

1188.107



PATENT SPECIFICATION

NO DRAWINGS

1188.107

Date of Application (No. 13200/69) and filing Complete Specification: 13 March, 1969.

Application made in Switzerland (No. 4201) on 20 March, 1968.

Complete Specification Published: 15 April, 1970.

Index at acceptance:—C2 C(1E4K3, 1E7D1, 1E7E2, 1E7N4, 1G4B, 1G6B6, 1H1A2, 1H1A3, 1H1C2, 1H2A3, 1H2A7, 1H2C2, 1Q2, 1Q4, 1Q6B1, 1Q6B2, 1Q8A, 1Q9B, 1K9C, 1Q9D2, 1Q9L, 1Q11G, 1Q11H, 1Q11J, 22Y, 22X, 220, 29Y, 29X, 31Y, 313, 32Y, 323, 334, 338, 345, 351, 354, 36Y, 360, 363, 509, 650, 662, 701, 709, 716, 719, 79Y, 790, 171—178—185, LF, LZ, MV)

International Classification:—C 07 c 135/02

COMPLETE SPECIFICATION

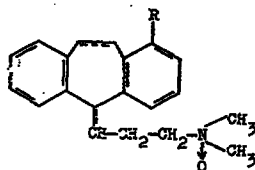
Dibenzocycloheptene Derivatives

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with dibenzocycloheptene derivatives and the manufacture thereof.

5H - Dibenzo[a,d]cycloheptenes and 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptenes having a basic side chain in the 5-position are already known as psychopharmacocons with antidepressant activity, for example, 10,11 - dihydro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene (amitriptyline).

It has now been surprisingly found that dibenzocycloheptene compounds of the general formula



wherein R represents a chlorine or fluorine atom and the dotted bonds can be hydrogenated,

as well as isomers and acid addition salts of these compounds which differ from the known members of the group of substances in question by the presence of a chlorine or fluorine atom in the 1-position and a nitrogen-bonded oxygen atom, are distinguished by a considerably increased antidepressant action and strongly decreased toxicity. The absent or only insignificant anticholinergic action is to be mentioned as particularly advantageous. The compounds of formula I are in addition distinguished by various actions on the nervous system. Narcosis-potentiating, adrenolytic, sedative, anti-histamine-like and local anaesthetic actions have been found.

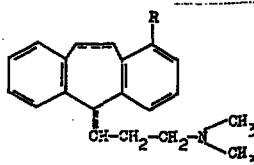
In formula I hereinbefore, R preferably represents a chlorine atom. Particularly interesting representatives of compound of formula I are, for example:

- 1 - Chloro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene-N-oxide,
- 1 - Chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene-N-oxide,
- 1 - Chloro - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene-N-oxide and
- 1 - Chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene-N-oxide.

[Price 5s. 0d.]

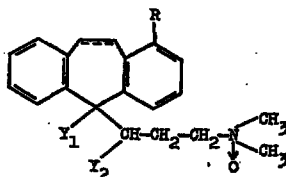
Particularly interesting is 1 - chloro - 5 - (3 - dimethylaminopropylidene) - 5H-dibenzo[a,d]cycloheptene-N-oxide.

Thus, the present invention relates to dibenzocycloheptene compounds of formula I, to isomers and acid addition salts thereof and to a process for the manufacture of said compounds. This process comprises oxidizing a tertiary amine of the general formula



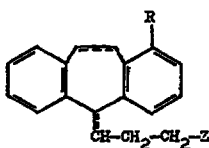
II

wherein R and the dotted bonds have the significance given above, or dehydrating a carbinol of the general formula

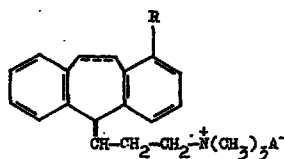


III

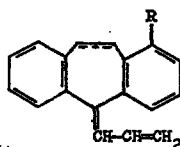
wherein R and the dotted bond have the significance given earlier, one of the symbols Y₁ and Y₂ represents a hydrogen atom and the other represents a hydroxy group, or an acid addition salt thereof, or treating a compound of the general formula



IV



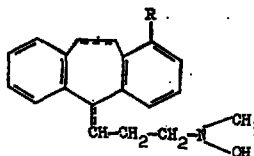
or



VI

wherein R and the dotted bonds have the significance given earlier, Z represents a halogen atom or a substituted sulphonyloxy residue and A represents the anion of an acid,

with dimethyl hydroxylamine, or treating a compound of the general formula



VII

wherein R and the dotted bonds have the significance given earlier, with a methylating agent, whereupon, in optional sequence, if desired, the isomers are isolated from an isomer mixture obtained and, if desired, a base obtained is converted into an acid addition salt.

According to a preferred embodiment of the process in accordance with the invention, a tertiary amine of general formula II is oxidized. As oxidizing agent there can be employed various compounds capable of yielding oxygen such as organic peroxides, e.g. monosubstituted organic peroxides such as C_1-C_4 alkyl- or alkanoyl hydroperoxides, for example, t-butyl hydroperoxide, performic acid and peracetic acid; as well as phenyl-substituted derivatives of these hydroperoxides, e.g. cumene hydroperoxide and perbenzoic acid. The phenyl substituent can, if desired, contain a further lower group (e.g. C_1-C_4 alkyl or alkoxy) or halogen or carboxy. Exemplary of such oxidizing agents are 4-methyl perbenzoic acid, 4-methoxy perbenzoic acid, 3-chloro perbenzoic acid and mono-perphthalic acid. As oxidizing agent there can also be used various inorganic oxidizing agents, e.g. hydrogen peroxide; ozone; hypochlorites such as sodium, potassium or ammonium hypochlorite; peroxy-mono- or peroxy-disulphuric acid. A preferred oxidizing agent is hydrogen peroxide. The oxidation is advantageously effected in a solvent such as methanol, ethanol, ether, benzene or chloroform and at a temperature between -50°C and $+100^{\circ}\text{C}$. After working up according to methods known *per se* (with the removal of excess oxidizing agent) the corresponding N-oxide of the formula I is recovered, conveniently in the form of an acid addition salt.

