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References Cited

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ABSTRACT


21 Claims, No Drawings
The acid addition salts are prepared by reacting the base form of the compound of formula I with either one equivalent or preferably an excess of the appropriate acid in an organic solvent, such as ether or an ethanol-ether mixture. These salts, when administered to mammals, possess the same pharmacologic activities as the corresponding bases. For many purposes it is preferable to administer the salts rather than the base compound. Among the acid addition salts suitable for this purpose are salts such as the sulfate, phosphate, oxalate, tartrate, maleate, citrate, and hydrochloride. Both the base compounds and the above acid addition salts have the distinct advantage of possessing a relatively low order of toxicity.

The useful central nervous system depressant activity and the anticonvulsant activity of the heterocyclic compounds of formula I and their acid addition salts with pharmaceutically acceptable acids may be demonstrated in standard pharmacologic tests, such as, for example, the tests described by R.A. Turner in "Screening Methods in Pharmacology," Academic Press, New York and London, 1965, pp. 69-99 and 164-172, respectively.

When the heterocyclic compounds of this invention are used as central nervous system depressants or anticonvulsant agents in warm-blooded mammals, e.g., rats and mice, alone or in combination with pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice. For example, they may be administered orally in solid form containing such excipients as starch, milk sugar, certain types of clay and so forth. They may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration they may be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

The dosage of the present therapeutic agents will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects and preferably at a level that is in a range of from about 0.1 mg to about 200 mg per kilo per day, although as aforementioned variations will occur. However, a dosage level that is in the range of from about 10 mg to about 100 mg per kilo per day is most desirably employed in order to achieve effective results.

The heterocyclic compounds of this invention may be prepared readily from the key intermediate of formula II:
This key intermediate may be synthesized by one of the following two processes:

In the first process, illustrated by FIG. 1, 10-methoxy-5H-dibenzo[a,d]cycloheptene-5-carboxamide (III), described by M.A. Davis, T.A. Dobson and J.M. Jordan, Can. J. Chem., 47, 2827 (1969), is used as the starting material.

![Diagram of the process](image)

The starting material of formula III on treatment with sodium hypochlorite in methanol gives the carbamate of formula IV. Subsequent treatment of the latter compound with a base, for example, sodium hydroxide, in the presence of water and an inert solvent, for example, dioxane, ethanol or a mixture thereof, affords the key intermediate of formula II.

In the above process a by-product is obtained in the first step, III → IV. In addition to the desired carbamate of formula IV, 11,12-dichloro-10,11-dihydro-10-methoxy-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one (V) is also obtained.

![Diagram of the formation of by-product](image)

The formation of the byproduct of formula V may be suppressed by very slow addition of the reagent, sodium hypochlorite, to the reaction mixture. This byproduct has useful antimicrobial activity and exhibits activity against a number of gram-positive and gram-negative microorganisms, such as, *Staphylococcus pyogenes*, both penicillin sensitive and penicillin resistant, *Sarcina lutea*, *Streptococcus fecalis*, *Escherichia coli*, *Aerobacter aerogenes*, *Salmonella pullorum*, *Proteus mirabilis* and *Proteus vulgaris* and has antifungal activity against a number of pathogenic fungi such as, *Candida albicans*, *Microsporum gypseum* and *Trichophyton granulosum*, in standard tests for antibacterial and antifungal activity, such as those described in "Antiseptics, Disinfectants, Fungicides and Sterilization," G.F. Reddish, Ed., 2nd ed., Lea and Febiger, Philadelphia, 1957 or by D.C. Grove and W.A. Randall in "Assay Methods of Antibiotics," Med. Encycl. Inc. New York 1955.

When this byproduct of formula V is employed as an antibiotic or antifungal agent in warm-blooded animals, e.g. rats, alone or in combination with pharmacologically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice. For example, it may be administered orally in solid form containing such excipients as starch, milk sugar, certain types of clay and so forth. It may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration it may be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

The dosage of the byproduct of formula V will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, this byproduct is most desirably administered by a concentration level that will generally afford effective results without causing any harmful or deleterious side effects and preferably at a level that is in a range of from about 0.1 mg to about 100 mg per kilo per day, although as aforementioned variations will occur. However, a dosage level that is in the range of from about 0.5 mg to about 50 mg per kilo per day is most desirably employed in order to achieve effective results.

In addition, the agent may be employed topically. For topical application it may be formulated in the form of solutions, creams, or lotions in pharmaceutically acceptable vehicles containing 0.1 – 5 percent, preferably, 2 percent of the agent and may be administered topically to the infected area of the skin.

The second process for the preparation of the key intermediate of formula II is illustrated by FIG. 2.

![Diagram of second process](image)

In this process the starting material, the epoxyketone of formula VI described by J. Rigaudy and L. Nedelec, Bull. Soc. Chim. France, 400 (1960), is reduced by hydrogenation in the presence of a noble metal catalyst, for example, palladium, to give the hydroxy ketone (VII). This latter compound is oxidized with hexavalent chromium ion, for example, chromic acid in sulfuric acid and water, to yield the diketone (VIII), which may be converted readily to the enol ether (IX) on treatment with methanol and an acid catalyst, for example, hydrochloric acid. Subsequent treatment of said enol ether with hydrox-
amine hydrochloride in pyridine gives the oxime (X) which may be reduced with Raney nickel in the presence of excess base, for example, sodium hydroxide, to afford the desired key intermediate of formula II.

Although the key intermediate of formula II is a preferred intermediate for preparing the heterocyclic compounds of this invention, an alternate intermediate, 5-amino-5,11-dihydro-10H-dibenzo[a,d]cyclohepten-10-one (XI), may also be used for their preparation.

This alternate intermediate may be prepared by one of the two following processes:

In the first process, illustrated by FIG. 3, the epoxymide of formula XII,

\[
\text{CONH}_2 \rightarrow \text{NHCOOCH}_3
\]

XII.

XIII.

XIV.

XV.

XVI.

described by T.A. Dobson, M.A. Davis, A.M. Hartung and J. Manson, Can. J. Chem., 46, 2843 (1968), is treated with sodium hypochlorite in methanol to give the carbamate (XIII), which when treated with hydrogen in the presence of a catalyst, for example, palladium on charcoal, affords the hydroxy carbamate of formula XIV. Oxidation of the latter compound by hexavalent chromium ion, for example, chromic acid in the presence of sulfuric acid and water, gives the ketocarbamate of formula XV. This ketocarbamate may also be obtained by acid hydrolysis, for example, with 15–20 percent aqueous hydrochloric acid, of the carbamate of formula IV, described above. The ketocarbamate (XV) may now be converted to the desired alternate intermediate of formula XI by alkaline hydrolysis, for example, by aqueous sodium hydroxide.

As experienced previously in the first process for the preparation of the key intermediate (II), treatment of the starting material of formula XII of the present process with sodium hypochlorite also results in a byproduct. Thus, in addition to the desired carbamate (XIII), N,N-dichloro-10,11-epoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-amine (XVI), is also obtained as a byproduct.

The formation of this byproduct during this reaction may be suppressed by slow addition of the reagent, sodium hypochlorite, to the reaction mixture. This byproduct has the useful antimicrobial activity described above for byproduct V and may be used as a antimicrobial agent in the same manner as byproduct V.

The second process for the preparation of the alternate intermediate of formula XI is illustrated by FIG. 4.

In this second process, the carbamate (XIII), described above, is heated with diethylamine, in an inert solvent, for example toluene, to yield the hydroxyamine (XVII). The latter compound, after treatment with an organic peracid in an inert solvent, for example, m-chloroperoxybenzoic acid in chloroform, yields the corresponding N-oxide of the hydroxyamine (XVIII) which loses the elements of diethylamine N-oxide upon treatment with aqueous alkali to give the ketocarbamate of formula XV. Conversion of the latter compound to the desired alternate intermediate (XI) is then effected in the same manner as described for the preceding process.

