinate.
3. 2-(dibenzo(a,d)-1,4-cycloheptadien-5-yloxy)-N,N-dimethylamino maleinate.
4. A non-toxic acid addition salt of 2-(dibenzo(a,d)-1,4-cycloheptadien-5-yloxy)-N,N-dimethylamino maleinate.
5. 2-(dibenzo(a,d)-1,4-cycloheptadien-5-yloxy)-N,N-dimethylamino maleinate.
6. A non-toxic acid addition salt of 2-(dibenzo(a,d)-1,4-cycloheptadien-5-yloxy)-N,N-dimethylamino maleinate.

References Cited by the Examiner

UNITED STATES PATENTS
2,948,732 8/1960 Schindler et al. 260—294.3
3,014,911 12/1961 Engelhardt 260—294.7

OTHER REFERENCES

WALTER A. MODANE, Primary Examiner.
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