The tertiary amine of formula II employed in the aforementioned oxidation can be prepared according to various methods. A tertiary amine of formula II carrying an exocyclic double bond is expediently prepared as follows:

1 - Chloro- (or fluoro) - 5H - dibenzo[a,d]cycloheptene - 5 - one or the corresponding 10,11-dihydro compound is reacted with a 3-dimethylamino-propyl magnesium halide. After hydrolysis of the resulting addition product, e.g. by means of saturated ammonium chloride solution, the resulting 5-carbinol is heated with mineral acid, e.g. with ethanolic hydrochloric acid, in order to effect dehydration. There is thus obtained a tertiary amine of formula II carrying an exocyclic double bond in the 5-position.

The preparation of exocyclically saturated tertiary amines of formula II can, for example, be effected as follows:

The 5-carbinol obtained as described earlier can be reduced with nascent hydrogen, e.g. zinc in glacial acetic acid, or with hydroiodic acid in the presence of red phosphorus. Another method which is particularly convenient for the preparation of exocyclically saturated 10,11-unsaturated tertiary amines of formula II is evident from the following: 1 - chloro - (or fluoro) - 5H - dibenzo[a,d]cycloheptene - 5 - one (or the corresponding 10,11-dihydro compound) is reduced to the corresponding 5-hydroxy compound with sodium borohydride in dioxan-water and the resulting 5-hydroxy compound is then treated with a hydrogen iodide to yield the corresponding 5-halogen compound, e.g., in ether, benzene or tetrahydrofuran, and by boiling heat, be converted into an exocyclically saturated tertiary amine of formula II by treatment with a 3-dimethylaminopropyl magnesium halogenide.

According to another embodiment of the process in accordance with the invention, a carbinol of general formula III is dehydrated. Preferred carbinol starting materials of formula III are those in which Y_1 represents a hydroxy group and Y_2 represents hydrogen.

The dehydration of carbinols of formula III leads to compounds of formula I having an exocyclic double bond in the 5-position. This dehydration is conveniently carried out using mineral acids such as hydrochloric or hydrobromic acid, in which case the dehydration can be carried out in an aqueous medium. The dehydration is preferably carried out in ethanolic hydrochloric acid at a temperature between room temperature and the boiling point of the dehydration mixture. The dehydration is also brought about by heating (e.g. at 50°C to reflux temperature, preferably at reflux temperature) with a high-boiling anhydrous solvent such as dimethyl sulphoxide. Other usual dehydrating agents can also be employed; for example, sulphuric acid, phosphorus oxychloride, zinc chloride or potassium bisulphate, for example, in an inert organic solvent such as chloroform or methylene chloride, and at a temperature between room temperature and the boiling point of the dehydration mixture.

The carbinol starting materials of formula III in which Y_1 represents hydroxy and Y_2 represents hydrogen can be obtained by oxidation of 1 - chloro - (or fluoro) - 5 - (3 - dimethylaminopropyl) - 5 - hydroxy - 5H - dibenzo[a,d]cycloheptene or the corresponding 10,11-dihydro compound. The oxidation is effected by treatment with one of the above mentioned oxidizing agents, preferably by treatment with hydrogen peroxide in a solvent such as methanol, ethanol, ether, benzene or chloroform at about room temperature. After destroying the excess hydrogen peroxide, e.g. with platinum black, the desired carbinol of the formula III can be obtained by evaporation of the

solvent. It is often possible to bring the product to crystallisation by strong cooling, e.g. to a temperature between about -20° and 0°C , whereafter the desired carbinol is obtained by simple filtration and washing of the crystals with a solvent.

Carbinols of formula III in which, *vice versa*, Y_1 signifies hydrogen and Y_2 signifies hydroxy, are obtained, for example, by reacting a corresponding tricyclic 5-ketone with ethyl magnesium bromide and hydrolysing the reaction product. The resulting 5-hydroxy-5-ethyl compound is dehydrated with acetyl chloride and subsequently treated with formic acid and hydrogen peroxide. There results a 5-hydroxy-5-(1-hydroxyethyl) compound which is dehydrated with aqueous sulphuric acid to yield the corresponding 5-acetyl compound. By treatment with formaldehyde and dimethylamine hydrochloride, there is obtained a 5-dimethylaminopropionyl compound which, after reduction with sodium borohydride, yields the corresponding carbinol. This carbinol is subsequently oxidized in the manner described above for the preparation of carbinols of formula III in which Y_1 represents hydroxy and Y_2 represents hydrogen.

A further embodiment of the process in accordance with the invention consists in treating a compound of general formula IV, V or VI with dimethyl hydroxylamine.

In formula IV hereinbefore, Z preferably represents a chlorine or bromine atom. When Z represents a substituted sulphonyloxy residue most preferred examples thereof are lower alkyl sulphonyloxy residues such as mesyloxy; phenyl sulphonyloxy; lower alkyl phenyl sulphonyloxy residues such as tosyloxy; or phenyl(lower alkyl) sulphonyloxy residues such as phenyl mesyloxy. The anion A in formula V is preferably derived from an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid or sulphuric acid.

The treatment of compounds of formulae IV, V and VI with dimethyl hydroxylamine is preferably carried out in the presence of excess dimethyl hydroxylamine. The treatment is expediently carried out in the presence of a basic catalyst, e.g. potassium carbonate, sodium amide or potassium amide. The treatment can be carried out in an organic solvent such as methanol, ethanol, acetone, benzene or toluene. The temperature at which the treatment is carried out is not critical, but lies conveniently between 0°C and the boiling point of the mixture.

The starting compounds of formula IV may, for example, be prepared by reaction of the corresponding tricyclic 5-ketone with a 3-methoxypropyl halide, hydrolysis of the resulting compound, subsequent reduction or of the resulting carbinol and treatment of the resulting 3-methoxypropyl compound with an excess of a hydrohalic acid, e.g. hydrobromic acid, whereupon a 3-halopropyl(idene) compound is obtained. If the 3-halopropyl(idene) compound is treated with dilute hydrohalic acid, the corresponding 3-methoxypropyl(idene) compound can be obtained. This can be treated with a substituted sulphonyl halide, e.g. the corresponding chloro-, to yield the correspondingly substituted 3-sulphonyloxypropyl(idene) compound.