The essential ring system of the heterocyclic compounds of this invention may be formed by allowing either the key intermediate (II) or the alternate intermediate (XI) to react with an appropriate aldehyde, R'=CHO in which R' is as defined above, according to the conditions of the Mannich reaction, see F.F. Blicke, Organic Reactions, 1, 303 (1942). In this manner the 11-keto compounds of formula I in which R1 and R2 together represent a ketonic oxygen, R3 represents hydrogen and R4 is as defined above, are obtained by an intramolecular Mannich reaction.

More specifically the above 11-keto compounds are readily obtained by allowing said intermediate (II) or (XI) to react with at least one equivalent, preferably
of a basic condensing agent, for example, sodium hydride in an inert solvent, for example, dimethylformamide to give the corresponding 1-lower alkoxy-N-acetyl derivatives. The latter compounds yields the desired 11-lower alkoxy compounds of formula I in which R1 and R2 are both hydrogen, R3 is lower alkoxy and R4 is as defined originally on hydrolysis with an aqueous solution of excess alkali metal hydroxide, for example, sodium or potassium hydroxide, preferably with an inert cosolvent, for example, ethanol.

The 11-lower alkoxy compounds of formula I in which R1 is hydrogen, R2 is a lower alkoxy, R2 is one of the organic radicals as defined in the first instance and R3 is as defined in the first instance may be prepared by treatment of the 11-lower alkoxy compound of formula I in which R1 and R2 are both hydrogen, R2 is lower alkoxy and R4 is as defined in the first instance, described above, with an appropriate organic halide of formula R3X in which R3 is one of the organic radicals as defined in the first instance for R3 X is a chlorine, bromine or iodine atom, in the presence of a basic condensing agent, for example, sodium hydride, in an inert solvent for example, benzene. The 11-lower alkoxy compounds of formula I in which R1 and R2 represent together a ketonic oxygen and R3 and R4 are as defined in the first instance may be reduced to their corresponding 11-hydroxy derivatives, compounds of formula I in which R1 represents hydrogen, R2 represents a hydroxyl and R3 and R4 are as defined in the first instance, by a variety of known methods for converting a carbonyl group to a carbinal group; for example, see O.H. Wheeler in "The Chemistry of the Carboxyl Group", S. Patali, Ed., Interscience Publishers, London, 1966, pp. 507-566. Preferred reagents for this reaction are lithium aluminium hydride and sodium borohydride.

The 11-esterified hydroxyl compounds of formula I in which R1 and R2 are hydrogen, R2 is an esterified hydroxyl containing two to four carbon atoms, R3 is as defined in the first instance, may be prepared by treating the corresponding 11-hydroxy derivatives in which R3 is hydrogen, described above, with an excess of the appropriate aliphatic acid, for example, acetic, propionic or butyric acid in the presence of at least one equivalent of a mineral acid, for example, 5.0 equivalents of hydrobromic acid.

The 11-esterified hydroxyl compounds of formula I in which R1 is hydrogen, R2 is an esterified hydroxyl containing two to four carbon atoms, R3 is one of the organic radicals as defined in the first instance, and R4 is as defined originally, may be prepared by treating the corresponding 11-hydroxy derivatives with the appropriate lower acyl anhydride, for example, acetic anhydride, propionic anhydride or butyric anhydride, in pyridine solution.

The 11-lower alkoxy compounds of formula I in which R1 is hydrogen, R2 is a lower alkoxy, R3 is hydrogen and R4 is as defined in the first instance may be prepared by treating the corresponding 11-keto compounds of formula I in which R3 is hydrogen, described above, with a lower aliphatic acyl halide, e.g. acetyl chloride, in pyridine solution to afford the corresponding 11-keto-N-acetyl derivatives which on subsequent treatment with sodium borohydride in an inert solvent, for example, tetrahydrofuran, afford the corresponding 11-hydroxy-N-acetyl derivatives of formula I. The latter compounds may then be treated with a lower alkyl chloride, bromide or iodide in the present
Alternatively, some of the heterocyclic compounds of this invention may be prepared conveniently by a different approach. This approach utilizes the amide intermediate, 10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one (XXI, R = H) or its corresponding N-substituted derivatives which may be prepared by the process illustrated by FIG. 5.

According to the process of FIG. 5, a mixture of 10-bromo-5H-dibenzo[a,d]cyclohepten-5-one (XVIII) described by W. Treibs and H.J. Klinkhammer, Chem. Bev., 84, 671 (1951), and a molar excess of cuprous cyanide optionally diluted with quinoline is heated at a temperature within the range of 150°-220°C for a period of 0.5 to 3 hours. The reaction mixture is partitioned between a suitable water immiscible solvent such as, for example, chloroform or methylene chloride and an aqueous mineral acid. Evaporation of the organic phase leaves 10-cyano-5H-dibenzo[a,d]cyclohepten-5-one (XIX).

In its turn a mixture of the latter compound and a molar excess of sodium or potassium or lithium borohydride and a solvent, for example, a lower alkanol containing from one to four carbon atoms or dimethyl sulfoxide is kept at a temperature within the range of 20°-100°C for a period of up to two days. The excess hydride is destroyed with a dilute mineral acid.

In its turn, the latter compound is treated with either a molar excess of aqueous ammonium hydrosulfate or a molar excess of an aqueous solution or suspension of a primary amine of formula R^2—NH_2, wherein R^2 is an organic group as defined in the first instance, at a temperature within the range 150°-230°C for a period of between 6 to 24 hours to give, after removal of the excess amine, a compound of formula XXI wherein R^3 is as defined in the first instance.

Optionally, the compounds of formula XXI wherein R^3 is limited to represent hydrogen may be alkylated with an organic halide of formula R^3—X wherein R^3 is an organic group as defined in the first instance and X represents a chlorine, bromine or iodine atom to give a compound of formula XXI wherein R^3 is an organic group as defined in the first instance. This alkylation is carried out in an inert solvent such as, for example, dioxane or benzene in the presence of a basic condensing agent, for example, sodium hydride.

The compounds of formula XXI in which R^3 is an organic radical as defined in the first instance are used to prepare certain compounds of formula I by the processes illustrated by FIG. 6.

Accordingly the processes illustrated by FIG. 6 are employed as follows:

Treatment of the compounds of formula XXI, in which R^3 is an organic radical as defined in the first instance, excluding alkynyl with a N-chloro- or N-bromo-amide or -imide, e.g. N-bromosuccinimide in an inert solvent, for example, carbon tetrachloride, yields the 11-bromo compounds of formula XXII. Preferably, this reaction is performed in the presence of a catalytic amount of an organic peroxide, preferably, benzoyl peroxide at temperatures ranging from 10° to 50°C for 1 to 5 hours. The 11-bromo compounds thus obtained may be employed in the first instance to prepare the alkoxy compounds of formula XXIII in which R^3 represents methyl, ethyl or propyl. When employed in this manner the 11-bromo compounds are allowed to react with a lower alkoxy ion. Suitable conditions for this reaction include mixing a solution of the 11-bromo compounds in lower alkanol, preferably methanol, with a solution of an alkali metal lower alkoxy in a lower alkanol, preferably sodium methoxide in methanol, and allowing the mixture to react at temperatures from 20° to the boiling point of the mixture from 6 hours to 2 or 3 days. The 11-alkoxy compound of formula XXIII in which R^3 is an organic radical as defined above excluding alkynyl and R^3 represents methyl, ethyl or propyl, thus obtained, are reduced readily by suitable reducing agents, preferably lithium aluminum hydride in an inert solvent, for example, tetrahydrofuran to yield those compounds of formula I in which R^1 and R^4 are both hydrogen, R^2 is lower alkoxy and R^3 is an organic radical as defined in the first instance excluding alkynyl.

In the second instance the 11-bromo compounds of formula XXIII in which R^3 is an organic radical as
II

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EXAMPLE 2

10-Methoxy-5H-Dibenzo[a,d]Cyclopehtene-5-amino
(II)

A solution of 10-methoxy-5H-dibenzo[a,d]cycloheptene-5-carboxylic acid methyl ester (IV, 4.2 g, 0.014 mole), described in Example 1, and sodium hydroxide (5.25 g) in a mixture of water (40 ml), dioxane (75 ml) and ethanol (112 ml) is heated under reflux for 18 hours. The organic solvents are removed under reduced pressure and the product is extracted into chloroform, washed with water and dired. Chromatography on alumina (neutral, activity II) with benzene gives the title compound, m.p. 101°-102°C; $\gamma_{\text{CH}}$ 3370, 3300 cm$^{-1}$ (NH$_2$); $\lambda_{\text{max}}$ $\text{E}_{\text{max}}$ 284 mp ($\varepsilon = 11,510$; nmr (CDCl$_3$) 2.50 (8-H, aromatic, m); 3.63 (1-H at C-11, s); 5.45 (1-H at C-5, s); 6.07 (OCH$_3$, s); 8.15 (NH$_2$, br. s); on addition of D$_2$O, 2 exchanged protons (8.15) are observed. EXAMPLE 3

11,12-Dichloro-10,11-Dihydro-10-Methoxy-10,5-(fiminomethano)-5H-Dibenzo[a,d]Cyclopehtene-13-one (V)

5 percent Sodium hypochlorite solution (63 ml) is added in one portion to a stirred solution of 10-methoxy-5H-dibenzo[a,d]cyclopehtene-5-carboxamide (III, 7.0 g, 0.028 mole) in dioxane (112 ml) and methanol (350 ml). The warm solution is cooled and then stirred at room temperature for 1 hour. Dilution with water and filtration give the crude title compound which is chromatographed on silica gel. Elution with benzene followed by crystallization from chloroform-hexane gives the pure title compound, m.p. 195°-197°C; $\gamma_{\text{max}}$ $\text{C}_{18} \text{H}_{13} 1,630$ cm$^{-1}$ (amide); $\lambda_{\text{max}}$ $\text{E}_{\text{max}}$ 264 mp ($\varepsilon = 457$; nmr (DMSO) $\tau$: 2.50 (8-H, aromatic, m); 3.80 (1-H at C-5, s); 4.62 (1-H at C-10, s); 6.25 (OCH$_3$, s).

EXAMPLE 4

10,11-Dihydro-10-Hydroxy-5H-Dibenzo[a,d]
Cyclopehtene-5-one (VII)

10,11-Dihydro-10,11-epoxy-5H-dibenzo[a,d]
cyclopehtene-5-one (VI, 22.2 g, 0.1 mole), dissolved in ethanol, is hydrogenated at atmospheric pressure and room temperature using 10 percent palladium on charcoal catalyst (2.2 g). After 3 hours the mixture is filtered and the filtrate is concentrated to dryness. Thin layer chromatography (TLC) reveals two spots (silica gel, 10 percent isopropyl alcohol-benzene). The residue is dissolved in benzene and poured onto a column of silica gel (300 g). Elution of the column with 5 percent ethyl-acetate-benzene yields the title compound (the pure polar spot in above TLC system) in fractions 7 to 15 when 250 ml fractions are taken. This product, which is suitable for use in the following Example, gives a white solid, m.p. 85°-87°C, $\lambda_{\text{max}}$ $\text{E}_{\text{max}}$ 268 mp ($\varepsilon = 13,300$), on trituration with hexane.

EXAMPLE 5

5H-Dibenzo[a,d]Cyclopehtene-5,10(11)H-dione
(VIII)

To a solution of 10,11-dihydro-10-hydroxy-5H-dibenzo[a,d]cyclopehtene-5-one (VII, 29.5 g, 0.132 mole), prepared as described in Example 4, in acetone

EXAMPLE 1

10-Methoxy-5H-Dibenzo[a,d]Cyclopehtene-5-
Carboxamic Acid Methyl Ester (IV)

5 percent Sodium hypochlorite solution (45 ml) is added at room temperature, over 2 hours to a solution of 10-methoxy-5H-dibenzo[a,d]cyclopehtene-5-carboxamide (III) (5.0 g, 0.019 mole) in dioxane (80 ml) and methanol (250 ml). The reaction mixture is then diluted with water and filtered to give the crude title compound, m.p. 195°-197°C. Recrystallization from chloroform gave the pure product, m.p. 200°-202°C; $\gamma_{\text{max}}$ 3440 cm$^{-1}$ (NH); 1710 cm$^{-1}$ (carbamate); $\mu_{\text{max}}$ $\text{E}_{\text{max}}$ 288 mp ($\varepsilon = 12400$; nmr (DMSO), $\tau$: 1.17 (NH$_2$, d); 2.55 (8-H, aromatic, m); 3.43 (1-H at C-11, s); 4.67 (1-H at C-5, d); 6.03 (10-OCH$_3$, s); 6.37 (CO$_2$CH$_3$).
(500 ml) is treated dropwise with 30.5 ml of chromic acid sulfuric acid reagent, A. Bower et al., J. Chem. Soc., 2548 (1953), at room temperature. The reaction mixture is then stirred for an additional 30 minutes. The reaction mixture is filtered. Concentration of the filtrate yields the title compound, which on crystallization from acetone-hexane gives a solid, m.p. 117°-119 °C.

**EXAMPLE 6**

**10-Methoxy-5H-Dibenzo[a,d]Cycloheptene-5-Ones (IX)**

A solution of 5H-dibenzo[a,d]cycloheptene-5,10-dione (VIII, 22.1 g, 0.995 mole), prepared as described in Example 5, in methanolic hydrochloric acid (300 ml) is boiled for 3 hours. On cooling the reaction mixture, the title compound, m.p. 96°-97°C, is obtained as a solid precipitate.

**EXAMPLE 7**

**10-Methoxy-5H-Dibenzo[a,d]Cycloheptene-5-one Oxime (X)**

A solution of 10-methoxy-5H-dibenzo[a,d]cycloheptene-5-one (IX, 16.5 g, 0.07 mole), prepared as described in Example 6, hydroxylamine hydrochloride (33.0 g), and pyridine (150 ml) is heated on a steam bath for 2 hours. Most of the pyridine is removed by evaporation under reduced pressure. The residue is dissolved in ether and washed well with water. Evaporation of the ether solution yields the title compound, which on recrystallization from methanol gives crystals, m.p. 184°-189°C.

**EXAMPLE 8**

**10-Methoxy-5H-Dibenzo[a,d]Cycloheptene-5-amine (II)**

10-Methoxy-5H-dibenzo[a,d]cycloheptene-5-one oxime (X, 15.2 g, 0.0605 mole), prepared as described in Example 7, is dissolved in methanol (600 ml) and 2N-sodium hydroxide (400 ml). Raney nickel alloy (22.0 g) is added in one portion. The reaction mixture is stirred for one hour; during the first ten minutes the temperature of the reaction mixture rises to 50°C. After filtering, the methanol is removed from the reaction mixture by evaporation. The resulting aqueous phase is extracted with benzene. The benzene extract is dried and concentrated. The residue is crystallized from ether-hexane to afford the title compound, identical to the product obtained in Example 2.

**EXAMPLE 9**

**5,11-Dihydro-10,11-Epoxy-5H-Dibenzo[a,d]Cycloheptene-5-Carbamic Acid Methyl Ester (XIII)**

5 percent Sodium hypochlorite solution (200 ml) is added, at room temperature, over 5 hours to a solution of 10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d] cycloheptene-5-carboxamide (XIII, 35.0 g, 0.14 mole) in dioxane (30 ml) and methanol (900 ml). The reaction mixture is diluted with a large volume of water. The resulting precipitate is collected and washed with water to give the title compound, m.p. 143°-146°C.

Recrystallization from ethyl acetate-hexane gives the pure product, m.p. 146°-147°C; \( \gamma_{\text{max}}^{\text{ethanol}} 262, \text{265 m} \mu \) (e 814), 274 m\( \mu \) (e 619).