The quaternary salts of formula V which can also be employed as starting materials, can be obtained by quaternisation of the corresponding dimethylamino compound with a methylating agent such as methyl chloride, methyl bromide, methyl iodide or dimethyl sulphate. The compounds of formula VI are obtainable, for example, by reaction of an allyl compound with the corresponding tricyclic 5-ketone, followed by hydrolysis.

In accordance with a further embodiment of the process of the invention, a tricyclic hydroxylamine of formula VII is treated with a methylating agent. Suitable methylating agents are, for example, compounds of the formula CH_3Z in which Z represents a halogen atom, preferably chlorine, bromine or iodine, or a substituted sulphonyloxy residue, e.g. a lower (cyclo-)alkylsulphonyloxy residue, such as mesyloxy, cyclopropyl sulphonyloxy; phenylsulphonyloxy; a lower alkyl phenylsulphonyloxy residue such as tosyloxy; or phenyl (lower alkyl) sulphonyloxy residue such as phenyl mesyloxy. As methylating agent there can also be employed dimethyl sulphate. The treatment is conveniently carried out in the presence of a polar solvent, for example, acetone, methanol or dimethylformamide and at a temperature between 0°C and the boiling point of the mixture.

The tricyclic hydroxylamines of formula VII which are used as starting materials in the last-mentioned embodiment of the process can be obtained, for example, by the following reaction sequence:

1 - Chloro - (or fluoro) - 5H - dibenzo[a,d]cycloheptene - 5 - one or the corresponding 10,11-dihydro compound is reacted with a 3-(N-methyl-N-benzylamino)-propyl-magnesium halogenide. After hydrolysis of the resulting addition product, e.g.

with the aid of saturated ammonium chloride solution, the 5-carbinol obtained is reacted with chloroformic acid ethyl ester. The resulting 5 - hydroxy - 5 - [3 - (methyl-carbethoxy - amino) - propyl] compound is subsequently hydrolysed in an alkaline medium, e.g. by boiling with aqueous potassium hydroxide solution. A decarboxylation thus ensues and the corresponding 5 - hydroxy - 5 - (3 - methylaminopropyl) compound is formed. This compound can be further treated with nascent hydrogen, e.g. zinc in glacial acetic acid, or with hydroiodic acid in the presence of red phosphorus to yield the corresponding 5-(3-methylaminopropyl) compound. If the said 5-hydroxy-5-(3-methylaminopropyl) compound is heated with mineral acid, e.g. with ethanolic hydrochloric acid, the corresponding 5-(3-methylaminopropylidene) compound is obtained. The product resulting from any of the said reduction and dehydration reactions is now oxidised in the manner described earlier, conveniently by treatment at about 0°C with benzoyl peroxide in an organic solvent such as ether or chloroform. The resulting N - methyl - N - benzoyloxy amino - propyl(idene) compound can be converted into the desired tricyclic hydroxylamine of formula VII by saponification with alkali, e.g. with ethanolic potassium hydroxide solution.

The above mentioned methods for the preparations of starting compounds of formulae II—VII are only mentioned in an exemplary way. Other methods known to the chemist can of course also be employed. As an example, the following examples 8 and 9 illustrate other modes of obtaining the starting compounds of formula VII.

Resulting compounds of formula I which carry an exocyclic double bond and/or a double bond in 10,11-position as well as their salts can be separated into their geometric isomers, e.g. α - and β -isomers. The methods of separation are known *per se*. The geometric isomers are preferably separated by fractional crystallisation of the acid addition salts from a solvent, e.g. acetone, or from a solvent mixture, e.g. methanol/diethyl ether.

Resulting compounds of the formula I as well as their salts are obtained as racemates. A racemate can be separated into its optical isomers according to methods known *per se*, e.g. by the reaction with optical active acids such as tartaric acid or camphor sulphonic acid and subsequent crystallisation.

The starting materials of formulae II—VII can also be separated into geometric and/or optical isomers. Thus, by so doing the process according to the invention can be carried out with geometrically and/or optically uniform starting materials of formulae

Compounds of formula I have basic properties and can be conveniently prepared from their acid addition salts. Such salts are, for example, those of such organic acids, citric acid, acetic acid, lactic acid, maleic acid, sulphuric acid, and mineral acids such as hydrochloric acid, hydrobromic acid. These salts are crystalline solids soluble in water, somewhat less soluble in polar solvents such as methanol and ether and relatively insoluble in non-polar solvents, such as benzene, ether and petroleum.

As stated earlier, the compounds of formula I are characterized by an outstanding antidepressant activity. By way of example, for the purpose of evaluation, compounds of formula I were administered subcutaneously in various amounts to groups of ten mice each. These treated animals, as well as a control group of ten mice given 5 mg/kg s.c. of the substance 2 - hydroxy - 2 - ethyl - 3 - isobutyl - 5,5-dimethoxy - 1,2,3,4,6,7 - hexahydro - 11bH - benzofuran - 3-carboxylic acid hydrochloride (substance A) 16 hours after administration of the substance A, 30 minutes after the administration of the substance A, the animals were given ethanol in a dose of 7.5 g/kg i.p. A further control group of ten animals was given only ethanol. The duration of sleep was then measured in all the animals. The percentage decrease in the duration of sleep as compared to the duration of the substance A potentiated ethanol sleep, which reflects the measure of antidepressant effect, was calculated for each dose of test compound.

The following table gives the percentage decrease in duration of sleep for various compounds of formula I.