**EXAMPLE 10**

**10,11-Dihydro-10-Hydroxy-5H-Dibenzo[a,d]Cycloheptene-5-Carbamic Acid Methyl Ester (XIV)**

A mixture of 10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]-cycloheptene-5-carbamic acid methyl ester (XIII, 27.9 g, 0.01 mole) is absolute alcohol is hydrogenated at room temperature and atmospheric pressure over 10 percent palladium-on-charcoal. The reaction product is redissolved with addition of dioxane and warming. After filtering the reaction mixture, the filtrate is concentrated, diluted with water, and the separated residue is crystallized from ethanol to give the title compound, m.p. 209°-210°C; \( \gamma_{\text{max}}^{\text{ethanol}} 5,350, 3,400 \text{ cm}^{-1} \) (assoc. OH): 3,320 cm\(^{-1}\) (NH); 1,690 cm\(^{-1}\) (carbamate); \( \lambda_{\text{max}}^{\text{ethanol}} 261 \text{ m} \mu \) (e 484).

**EXAMPLE 11**

**10,11-Dihydro-10-Oxo-5H-Dibenzo[a,d]Cycloheptene-5-Carbamic Acid Methyl Ester (XV)**

A solution of 10-hydroxy-5H-dibenzo[a,d]cycloheptene-5-carbamic acid methyl ester (XIV, 11.0 g, 0.038 mole), prepared as described in Example 10, in dioxane (120 ml) and acetone (350 ml) is treated dropwise over 15 minutes with 14 ml of chromic acid-sulfuric acid reagent at 5°C. The reaction mixture is stirred for 45 minutes during which time it is allowed to come to room temperature and then filtered. The filtrate is concentrated under reduced pressure. The residue is triturated with water and crystallized from benzene to afford the title compound, m.p. 233°-235°C, \( \lambda_{\text{max}}^{\text{ethanol}} 288 \text{ m} \mu \).

**EXAMPLE 12**

**5-Amino-5,11-Dihydro-10H-Dibenzo[a,d]Cycloheptene-10-one (IX)**

10-Oxo-5H-dibenzo[a,d]cycloheptene-5-carbamic acid methyl ester (XV, 2 g, 0.007 mole) prepared as described in Example 11, and sodium hydroxide (2.4 g) are refluxed in a mixture of water (10 ml), dioxane (28 ml) and ethanol (50 ml) for 5 hours. The reaction mixture is evaporated to dryness and the residue is partitioned between chloroform and water. The product from the chloroform phase is crystallized from benzene to afford the title compound, m.p. 146°-147°C; \( \gamma_{\text{max}}^{\text{chloroform}} 1,695 \text{ (sh), 1,670 cm}^{-1} \) (ketone); \( \lambda_{\text{max}}^{\text{chloroform}} 292 \text{ m} \mu \) (e 580).

**EXAMPLE 13**

**N,N-Dichloro-10,11-Dihydro-10,11-Epoxy-5H-Dibenzo[a,d]Cycloheptene-5-amine (XVI)**

5 percent Sodium hypochlorite solution (80 ml) is added in one portion to a stirred solution of 10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene-5-carboxamide (XII, 5.0 g, 0.02 mole) in methanol (200 ml) and the stirring is continued for 1 hour at room temperature. Dilution with water and filtration gives a
residue which is dissolved in chloroform, washed with water and dried. Concentration of the chloroform solution affords solid which on crystallization from chloroform-hexane gives the title compound, m.p. 139°-140°C; λ max 284 μ (ε 2,330); nmr (CDCl₃), τ: 2.58 (8-H, aromatic, m); 4.62 (1-H at C-5, s); 5.62 (2-H at C-10 and C-11, s).

**EXAMPLE 14**

10,11-Dihydro-10-Oxo-5H-Dibenzo[a,d]
JCyloheptene-5-Carboxylic Acid Methyl Ester (XVII)
via the intermediate, 10-Diethylamino-10,11-Dihydro-
5H-Dibenzo[a,d]Cyloheptene-5-Carboxylic Acid

Methyl Ester (XVII)

A solution of 10,11-dihydro-10,11-epoxy-5-dibenzo-
[a,d]J-carboxylic acid methyl ester (XIII), 2.8 g. 0.01 mole) in dry toluene (60 ml) and diethylamine (7.2 g. 0.01 mole) is boiled for 74 hours. The reaction mixture is concentrated to dryness under reduced pressure. Starting material is recovered by crystallization of the resulting residue from chloroform.

Concentration of the mother liquors affords the title intermediate, \( \gamma_{max} = 1,720 \text{ cm}^{-1} \). This crude intermediate is further characterized as its corresponding hydrochloride by treating a portion thereof with ethereal hydrogen chloride to give the said hydrochloride, which on recrystallization from ethanol has m.p. 245°C (dec.).

Treatment of the title intermediate with m-chloroperbenzoic acid in chloroform followed by treatment with alkali accord to the conditions of N.L. Baud and Y.S. Kim, J. Am. Chem. Soc., 89, 179 (1967), affords the title compound (XV) identical with the product of Example 11.

**EXAMPLE 15**

13-Methyl-5,10-(iminomethano)-5H-Dibenzo[a,d]
JCyloheptene-11(10H)-one (I, \( R^1 = O, R^2 = CH_3 \) and \( R^4 = H \))

Method A:

A solution of 10-methoxy-5-dibenzo[a,d]cyloheptene-5-amine (II, 1.7 g. 0.007 mole), prepared as described in Example 2 or 8, acetaldehyde (1.4 g. 0.032 mole) and concentrated hydrochloric acid (1.7 ml) in 1,2-dimethoxyethane (350 ml) is refluxed, with stirring, for 1 hour. The mixture is cooled and filtered. The collected precipitate is washed with ether to give the title compound in the form of its corresponding hydrochloric acid addition salt, m.p. 244°-245°C (dec.), which is crystallized from ethanol-ether without change in m.p.; \( \gamma_{max} = 1685 \text{ cm}^{-1} \) (ketone); \( \lambda_{max} = 290 \text{ μ} (ε 1650)\); nmr (DMSO), \( 1.65 \) (8-H. aromatic, m); 3.93 (1-H at C-5, s); 5.50 (1-H at C-10, d); 6.05 (1-H at C-13, m); 8.63 (CH₃).

This hydrochloric acid addition salt may be decomposed to its corresponding free base, m.p. 144°-145°C, \( \gamma_{max} = 1,682 \text{ cm}^{-1} \), by conventional means such as dissolution in chloroform, washing of the chloroform solution with 5 percent aqueous sodium bicarbonate, followed by concentration of the chloroform solution.

**EXAMPLE 22**

12-Methyl-5,10-(iminomethano)-5H-dibenzo[a,d]
JCyloheptene-11(10H)-one (I, \( R^1 = O, R^2 = CH_3 \) and \( R^4 = H \))

5,10-(iminomethano)-5H-dibenzo[a,d]cyloheptene-
11(10H)-one (I, \( R^1 = O, R^2 = CH_3 \) and \( R^4 = H \)), prepared as described in Example 16, and sodium hydride (190 mg, 55 percent dispersion in oil) in dry benzene (80 ml) is boiled for 30 minutes and then treated with the organic halide, methyl iodide (2 ml).

After boiling for an additional 2 hours, the reaction mixture is cooled and treated with ice water (250 ml). The organic phase is separated, dried over magnesium sulfate, and evaporated. The residue is recrystallized from benzene and then ethanol to afford the title compound. \( \gamma_{CHCl_3} = 1678, 1,594 \) and 1,489 cm⁻¹.

The product of this Example is further characterized by its oxalic acid addition salt, m.p. 195°-197°C.

**EXAMPLE 23**

In the same manner as described in Example 22, but using an equivalent amount of the appropriate organic halide of formula R³X in which R³ and X are as defined above instead of methyl iodide, the 12-ethyl, 12-propyl, 12-allyl, 12-cyclopropylmethyl, 12-benzyl, 12-phenethyl, 12-trimethoxybenzyl, 12-dimethylaminomethyl, 12-diethyldiethylaminoethyl, 12-diisopropylaminopropyl, 12-pyrrolidinomethyl, 12-piperidinoethyl, 12-(4'-methylpiperidinomethyl), 12-(4'-phenylpiperazinomethyl) and 12-morpholinoethyl-5,10-(iminomethano)-5H-dibenzo[a,d]-cyloheptene-11(10H)-ones, are obtained.
EXAMPLE 24

In the same manner as described in Example 22, using an equivalent amount of the appropriate organic halide of formula R'R in which R' and X are as defined above together with the appropriate product obtained in Example 15 and 17 to 21 inclusive, there is obtained, respectively, the 12-methyl-, 12-ethyl-, 12-propyl-, 12-allyl-, 12-cyclopentylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl, 12-dimethylaminoethyl, 12-diethylaminoethyl, 12-diisopropylaminopropyl, 12-pyrrolidinoethyl, 12-piperidinoethyl, 12-(4'-methylpiperidinoethyl), 12-(4'-phenylpiperazinoyethyl) and 12-morpholinoethyl-derivatives of 13-methyl-, 13-ethyl, 13-propyl, 13-benzyl-, 13-phenethyl- and 13-phenyl-5,10-(iminomethano)-5H-dibenz[a,d]11(10H)-one.

EXAMPLE 25

10,11-Dihydro-11-Hydroxy-12-Methyl-5,10-(Iminomethano)-5H-Dibenzo[a,d]Cycloheptene (1, R' and R" = CH₃ and R" = OH)

To a stirred solution of 12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]11(10H)-one (R' = H, R" = CH₃ and R" = OH), prepared as described in Example 22, in methanol (100 ml), sodium borohydride (2.0 g) is added. The mixture is stirred for 3 hours, concentrated to one-third volume, diluted with water and extracted with chloroform. The chloroform extract is washed with brine, dried, and concentrated to dryness, to yield the title compound, γ max 3,500 cm⁻¹.

EXAMPLE 26


EXAMPLE 27

The 11-acetoxy-, 11-propionoxy- and 11-butyryloxy-derivatives of 10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]11-ol and the 13-methyl-, 13-ethyl-, 13-propyl-, 13-benzyl-, 13-phenethyl- and 13-phenyl-derivatives thereof, may be prepared by allowing the corresponding 11-hydroxy derivative, prepared as described in Example 26, 5 molar equivalents of gaseous hydrobromic acid and 50 molar equivalents of the respective appropriate acid, acetic, propionic or butyric acid, to stand at room temperature for 24 hours, followed by dilution with water, extraction of the mixture with benzene, washing of the benzene extract with 5 percent aqueous sodium bicarbonate and evaporation of the extract.

EXAMPLE 28

The 11-acetoxy-, 11-propionoxy- and 11-butyryloxy-derivatives of 12-methyl-, 12-ethyl-, 12-propyl-, 12-allyl-, 12-cyclopentylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-dimethylaminoethyl, 12-diethylaminoethyl, 12-diisopropylaminopropyl, 12-pyrrolidinoethyl, 12-(4'-methylpiperidinoethyl), 12-(4'-phenylpiperazinoyethyl) and 12-morpholinoethyl-derivatives of 13-methyl-, 13-ethyl, 13-propyl-, 13-benzyl-, 13-phenethyl- and 13-phenyl-10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11-ol may be prepared by allowing a solution of the corresponding 11-hydroxy derivative, prepared as described in Examples 25 and 26, 20 molar equivalents of the respective appropriate acyl anhydride, acetic, propionic or butyric anhydride, and 50 molar equivalents of pyridine, to stand at room temperature for 24 hours, followed by evaporation of the reaction mixture under reduced pressure on a steam bath.

EXAMPLE 29

The 11-methoxy-, 11-ethoxy- and 11-propoxy-derivatives of 10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11-ol and the 13-methyl-, 13-ethyl-, 13-propyl-, 13-benzyl-, 13-phenethyl- and 13-phenyl-derivatives thereof, may be prepared by allowing a solution of the corresponding 11-keto derivative, prepared as described in Example 15 to 21 inclusive, 10 molar equivalents of acetyl chloride and 50 molar equivalents of pyridine to stand at room temperature for 24 hours, followed by evaporation of the mixture under reduced pressure on a steam bath, dissolving the residue in 100 molar equivalents of methanol, stirring the methanolic solution with 10 molar equivalents of sodium borohydride for 3 hours, followed by concentration of the mixture to one-third volume, dilution with water, extraction of the mixture with chloroform, evaporation of the chloroform extract to give the corresponding 11-hydroxy-N-acetyl derivative of formula I, followed by treatment of last said
derivative according to the manipulative procedure of Example 22 using the appropriate organic halide, methyl iodide, ethyl chloride or propyl iodide, and after the work-up described in said Example, treating the resulting residue is boiled in a mixture of 100 molar equivalents of ethanol, 6 molar equivalents of potassium hydroxide and 50 molar equivalents of water for 6 hours, followed by dilution with water and extraction with chloroform, followed by evaporation of the chloroform extract.

EXAMPLE 30


The 11-methoxy derivative of 12-methyl-10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11-ol, 10,11-dihydro-11-methoxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene (I, $R^1$ and $R^2$ both = H, $R^3$ = OCH$_3$ and $R^4$ = CH$_3$), has $\gamma_{DCH}^\text{max}$ 2,810, 1,470 and 1,090 cm$^{-1}$. Its corresponding hydro-chloride acid addition salt has m.p. 245°-248°C. after recrystallization from methanol.

EXAMPLE 31

10,11-Dihydro-11-pyrrolidino-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene (I, $R^1$, $R^3$ and $R^4$ = H and $R^2$ = pyrrolidino)

A solution of the 11-hydroxy-N-acetyl derivative of formula I, 10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11-ol N-acetate (7.8 g), prepared as described in Example 29, in 60 ml of pyridine is treated with 7.8 g p-toluenesulfonyl chloride at 5°C. The mixture is then allowed to stand at room temperature for 24 hours. The mixture is then diluted with water and extracted with ether. The ether extract is washed successively with 10 percent aqueous hydrochloric acid and 5 percent sodium carbonate solution, dried, and evaporated to dryness. The residue is dissolved in 200 ml of acetone and the resulting solution is stirred with 5.0 g of lithium bromide at 50°C for 5 hours. The reaction mixture is concentrated to one-fourth of its volume, diluted with water and extracted with chloroform. The chloroform extract is dried, evaporated to dryness. The residue is dissolved in 25 ml of pyrrolidine and the solution boiled for 1 hour. Concentration of the reaction mixture under reduced pressure on a steam bath yields the residue which is redissolved in chloroform. The chloroform solution is washed with water, dried and evaporated to dryness. The resulting residue is boiled for 6 hours in a solution of sodium hydroxide (8 g), water (30 ml) and ethanol (250 ml) for 6 hours. The solution is evaporated to dryness and the residue diluted with water and extracted with chloroform. The chloroform extract is dried and evaporated to yield the title compound, $\gamma_{DCH}^\text{max}$ 2,790, 1,500, 1,453, and 1,100 cm$^{-1}$.

EXAMPLE 32

In the same manner as described in Example 31, but using an equivalent amount of the 13-methyl-, 13-ethyl-, 13-propyl-, 13-benzyl-, 13-phenethyl or 13-phenyl-10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11-ol N-acetate, prepared as described in Example 29, instead of 10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11-ol, the corresponding 13-methyl-, 13-ethyl-, 13-propyl-, 13-benzyl-, 13-phenethyl- and 13-phenyl-10,11-dihydro-11-pyrrolidino-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptenes are obtained, respectively.