	Dose mg/kg s.c.	Decrease in duration of sleep (%)
1-chloro-5-(3-dimethyl-aminopropylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride	5-20	54-86
1-chloro-10,11-dihydro-5-(3-dimethylamino-propylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride	5-40	22-83
1-chloro-5-(3-dimethyl-aminopropyl)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride	5-20	39-74
1-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene-N-oxide oxalate	5-20	26-57
1-fluoro-10,11-dihydro-5-(3-dimethylamino-propylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride	20	42-53
Amitriptyline	20-40	

The minimal toxicity of the compounds of formula I can be determined by the following values for the acute toxicity in mice (24 hour LD₅₀)

	LD ₅₀	
	i.v.	p.o.
1-chloro-5-(3-dimethyl-aminopropylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride	140	810
1-chloro-10,11-dihydro-5-(3-dimethylamino-propylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride	90	1000-2000
1-chloro-5-(3-dimethyl-aminopropyl)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride	60-120	1000-2000
1-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene-N-oxide oxalate	90	1500
Amitriptyline	20	100

The substantial absence of anticholinergic effect can be demonstrated by the non-appearance of inhibition of salivation in rabbits. The salivation is increased in urethane-narcotised rabbits by the injection of pilocarpine and the saliva drippings are measured at 5-minute intervals. 1 - Chloro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo-[a,d]cycloheptene-N-oxide hydrochloride, when administered in amounts of 1 and 3 mg/kg i.v., respectively, did not inhibit the salivation and when administered in an amount of 6 mg/kg the compound resulted in only a minimal inhibition. When administering this compound or any one of 1 - chloro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene - N - oxide hydrochloride, 1 - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene - N - oxide hydrochloride, 1 - chloro - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene - N - oxide hydrochloride, 1 - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene - N - oxide oxalate and 1 - fluoro - 10,11 - dihydro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene - N - oxide hydrochloride, a lesser inhibition of the salivation was observable than when corresponding amounts of amitriptyline were administered.

The dibenzocycloheptene derivatives of this invention may be used as medicaments in the form of pharmaceutical preparations, which contain them in association with a compatible pharmaceutical carrier. This carrier can be an organic or inorganic, solid or liquid carrier suitable for enteral (e.g. oral) or parenteral administration. For making up the preparations there may be employed inert substances such as water, gelatine, gums, lactose, starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, petroleum jelly or any other known carrier used for the preparation of medicaments. The pharmaceutical preparations may be in solid form (for example, tablets, dragées, suppositories or capsules) or in liquid form (for example, solutions, emulsions or suspensions). If desired, they may be sterilized and/or may contain auxiliary substances, such as preserving agents, stabilizing agents, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They may also contain, in combination, other therapeutically useful substances.

A suitable pharmaceutical dosage unit contains from 1 to 200 mg of a compound of formula I. Suitable oral dosage regimens fall within the range of from 0.1 mg/kg per day to 5 mg/kg per day. Suitable parenteral dosage regimens fall within the range of from 0.01 mg/kg per day to 1 mg/kg per day. However, higher or lower amounts may be employed in particular cases and the specific dosage regimen may be adjusted to individual need and the professional judgment of the person supervising the administration of a compound of formula I.

In a clinical trial, hospitalized patients, suffering from depression, were treated with 1 - chloro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene-N-oxide hydrochloride as follows:

Daily dose, mg	150 mg	100 mg
Number of patients	16 women 8 men	8 women 9 men
Duration of treatment	36 days	

The preparation gave rise to a distinct antidepressant activity in all patients. The preparation was well tolerated by all patients. Particularly outstanding was the absence of various disadvantageous side effects such as anticholinergic effects (e.g. dryness of mouth, constipation and disturbance of micturition), sedative action and disturbances of vital functions (disturbances of sleep and/or appetite). In this respect a favourable result was obtained than when corresponding amounts of amitriptyline were used.

Moreover, in comparison with amitriptyline, a quicker onset of action was observed. At the same time, patients had been treated with 1 - chloro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene-N-oxide hydrochloride, a retrogression of the disease symptoms was observed. As a result thereof it was possible to discharge the majority of patients from in-patient treatment.

The following examples illustrate the invention.

EXAMPLE 1

10 g of 1 - Chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5H-dibenzo[a,d]cycloheptene are dissolved in 100 ml of methanol. To this solution are added drop by drop 10.6 g of 30% aqueous hydrogen peroxide solution. The mixture is stirred for 24 hours at room temperature, whereafter, with cooling, the excess hydrogen peroxide still present is destroyed by the addition of platinum black. The mixture is filtered, evaporated under reduced pressure and the residue dissolved in ethanol. To the ethanol solution is added a solution of 6.5 g of oxalic acid in 100 ml of ether. The precipitate formed is filtered off. 1 - Chloro - 10,11 - dihydro - 5 - (3-dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene - N - oxide - oxalate is obtained, which melts at 125—128°C.

The 1 - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene used as starting material can be prepared as follows:

86.6 g of Gilman alloy or magnesium turnings are heated under reflux conditions in 800 ml of absolute ether with a trace of iodine. Subsequently, a solution of 390 g of 3-dimethylaminopropyl chloride in 500 ml of absolute tetrahydrofuran is added dropwise within 2 hours. The mixture is heated under reflux conditions for a further 3 hours. To the suspension obtained, cooled to 15°C, there is added dropwise within 15 minutes a solution of 242.7 g of 1 - chloro - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene-5-one in 500 ml of absolute tetrahydrofuran and the whole is heated under reflux conditions for a further 12 hours. The reaction mixture is subsequently cooled to 15°C and hydrolysed with 500 ml of saturated ammonium chloride solution. The whole is filtered and washed with methylene chloride. The filtrate is dried with sodium sulphate and evaporated under reduced pressure. The residual yellow crude substance is recrystallized from 6000 ml of high-boiling petroleum ether. There is obtained 1 - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5 - hydroxy-5H-dibenzo[a,d]cycloheptene which melts at 131—132°C.

500 g of 1 - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5-hydroxy-5H-dibenzo[a,d]cycloheptene, 437 g of red phosphorus, 4,000 ml of glacial acetic and 2,160 ml of 57% hydroiodic acid are heated under reflux conditions in an argon atmosphere for 3 hours. The suspension is filtered, the filtrate is washed with 2,000 ml of boiling water and subsequently cooled to 20°C. The crystals which separate out are separated by decantation and the mother liquor is concentrated under reduced pressure. The combined residues are suspended in 15,000 ml of water with ice and adjusted to pH 10—12 with stirring with concentrated caustic soda solution. The mixture is extracted with 4,000 ml of methylene chloride and the organic phase is washed with saturated sodium chloride solution and sodium sulphate. The residue is washed with saturated sodium chloride solution and sodium sulphate and evaporated under reduced pressure. The residue is dissolved in 2,000 ml of ether, filtered from insoluble portions and evaporated. There is obtained 1 - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene as a solid. The hydrochloride of this compound crystallizes from a mixture of ether and alcohol at 153°C.