EXAMPLE 33

In the same manner as described in Example 31 and using the appropriate 11-hydroxy-N-acetyl derivative of formula I, 10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11-ol N-acetate, or its 13-methyl-, 13-ethyl-, 13-propyl-, 13-benzyl-, 13-phenethyl- or 13-phenyl-derivatives, prepared as described in Example 29, together with the appropriate secondary amine, dimethylamine, diethyamine, (note: when using the latter two amines, the reaction is performed in a sealed pressurized vessel at 100°C, a minimum amount of toluene is employed as a solvent for the secondary amine), piperidine, or morpholine, instead of pyrrolidine, the 11-diethylamino-, 11-diethylamino-, 11-piperidino- and 11-morpholino-derivatives of 10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptane and the 13-methyl-, 13-ethyl-, 13-propyl-, 13-benzyl-, 13-phenethyl- and 13-phenyl-derivatives thereof, are obtained.

EXAMPLE 34

10,11-Dihydro-12-methyl-11-pyrrolidino-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene (I, $R^1$ and $R^2$ both = H, $R^3$ = pyrrolidino and $R^4$ = CH$_3$)

In the same manner as described for Example 31, but using an equivalent amount of 10,11-dihydro-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11-ol, prepared as described in Example 25, instead of 10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11-ol N-acetate, and foregoing the final treatment with boiling aqueous sodium hydroxide in the ethanol, the title compound, m.p. 106°-107°C, may be obtained after purification by elu-
tion from a column of neutral alumina (activity = III), with benzenechloroform (3:1) and recrystallization from ethanol.

**EXAMPLE 35**

In the same manner as described in Example 32, but using an equivalent amount of 13-methyl-, 13-ethyl-, 13-propyl-, 13-benzyl-, 13-phenethyl- or 13-phenyl-12-methyl-10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11-ol, prepared as described in Example 26, the corresponding 13-ethyl-, 13-propyl-, 13-benzyl-, 13-phenethyl- and 13-phenyl-12-methyl-11-pyrrolidino-10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptenes may be obtained, respectively.

**EXAMPLE 36**


**EXAMPLE 37**


**EXAMPLE 38**

10-Cyano-5H-dibenzo[a,d]cyclohepten-5-one

A mixture of 10-bromo-5H-dibenzo[a,d]cyclohepten-5-one (99.0 g), cuprous cyanide (40 g) and quinoline (200 ml) is stirred and heated at 190°-200°C (internal temperature) for 1 hour. The mixture is cooled and the resulting solid mass is broken up and stirred under ether. The mixture is filtered and the solids are washed with ether. The remaining solids are triturated under chloroform. The mixture is filtered and the solids are washed with hot chloroform. The green insoluble residue is discarded.

The ether filtrate and washings are exhaustively washed with 2N HCl, then water, and then dried and evaporated. The chloroform filtrate and washings are similarly processed.

The solid residues so obtained are combined and recrystallized from ethanol to give the title product, m.p. 170°-173°C.

The title product is further characterized by its infrared spectrum with maxima at 2,230 and 1,645 cm⁻¹(CHCl₃).

The title product is also obtained when the above procedure is carried out in the absence of quinoline.

**EXAMPLE 39**

5,10-Epoxyethano-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-13-one

10-Cyano-5H-dibenzo[a,d]cyclohepten-5-one (5.0 g), prepared as described in Example 38 is suspended in ethanol (80 ml) and sodium borohydride (2.5 g) is added. The mixture is stirred at room temperature overnight and then refluxed for two hours. The mixture is cooled, treated with 2N HCl and evaporated to small volume. The solids are collected, washed with water and dried to give a solid. This material is dissolved in chloroform (minimum volume) and chromatographed on alumina. Benzene elutes the title product which crystallizes from methanol as needles, m.p. 148°-150°C.

The title product is also obtained when the above procedure is followed except that dimethyl sulfoxide (20 ml) is used in place of ethanol (80 ml). **EXAMPLE 40**
10,11-Dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one

A mixture of 5,10-(epoxymethano)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-13-one (1.12 g) prepared as described in Example 39, and ammonium hydroxide (100 ml; 0.88) is heated for 7 hours at 190°C.

The solid product is collected and dried and crystallized from ethanol to give the title product, m.p. 227°-229°C. EXAMPLE 41

In a similar manner to that described in Example 40, but using methylyamine, ethylyamine, propylamine, alkylyamine, cyclopropylmethyamine, benzylamine, penethylamine, trimethoxybenzylamine, dimethyldiethyloxalkyamine, diethylaminobenzylamine, diethylaminomethyamine, diisopropylaminopropylamine, pyridylaminobenzylamine, piperidinoethyamine, 4'-methylpiperoxazinoethyamine, 4'-phenylpiperoxazinoethyamine, or morpholinoethylamine in place of ammonia, the corresponding 12-methyl-, 12-ethyl-, 12-propyl-, 12-allyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl, 12-diethylaminocarbonyl-1,12-diisopropylaminopropyl-, 12-pyrrolidinoethy-, 12-piperidinoethy-, 12-4′-methyl-piperoxazinoethy-, or 12-4′-phenylpiperoxazinoethyamine, may be obtained, respectively.

EXAMPLE 42

11-Bromo-10,11-dihydro-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one (XII, R = CH₃)

A suspension of 12-methyl-10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one (XII, R = CH₃, 15.11 g), m.p. 239°-241°C, prepared as described in Example 41, and N-bromosuccinimide (11.4 g) in carbon tetrachloride (300 ml) containing about 50 mg of benzyl peroxide is boiled for 75 minutes. The mixture is filtered and the filtrate evaporated to dryness. The residue is crystallized from ethyl acetate to yield the title compound, m.p. 205°-207°C, [α]lim = 1,670 cm⁻¹.

EXAMPLE 43

In the same manner as described in Example 42, but using an equivalent amount of 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-diethylaminocarbonyl-1,12-diisopropylaminopropyl-, 12-pyrrolidinoethy-, 12-piperidinoethy-, 12-4′-methyl-piperoxazinoethy-, or 12-4′-phenylpiperoxazinoethyamine, 5H-dibenzo[a,d]cyclohepten-13-one, as prepared as described in Example 41, in place of 12-methyl-11,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one, the corresponding 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl, 12-diethylaminocarbonyl-1,12-diisopropylaminopropyl-, 12-pyrrolidinoethy-, 12-piperidinoethy-, 12-4′-methyl-piperoxazinoethy-, and 12-morpholinoethyl-11,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one may be obtained, respectively.

EXAMPLE 44

10,11-Dihydro-11-methoxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one (XXIII, R = CH₃)

A solution of 11-bromo-10,11-dihydro-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one (XXII, R = CH₃, 6.7 g), prepared as described in Example 42, in 13.4 ml of a solution of sodium methoxide, prepared by dissolving 3.5 g of sodium in 100 ml of methanol, is stirred and boiled for 18 hours. The reaction mixture is concentrated, diluted with water and extracted with chloroform. The chloroform extract is dried, and then concentrated to dryness. Crystallization of the residue from isopropanol affords the title compound, m.p. 190°-193°C.

EXAMPLE 45

In the same manner as described in Example 44, but using an equivalent amount of 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl, 12-diethylaminocarbonyl-1,12-diisopropylaminopropyl-, 12-pyrrolidinoethy-, 12-piperidinoethy-, 12-4′-methyl-piperoxazinoethy-, or 12-4′-phenylpiperoxazinoethyamine, 5H-dibenzo[a,d]cyclohepten-13-one, in place of 10,11-dihydro-11-methoxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one, prepared as described in Example 43, the corresponding 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl, 12-diethylaminocarbonyl-1,12-diisopropylaminopropyl-, 12-pyrrolidinoethy-, 12-piperidinoethy-, 12-4′-methyl-piperoxazinoethy-, and 12-4′-phenylpiperoxazinoethyamine, 11,11-dihydro-11-methoxy-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one may be obtained, respectively.

EXAMPLE 46

By substituting an equivalent amount of sodium ethoxide solution or sodium propoxide solution for
sodium methoxide solution in the procedures of Examples 44 or 45, the corresponding 11-ethoxy- and 11-propoxy-, instead of 11-methoxy, derivatives of the products listed in said Examples may be obtained, respectively.