EXAMPLE 2

500 g of 1 - Chloro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene (isomeric mixture 1:1) are dissolved in 4,000 ml of methanol. To this solution there is added within 15 minutes 920 g of 30% aqueous hydrogen peroxide solution. The mixture is stirred at room temperature for further 64 hours. The mixture is subsequently extracted on 6000 ml of ice water and 1200 ml of 25% aqueous ammonia solution and extracted with 3 times 2000 ml of methylene chloride. The methylene chloride solution is washed with water until no more hydrogen peroxide can be detected, filtered and acidified with methanolic hydrochloric acid. The solution is evaporated under reduced pressure, dissolved in 1500 ml of methanol and filtered. The residue is washed with 500 ml of methanol. To the combined filtrates are added 6000—7000 ml of ether. After storage at -2°C crystalline 1-chloro-5-(3-dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene - N - oxide hydrochloride is obtained which melts at 170—176°C.

The oxidation of 1 - chloro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene can also be carried out as follows:

500 g of 1 - chloro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene (isomeric mixture 1:1) are dissolved in 2500 ml of methanol. The solution is cooled to 0—5°C. 550 g of 30% aqueous hydrogen peroxide solution are added within 60 minutes and the mixture is stirred at 20°C for about 60 hours. The mixture is subsequently poured onto 3500 ml of ice water and 680 ml of 25% aqueous ammonia

solution and extracted twice with 2000 ml of methylene chloride. The combined extracts are washed several times with 100 ml each of water until no more hydrogen peroxide can be detected, acidified with methanolic hydrochloric acid and evaporated under reduced pressure at 50°C. The residue is evaporated twice to three times with 500 ml of absolute benzene each time and subsequently dried for about 2 to 3 hours at 40°C under strongly reduced pressure. The yellow, viscous residue is dissolved in 2000 ml of absolute methanol and 5000 ml of absolute ether are added to cause crystallisation. After addition of decolouring carbon the mixture is filtered. 2000 ml of absolute ether are added to the solution (the solution should be clear; if necessary it should be filtered once more). After seeding and scratching, the solution is left for at least 48 hours at -2°C. After filtration and washing with ether, 1-chloro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride is obtained in crystalline form, melting at 175—176°C. From the mother liquor a second batch of crystals can be obtained by evaporation and renewed crystallisation. These crystals melt at 169—173°C.

The 1-chloro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene used as starting material can be prepared as follows:

17 g of magnesium and 85 g of 3-dimethylaminopropyl chloride are reacted which each other according to the procedure given in Example 1. The resulting Grignard compound is then treated with a solution of 52 g of 1-chloro-5H-dibenzo[a,d]cycloheptene-5-one in 500 ml of absolute tetrahydrofuran. Working up is performed in the same manner as described in Example 1 for the preparation of 1-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene. There is obtained 1-chloro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene of melting point 134—136°C. The hydrochloride prepared therefrom melts at 226—227°C after recrystallisation from methanol/ether.

10 g of 1-chloro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene are heated under reflux conditions for 1 hour in 50 ml of absolute ethanol and 11 ml of 30% ethanolic hydrochloric acid. The mixture is evaporated under reduced pressure, taken up in water, washed with ether and made alkaline with 2N caustic. This solution is shaken out with methylene chloride. The organic phase is washed with water dried over sodium sulphate and evaporated. 1-chloro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene is obtained as a viscous oil. This represents a mixture of the two isomers in the proportion about 1:1. The hydrochloride which can be prepared by treatment with methanol/ether melts at 208—210°C, after recrystallisation from ethanol/

EXAMPLE 2

If, in Example 2, the 1-chloro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene starting material is replaced by an equivalent amount of 1-chloro-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene there is obtained as the end product, when working up under similar conditions, 1-chloro-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride of melting point 165—166°C.

The 1-chloro-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene used as starting material can be prepared as follows:

10 g of 1-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene are heated under reflux conditions for 1 hour with 50 ml of absolute ethanol and 11 ml of 30% ethanolic hydrochloric acid. The mixture is evaporated under reduced pressure and subsequently recrystallized from methanol/ether. There is obtained 1-chloro-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene hydrochloride which melts at 208—210°C. This compound is a mixture of the two geometric isomers α + β in the proportion 1:1.

EXAMPLE 4

1-chloro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene is dissolved in 100 ml of methanol. To this solution are added 9.05 g of 30% aqueous hydrogen peroxide solution. The mixture is stirred 41 hours at 50°C. After destroying excess hydrogen peroxide by the addition of platinum black the mixture is filtered, acidified with 30% methanolic hydrochloric acid and evaporated under reduced pressure. The residue crystallises from acetone. 1-chloro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride is obtained melting at 179—181°C.

The 1-chloro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene used as starting material can be prepared as follows:

200 g of 1-chloro-5H-dibenzo[a,d]cycloheptene-5-one are dissolved in 1000 ml of dioxan. To this solution is added a solution of 69 g of sodium borohydride in 200 ml of water. This mixture is stirred for 12 hours at room temperature, subsequently evaporated under reduced pressure and the residue is distributed between water and ether. The ether solution is washed, dried and evaporated. The 1-chloro-5-hydroxy-5H-dibenzo[a,d]cycloheptene so obtained, is recrystallized from ether/petroleum ether and thereafter melts at 143—144°C.

70 g of 1-chloro-5-hydroxy-5H-dibenzo[a,d]cycloheptene are dissolved in 250 ml of absolute benzene and heated together with 105 ml of thionyl chloride for 2 hours at reflux conditions. The mixture is evaporated under reduced pressure and the residue crystallized from carbon tetrachloride. The crystals so obtained are filtered off and washed with petroleum ether. There is obtained 1,5-dichloro-5H-dibenzo[a,d]cycloheptene melting at 143—145°C.

5.6 g of magnesium turnings are suspended in 100 ml of absolute tetrahydrofuran and treated with a trace of iodine and methyl iodide. To this mixture there is added dropwise under reflux conditions within about 20 minutes a solution of 26 g of 3-dimethylaminopropyl chloride in 100 ml of tetrahydrofuran. The mixture is further boiled for a further 3 hours. After cooling to 20°C, a solution of 25.2 g of 1,5-dichloro-5H-dibenzo[a,d]cycloheptene in 250 ml of tetrahydrofuran is added dropwise within 15 minutes. The mixture is subsequently heated under reflux conditions for 15 hours, cooled and hydrolysed with 200 ml of saturated ammonium chloride solution. The mixture is filtered and washed with methylene chloride. The filtrate is dried with sodium sulphate and evaporated under reduced pressure. 1-chloro-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptene is obtained as a viscous oil which boils at about 160°C/0.01 mm. The salt with maleic acid melts at 146—147°C.

EXAMPLE 5

5 g of 1-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride are dissolved in 20 ml of absolute methanol and heated under reflux conditions with 2 ml of 24% (weight per volume) methanolic hydrochloric acid for 2 hours. After cooling, ether is added. 1-chloro-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride is obtained as crystals melting at 165°C.

The 1-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride

40 g of 1-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride are dissolved in 1000 ml of methanol. After the addition of 61 g of 30% aqueous hydrogen peroxide solution, the mixture is stirred at room temperature for 160 hours. Excess hydrogen peroxide is subsequently destroyed by the addition of platinum black. The mixture is filtered and evaporated to dryness. 1-chloro-10,11-dihydro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride is obtained as crystals melting at 164—166°C.

EXAMPLE 6

If, in Example 5, instead of 1-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride, 1-chloro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride is employed, there is obtained, under otherwise equal conditions, 1-chloro-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride which melts at 172—174°C after recrystallization from methanol/ether.

The 1-chloro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride used as starting material can be prepared as follows:

2 g of 1-chloro-5-(3-dimethylaminopropyl)-5-hydroxy-5H-dibenzo[a,d]cycloheptene are dissolved in 60 ml of methanol. To this solution are added 2.1 g of 30% aqueous hydrogen peroxide solution. The mixture is stirred at 50°C for 35 hours. After cooling to -10°C crystals precipitate out. These are filtered off and washed with ether. 1-chloro-5-(3-dimethylaminopropylidene)-5-hydroxy-5H-dibenzo[a,d]cycloheptene-N-oxide, melting at 161—165°C (dec.) is obtained.

This compound is dissolved in ether and yields, after the addition of methanolic hydrochloric acid, 1 - chloro - 5 - (3 - dimethylaminopropyl) - 5 - hydroxy - 5H-dibenzo[a,d]cycloheptene-N-oxide hydrochloride which melts at 174—177°C after recrystallization from methanol/ether.

EXAMPLE 7

3 g of 1 - Fluoro - 10,11 - dihydro - 5 - (3 - dimethylaminopropylidene) - 5H-dibenzo[a,d]cycloheptene are dissolved in 30 ml of methanol in an argon atmosphere. To this solution are added 3.5 g of 30% aqueous hydrogen peroxide solution. The mixture is kept at 50°C with stirring for 24 hours. After cooling to 0°C the excess hydrogen peroxide is destroyed by means of addition of platinum black. The solution is filtered, acidified with methanolic hydrochloric acid and evaporated under reduced pressure. The residue is crystallized from methanol/ether, the crystals formed filtered off and dried under reduced pressure at 100°C. 1 - Fluoro - 10,11 - dihydro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene - N - oxide hydrochloride melting at 166—168°C, is obtained. This compound consists of a mixture of the two α - and β -isomers in a ratio of about 1:1.

The 1 - fluoro - 10,11 - dihydro - 5 - (3 - dimethylaminopropylidene) - 5H-dibenzo[a,d]cycloheptene used as starting material for this Example can be prepared as follows:

14.8 g of pulverised phthalic anhydride, 18.5 g of ortho fluorophenyl acetic acid and 0.5 g of freshly melted sodium acetate are heated for 3 hours at 235—240°C and the resulting water is distilled off. The hot mixture is transferred into a mortar and pulverised. The crude product is recrystallized from acetone/petroleum ether. There is obtained ortho fluorobenzylidene phthalide, which melts at 148—151°C.

72.6 g of ortho-fluorobenzylidene phthalide are heated in an argon atmosphere for 24 hours under reflux conditions together with 55.0 g of red phosphorus and 450 ml of hydriodic acid (density 1.75). The mixture is cooled, supplied with 500 ml of water and filtered. The residue is heated with 2N caustic soda to 80°C and again filtered to remove the phosphorus. The alkaline solution is acidified and extracted with methylene chloride, washed with water, dried and evaporated to dryness. The crude product obtained is recrystallized from acetone/low boiling petroleum ether. 2-(ortho-fluorophenethyl)-benzoic acid is obtained as white crystals melting at 93—94°C.

280 g of phosphoric acid are heated to 120°C and, in an atmosphere of argon, 70.0 g of (ortho-fluorophenethyl)-benzoic acid are added. The heating is continued at 150°C. The mixture is poured over ice water and extracted with ether. The ether extract is washed with water, 2N caustic soda and again with water. The residue is dried and evaporated to dryness. The residue is recrystallized from acetone/low boiling petroleum ether. There is obtained 2-(ortho-fluorophenethyl)-benzoic acid, m.p. 93—94°C.

10.1 g of 2-(ortho-fluorophenethyl)-benzoic acid and 10.1 g of 1,1-dichloro-2,2-difluoroethane are heated to 120°C and, in an atmosphere of argon, 70.0 g of (ortho-fluorophenethyl)-benzoic acid are added. The heating is continued at 150°C. The mixture is poured over ice water and extracted with ether. The ether extract is washed with water, 2N caustic soda and again with water. The residue is dried and evaporated to dryness. The residue is recrystallized from acetone/low boiling petroleum ether. There is obtained 2-(ortho-fluorophenethyl)-benzoic acid, m.p. 93—94°C.

19.1 g of Gilman alloy and a trace of iodine are heated in 100 ml of ether and reacted with 88 g of dimethylaminopropylidene. The mixture is cooled, supplied with 500 ml of water and filtered. The residue is heated with 2N caustic soda to 80°C and again filtered to remove the phosphorus. The alkaline solution is acidified and extracted with methylene chloride, washed with water, dried and evaporated to dryness. The crude product obtained is recrystallized from acetone/low boiling petroleum ether. 2-(ortho-fluorophenethyl)-benzoic acid is obtained as white crystals melting at 93—94°C.