EXAMPLE 47

10,11-Dihydro-11-methoxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene (I, R¹ and R² both ≡ H, R³ ≡ OCH₃ and R⁴ ≡ CH₃)

Lithium aluminum hydride (1.2 g) is added portionwise to a solution of 10,11-dihydro-11-methoxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one (XXIII, R³ ≡ CH₃, 3.5 g), prepared as described in Example 44, in anhydrous tetrahydrofuran. The mixture is boiled for 5 hours. Excess reagent is decomposed by careful addition of water. The mixture is filtered and the filtrate is concentrated to dryness to yield the title compound, ¹HNMR 2.810, 1.470 and 1.090 cm⁻¹, identical to the product obtained in Example 30.

This product is characterized further as its corresponding hydrochloric acid addition salt, m.p. 245⁰–248⁰C after recrystallization from methanol.

EXAMPLE 48

In the same manner as described in Example 47, but using an equivalent amount of 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-diethylnaphthyl-, 12-diethylaminomethyl-, 12-diisopropylaminomethyl-, 12-pyrrolidinomethyl-, 12-piperidinoethyl-, 12-(4'-methylpiperazinoethyl), 12-(4'-phenylpiperazinoethyl), or 12-morpholinoethyl-10,11-dihydro-11-methoxy-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one, prepared as described in Example 45, in place of 10,11-dihydro-11-methoxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one, the corresponding 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-diethylaminomethyl-, 12-diethylnaphthyl-, 12-diisopropylaminomethyl-, 12-pyrrolidinomethyl-, 12-piperidinoethyl-, 12-(4'-methylpiperazinoethyl), 12-(4'-phenylpiperazinoethyl), or 12-morpholinoethyl-10,11-dihydro-11-methoxy-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene may be obtained, respectively.

EXAMPLE 49

By substituting an equivalent amount of the appropriate 11-ethoxy- or 11-propoxy- derivatives described in Example 46 in place of 10,11-dihydro-11-methoxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one in Example 47, the 11-ethoxy- or 11-propoxy- derivatives of 12-methyl-, 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-diethylnaphthyl-, 12-diethylaminomethyl-, 12-diethylnaphthyl-, 12-diisopropylaminomethyl-, 12-pyrrolidinomethyl-, 12-piperidinoethyl-, 12-(4'-methylpiperidinoethyl), 12-(4'-phenylpiperazinoethyl), or 12-morpholinoethyl-10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene may be obtained.

EXAMPLE 50

10,11-Dihydro-11-hydroxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one (XXIII, R³ ≡ CH₃, R⁴ ≡ H).

A mixture of 11-bromo-10,11-dihydro-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one (0.5 g), prepared as described in Example 42, dioxane (10 ml), potassium hydroxide (0.1 g), and water (2.0 ml) is heated under reflux and stirred for 3 hours. The mixture is evaporated, diluted with water, and the precipitate is crystalized from methanol to give the title product m.p. 259⁰–261⁰C, ¹HNMR 3.435, 1.658 cm⁻¹.

EXAMPLE 51

In the same manner as described in Example 50, but using an equivalent amount of 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-diethylnaphthyl-, 12-diethylaminomethyl-, 12-diisopropylaminomethyl-, 12-pyrrolidinomethyl-, 12-piperidinoethyl-, 12-(4'-methylpiperazinoethyl), 12-(4'-phenylpiperazinoethyl), or 12-morpholinoethyl-10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one, prepared as described in Example 43, in place of 11-bromo-10,11-dihydro-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one, the corresponding 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-diethylaminomethyl-, 12-diethylnaphthyl-, 12-diisopropylaminomethyl-, 12-pyrrolidinomethyl-, 12-piperidinoethyl-, 12-(4'-methylpiperazinoethyl), 12-(4'-phenylpiperazinoethyl), 12-morpholinoethyl-10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one may be obtained, respectively.

EXAMPLE 52

10,11-Dihydro-11-hydroxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene (I, R¹ and R² both ≡ H, R³ ≡ OH and R⁴ ≡ CH₃)

Lithium aluminum hydride (1.2 g) is added portionwise to a solution of 10,11-dihydro-11-hydroxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-13-one (XXIII, R³ ≡ CH₃, 3.5 g), prepared as described in Example 50, in anhydrous tetrahydrofuran. The mixture is boiled for 5 hours. Excess reagent is decomposed by careful addition of water. The mixture is filtered and the filtrate is concentrated to dryness to yield the title compound, ¹HNMR 3.500 cm⁻¹.

This product is further characterized as its corresponding hydrochloric acid addition salt, m.p. 265⁰–268⁰C after crystallization from isopropanol-ether.

EXAMPLE 53

In the same manner as described in Example 52, but using an equivalent amount of 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-diethylnaphthyl-, 12-diethylaminomethyl-, 12-diisopropylaminomethyl-, 12-pyrrolidinomethyl-, 12-piperidinoethyl-, 12-(4'-methyl-
piperazinoethyl, 12-(4' pheny1piperazinoethyl), or 12-morpholinoethyl10,11-dihydro-11-hydroxy-5,10- (iminomethano)-5H dibenzo[a,d]cyclohepten-13-one, prepared as described in Example 51, in place of 10,11-dihydro-11-hydroxy-12-methyl-5,10- (iminomethano)-5H dibenzo[a,d]cyclohepten-13-one, the corresponding 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-dimethyldi50 oethy1-, 12-diethylaminoethyl-, 12-diethylaminoethyl, 12-diisopropylaminopropyl-, 12-pyrrrolidinoethyl-12-piperidinoethyl, 12-(4'-methylpiperazinoethyl), 12-(4'-phenylpiperazinoethyl)- and 12-morpholinoethyl10,11-dihydro-11-hydroxy-5,10- (iminomethano)-5H dibenzo[a,d]cycloheptene may be obtained, respectively.

EXAMPLE 54

10,11-Dihydro-12-methyl-11-pyrrolidino-5,10-(iminomethano)-5H dibenzo[a,d]cyclohepten-13-one (XXIV, R^3=CH and NR^3=R^3=pyrrolidino)

A mixture of 11-bromo-10,11-dihydro-12-methyl-5,10-(iminomethano)-5H dibenzo[a,d]cyclohepten-13-one (XXII, R^3=CH_3, 4.7 g), prepared as described in Example 42, and pyrrolidine is boiled for 1 hour. The reaction mixture is concentrated to dryness and the residue dissolved in water. The aqueous solution is extracted with chloroform. The extract is dried and evaporated. The residue is recrystallized from ethanol to give the title compound, m.p. 189°-192°C; [x]_D^277 (c=1.470) and 268 (c=1910).

EXAMPLE 55

In the same manner as described in Example 54 but using an equivalent amount of 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-dimethylaminoo'ethyl-, 12-diethylaminoethyl-, 12-diisopropylaminopropyl-, 12-pyrrrolidinoethyl-, 12-piperidinoethyl-, 12- (4'-methy/1piperazinoethyl), 12-(4'-phenylpiperazinoethyl)-, 12-morpholinoethyl-10,11-dihydro-11-bromo-12-methyl-5,10-(iminomethano)-5H dibenzo[a,d]cyclohepten-13-one, prepared as described in Example 43, in place of 11-bromo-10,11-dihydro-12-methyl-5,10- (iminomethano)-5H dibenzo[a,d]cyclohepten-13-one, the corresponding 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-dimethyldi50 oethy1-, 12-diethylaminoethyl-, 12-diisopropylaminopropyl-, 12-pyrrrolidinoethyl-12-piperidinoethyl, 12-(4'-methylpiperazinoethyl), 12-(4'-phenylpiperazinoethyl) and 12-morpholinoethyl-10,11-dihydro-11-pyrrolidino-5,10-(iminomethano)-5H dibenzo[a,d]cyclohepten-13-one may be obtained, respectively.