1 - Fluoro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5 - hydroxy - 5H-dibenzo[a,d]cycloheptene are heated under reflux conditions for 2 hours with 100 ml of ethanol and 12 ml of 30% ethanolic hydrochloric acid. The mixture is evaporated under reduced pressure. The working up is effected in the same manner as in Example 1. There is obtained 1 - fluoro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5 - hydroxy - 5H-dibenzo[a,d]cycloheptene which crystallizes from high boiling petroleum ether at melting point 115—117°C.

1 - Fluoro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5 - hydroxy - 5H-dibenzo[a,d]cycloheptene are heated under reflux conditions for 2 hours with 100 ml of ethanol and 12 ml of 30% ethanolic hydrochloric acid. The mixture is evaporated under reduced pressure. The working up is effected in the same manner as in Example 1. There is obtained 1 - fluoro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5 - hydroxy - 5H-dibenzo[a,d]cycloheptene which crystallizes from high boiling petroleum ether at melting point 115—117°C.

EXAMPLE 8

0.2 g of 1 - Chloro - 10,11 - dihydro - 5 - (3 - N - hydroxy - N - methylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene are treated for one hour at room temperature with a solution of 0.97 g of sodium hydroxide in 5 ml of acetone. After evapora-

tion under reduced pressure there is obtained as the product crude 1 - chloro - 10,11-dihydro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene - N-oxide hydroiodide, which, after recrystallization from methanol-ether, melts at 103—104°C (dec.). This product is converted into the corresponding hydrochloride by neutralisation with sodium hydroxide solution and reaction of the liberated base with ethanolic hydrochloric acid. The hydrochloride melts at 165—168°C.

The 1 - chloro - 10,11 - dihydro - 5 - (3 - N - hydroxy - N - methylamino-propylidene)-5H-dibenzo[a,d]cycloheptene used as starting material for this Example can be prepared as follows:

To 14 g of Gilman alloy in 100 ml of absolute ether, after the addition of a trace of iodine or methyl iodide, there is added dropwise within about 30 minutes under reflux conditions a solution of 45.6 g of 1-chloro-3-methoxypropane in 300 ml of absolute ether. The mixture is further heated for a further 3 hours. After cooling to 20°C, a solution of 48.5 g of 1 - chloro - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten-5-one in 160 ml of tetrahydrofuran is added within 30 minutes. The mixture is subsequently heated under reflux conditions for 12 hours. The mixture is then hydrolysed, with cooling, with 150 ml of saturated ammonium chloride solution, filtered, washed with chloroform, dried with sodium sulphate and evaporated. The crude 1 - chloro - 10,11 - dihydro - 5 - (3 - methoxypropyl) - 5 - hydroxy - 5H-dibenzo[a,d]cycloheptene obtained melts at 80—81°C after recrystallization from ether/petroleum ether.

53.3 g of 1 - chloro - 10,11 - dihydro - 5 - (3 - methoxypropyl) - 5 - hydroxy-5H-dibenzo[a,d]cycloheptene are heated under reflux conditions for 1 hour in 250 ml of methanol and 53 ml of 30% methanolic hydrochloric acid. The mixture is evaporated under reduced pressure, taken up in ether, washed with water, dried with sodium sulphate and again evaporated. 1 - Chloro - 10,11 - dihydro - 5 - (3 - methoxypropylidene) - 5H - dibenzo[a,d]cycloheptene is obtained as a yellow oil.

48.5 g of 1 - Chloro - 10,11 - dihydro - 5 - (3 - methoxypropylidene) - 5H-dibenzo[a,d]cycloheptene are dissolved in 150 ml of methylene chloride, cooled to 10°C and treated within 15 minutes with a solution of 30 g of boron trichloride in 150 ml of methylene chloride. The mixture is stirred at room temperature for a further 19 hours. The mixture is then poured on ice-water, extracted with methylene chloride, washed with water and dried over sodium sulphate. After evaporation, 1 - chloro - 10,11 - dihydro - 5 - (3 - chloropropylidene) - 5H - dibenzo[a,d]cycloheptene is obtained as a yellow-orange oil which slowly crystallizes out. Melting point 30°C.

A mixture of 20 g of 1 - chloro - 10,11 - dihydro - 5 - (3 - chloropropylidene) - 5H-dibenzo[a,d]cycloheptene, 80 ml of absolute methanol and 10 ml of concentrated hydrochloric acid is heated in an autoclave for 12 hours at 120°C under pressure. The solution is then evaporated under reduced pressure and the resulting oily residue is treated with concentrated hydrochloric acid. 1 - Chloro - 10,11 - dihydro - 5 - (3 - N - methylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene hydrochloride is obtained. After recrystallization from methanol/ether, this compound melts at 209—210°C. It consists of a mixture of the α - and β -isomers in the proportion of about 1:1.

10 g of 1 - chloro - 10,11 - dihydro - 5 - (3 - methylaminopropylidene) - 5H-dibenzo[a,d]cycloheptene are heated under reflux conditions for 1 hour. The base is recovered by neutralization with concentrated hydrochloric acid. The free base is dissolved in 300 ml of ether and 6.65 g of benzoyl chloride in 50 ml of ether and 30 ml of chloroform. The mixture is stirred for 3 hours at -5—0°C, whereby gradually a precipitate is formed. The precipitate is filtered off and washed with ether. The ethereal solution is successively washed with dilute hydrochloric acid, sodium bicarbonate solution and over sodium sulphate and evaporated. 1 - Chloro - 10,11 - dihydro - 5 - (3 - N - benzoyloxy - N - methyl - aminopropylidene) - 5H - dibenzo[a,d]cycloheptene is obtained as an oil.