EXAMPLE 56

By substituting an equivalent amount of the secondary amines, dimethy1amines, diethylamine, piperidine or morpholine, for pyrrolidine in the procedures of Example 54 or 55, the corresponding 11-dimethylamino-, diethylamino-, 11-piperidino- and 11-morpholino- derivatives of the products listed in said Examples may be obtained, respectively. Note that when dimethy1amine and diethylamine are employed in the method of this Example, the reaction is performed in a sealed, pressurized vessel at 100°C with a minimum amount of toluene being employed as a solvent for the secondary amine.

EXAMPLE 57

10,11-Dihydro-12-methyl-11-pyrrolidino-5,10-(iminomethano)-5H dibenzo[a,d]cycloheptene (1, R^1 and R^4=H, R^2=pyrrolidino and R^3=CH_3)

A solution of 10,11-dihydro-12-methyl-11-pyrrolidino-5,10-(iminomethano)-5H dibenzo[a,d]cycloheptene (3.5 g), prepared as described in Example 54, in anhydrous tetrahydrofuran (30 ml) is added dropwise to a stirred suspension of lithium aluminum hydride (3.3 g) in anhydrous tetrahydrofuran (30 ml). The mixture is boiled for 4 hours, cooled and then treated cautiously with water-tetrahydrofuran (1:4, 100 ml). The mixture is filtered. The filtrate is evaporated. The residue is dissolved in ether. The ether solution is washed with brine, dried, and evaporated. The residue is subjected to chromatography on neutral alumina (activity=III). Elution with benzene-chloroform (3:1) and subsequent recrystallization of the eluate from ethanol gives the title compound, m.p. 106°-107°C, identical with the product of Example 34.

EXAMPLE 58

In the same manner as described in Example 57, but using an equivalent amount of 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-dimethylaminoo'ethyl-, 12-diethylaminoethyl-, 12-diisopropylaminopropyl-, 12-pyrr rolidinoethyl-, 12-piperidinoethyl-, 12-(4'-methylpiperazinoethyl), 12-(4'-phenylpiperazinoethyl), or 12-morpholinoethyl-10,11-dihydro-11-pyrrolidino-5,10-(iminomethano)-5H dibenzo[a,d]cyclohepten-13-one, prepared as described in Example 53, instead of 10,11-dihydro-12-methyl-11-pyrrolidino-5,10-(iminomethano)-5H dibenzo[a,d]cyclohepten-13-one, the corresponding 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-dimethylaminoo'ethyl-, 12-diethylaminoethyl-, 12-diisopropylaminopropyl-, 12-pyrrolidinoethyl-12-piperidinoethyl, 12-(4'-methylpiperazinoethyl), 12-(4'-phenylpiperazinoethyl) and 12-morpholinoethyl-10,11-dihydro-11-pyrrolidino-5,10-(iminomethano)-5H dibenzo[a,d]cycloheptenes may be obtained, respectively.

EXAMPLE 59

In the same manner as described in Example 57 but using an equivalent amount of the 11-dimethylamino-, 11-diethylamino-, 11-piperidino- or 11-morpholino- derivatives of 12-methyl-, 12-ethyl-, 12-propyl-, 12-cyclopropylmethyl-, 12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-dimethylaminoo'ethyl-, 12-diethylaminoethyl-, 12-diisopropylaminopropyl-, 12-pyrr rolidinoethyl-, 12-piperidinoethyl-, 12-(4'-methylpiperazinoethyl), 12-(4'-phenylpiperazinoethyl), or 12-morpholinoethyl-10,11-dihydro-11-pyrrolidino-5,10-(iminomethano)-5H dibenzo[a,d]cyclohepten-13-one may be obtained, respectively.
12-benzyl-, 12-phenethyl-, 12-trimethoxybenzyl-, 12-dimethylaminomethyl-, 12-diethylaminomethyl-, 12-diisopropylaminopropyl-, 12-pyrrolidinoethyl-, 12-piperidinoethyl, 12-(4'-methylpiperazinomethyl), 12-(4'-phenylpiperazinomethyl), or 12-morpholinomethyl-10,11-dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptenes may be obtained, respectively.

We claim:
1. A compound selected from those of the formula
\[
\text{R}^3=N-\text{CHR}^4
\]
wherein \(\text{R}^2\) represents hydrogen, lower alkyl having one to four carbon atoms, allyl, cyclopropylmethyl, benzyl, phenethyl, trimethoxybenzyl, dimethylaminomethyl, diethylaminomethyl, diisopropylaminopropyl, pyrrolidinoethyl, piperidinoethyl, 4'-methylpiperidinoethyl, 4'-phenylpiperazinomethyl and morpholinomethyl; \(\text{R}^3\) represents hydrogen, lower alkyl having one to four carbon atoms, benzyl, phenyl and phenethyl; and acid addition salts thereof with pharmaceutically acceptable acids.

2. A compound selected from those of the formula
\[
\text{R}^3=N-\text{CHR}^4
\]
wherein \(\text{R}^3\) represents hydrogen or lower alkyl of one to four carbon atoms; \(\text{R}^2\) represents hydrogen, lower alkyl of one to four carbon atoms, benzyl, phenyl and phenethyl; and acid addition salts thereof with pharmaceutically acceptable acids.

3. 10,11-Dihydro-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11(10H)-one, as claimed in claim 2.

4. The hydrochloric acid addition salt of 5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11(10H)-one, as claimed in claim 2.

5. 13-Methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11(10H)-one, as claimed in claim 2.

6. The hydrochloric acid addition salt of 13-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11(10H)-one, as claimed in claim 2.

7. 13-Ethyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11(10H)-one, as claimed in claim 2.

8. 13-Propyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11(10H)-one, as claimed in claim 2.

9. 13-Benzyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11(10H)-one, as claimed in claim 2.

10. 13-Phenethyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11(10H)-one, as claimed in claim 2.

11. 13-Phenyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11(10H)-one, as claimed in claim 2.

12. 12-Methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11(10H)-one, as claimed in claim 2.

13. The oxalic acid addition salt of 12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cyclohepten-11(10H)-one, as claimed in claim 2.

14. A compound selected from those of the formula
\[
\text{R}^3=N-\text{CHR}^4
\]
wherein \(\text{R}^1\) represents hydrogen and \(\text{R}^2\) represents hydroxyl, lower alkoxy having one to three carbon atoms, dimethylamino, diethylamino, pyrrolidino, piperidino and morpholinol; \(\text{R}^3\) represents hydrogen, lower alkyl having one to four carbon atoms, allyl, cyclopropylmethyl, benzyl, phenethyl, trimethoxybenzyl, dialkylaminoalkyl having from two to three carbon atoms in the alkyl radical and from one to three carbon atoms in each of the dialkyl radicals, pyrrolidinoethyl, piperidinoethyl, 4'-methylpiperazinomethyl and morpholinomethyl; and \(\text{R}^4\) represents hydrogen, lower alkyl having one to four carbon atoms, benzyl, phenyl and phenethyl; and acid addition salts thereof with pharmaceutically acceptable acids.

15. A compound selected from those of the formula
\[
\text{R}^3=N-\text{CHR}^4
\]
wherein \(\text{R}^1\) represents hydrogen, lower alkoxy having one to three carbon atoms or pyrrolidino; \(\text{R}^3\) represents hydrogen or lower alkyl having one to four carbon atoms; and \(\text{R}^4\) represents hydrogen; and acid addition salts thereof with pharmaceutically acceptable acids.

16. 10,11-Dihydro-11-methoxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene, as claimed in claim 15.

17. The hydrochloric acid addition salt of 10,11-dihydro-11-methoxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene, as claimed in claim 15.

18. 10,11-Dihydro-11-pyrrolidino-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene, as claimed in claim 15.

19. 10,11-Dihydro-12-methyl-11-pyrrolidino-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene, as claimed in claim 15.

20. 10,11-Dihydro-11-hydroxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene, as claimed in claim 15.

21. The hydrochloric acid addition salt of 10,11-dihydro-11-hydroxy-12-methyl-5,10-(iminomethano)-5H-dibenzo[a,d]cycloheptene, as claimed in claim 15.