10 g of 1 - Chloro - 10,11 - dihydro - 5 - (3 - N - benzoyloxy - N - methylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene are, together with 100 ml of ethanol and a solution of 2 g of potassium hydroxide in 20 ml of ethanol, heated for 1 hour under reflux conditions. After cooling, the mixture is filtered and the ethanol is evaporated under reduced pressure. The residue is taken up in ether and the ethereal solution is shaken with dilute hydrochloric acid. The acid extracts are made alkaline with concentrated ammonia, extracted with ether, dried and evaporated. 1-Chloro-10,11 - dihydro - 5 - (3 - N - hydroxy - N - methyl - aminopropylidene) - 5H-dibenzo[a,d]cycloheptene is obtained. It melts at 112°C after recrystallization from ether/petroleum ether.

from benzene/petroleum ether. The compound consists of a mixture of the geometric isomers in a ratio of about 1:2.

EXAMPLE 9

5 1 - Chloro - 10,11 - dihydro - 5 - (3 - N - hydroxy - N - methyl - aminopropyl) - 5H-dibenzo[a,d]cycloheptene is treated at room temperature with a solution of methyl iodide in acetone. As the product there is obtained 1 - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene - N - oxide hydroiodide. This compound is converted into the corresponding oxalate by neutralisation with sodium hydroxide solution and treatment of the liberated base in ethanolic solution with a solution of oxalic acid in ether. The oxalate melts at 125—128°C.

10 The 1 - chloro - 10,11 - dihydro - 5 - (3 - N - hydroxy - N - methylaminopropyl) - 5H-dibenzo[a,d]cycloheptene used as starting material for this Example can be prepared as follows:

15 A solution of 102.5 g of 1 - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene in 500 ml of methylene chloride is added dropwise to a solution of 55 g of cyanogen bromide in 500 ml of methylene chloride. The mixture is stirred at room temperature for 12 hours and subsequently poured on ice-water. The methylene chloride phase is washed with 2N hydrochloric acid and water, dried with sodium sulphate and evaporated under reduced pressure. The residue consists of a yellow oil which is crystallized from ether. There is obtained 1-chloro-10,11 - dihydro - 5 - (3 - N - cyano - N - methyl - aminopropyl) - 5H - dibenzo[a,d]cycloheptene, melting point 69—71°C. After dissolving this compound in benzene/ether, it can be further purified by chromatography on 500 g of silica gel.

25 A mixture of 650 g of 1 - chloro - 10,11 - dihydro - 5 - (3 - N - cyano - N - methyl - aminopropyl) - 5H - dibenzo[a,d]cycloheptene, 4,000 ml of glacial acetic, 2,000 ml of water and 1,000 ml of concentrated hydrochloric acid are heated under reflux conditions for 24 hours. The mixture is concentrated under reduced pressure, diluted with 20,000 ml of ice-cold water and washed with 5,000 ml of methylene chloride. The whole is made alkaline with concentrated caustic soda and the resulting precipitate taken up in methylene chloride. By concentration of the methylene chloride solution, there results a brown-red oil which is converted into crystalline 1-chloro-10,11 - dihydro - 5 - (3 - methyl - aminopropyl) - 5H - dibenzo[a,d]cycloheptene hydrochloride by the addition of methanolic hydrochloric acid. After recrystallization from benzene/ether, this compound melts at 168—169°C. The free base is recovered from the hydrochloride by neutralization with sodium hydroxide solution.

35 1 - chloro - 10,11 - dihydro - 5 - (3 - methyl - aminopropyl) - 5H - dibenzo[a,d]cycloheptene according to the preceding paragraph is treated with methanolic hydrochloric acid according to the directions given in Example 8 and the 1 - chloro - 10,11 - dihydro - 5 - (3 - methoxypropyl) - 5H - dibenzo[a,d]cycloheptene so obtained is boiled with ethanolic sodium hydroxide solution according to the directions of Example 8. 1 - chloro - 10,11 - dihydro - 5 - (3 - N - hydroxy - N - methyl - aminopropyl) - 5H - dibenzo[a,d]cycloheptene is obtained as a crystalline powder melting at 104—105°C.

EXAMPLE 10

45 1 - chloro - 10,11 - dihydro - 5 - (3 - N - hydroxyl - aminopropyl) - 5H - dibenzo[a,d]cycloheptene is treated with a solution of sodium methoxide in methanol and a solution of nitromethane. To this solution is added a solution of 1 - chloro - 3 - bromopropylidene - 5H - dibenzo[a,d]cycloheptene in nitromethane. The mixture is stirred for 24 hours at 35°C and is subsequently evaporated under reduced pressure. The residue is boiled with ethanolic sodium hydroxide solution and methanolic hydrochloric acid and again evaporated under reduced pressure. The residue is crystallized from methanol/ether, 1 - chloro - 10,11 - dihydro - 5 - (3 - aminopropylidene) - 5H - dibenzo[a,d]cycloheptene - N - oxide hydrochloride, melting at 165—168°C.

55 1 - chloro - 10,11 - dihydro - 5 - (3 - bromopropylidene) - 5H - dibenzo[a,d]cycloheptene used as a starting material for this Example can be prepared as follows:

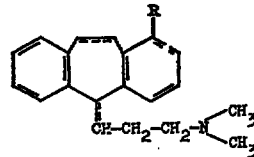
60 A solution of 45.6 g of 1 - chloro - 3 - methoxypropane in 300 ml of absolute ether, after the addition of a trace of iodine and methyl iodide, there is added dropwise within about 30 minutes under reflux conditions a solution of 48.5 g of 1 - chloro - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohept-5-one in 160 ml of absolute ether. The mixture is further heated for a further 3 hours. After cooling to 20°C, a solution of 48.5 g of 1 - chloro - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohept-5-one in 160 ml of absolute ether is added within 30 minutes. The



6) 5-Chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo-[a,d]cycloheptene-N-oxide and acid addition salts thereof.

7) A pharmaceutical preparation comprising a dibenzocycloheptene compound as formulated in claim 1, an isomer thereof or an acid addition salt of such a compound or an isomer thereof in association with a compatible pharmaceutical carrier.

8) A process for the manufacture of the dibenzocycloheptene compounds formulated in claim 1, isomers thereof and acid addition salts of said compounds and isomers, which process comprises oxidizing a tertiary amine of the general formula

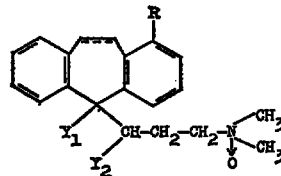


II

10

wherein R and the dotted bonds have the significance given in claim 1, or dehydrating a carbinol of the general formula

10

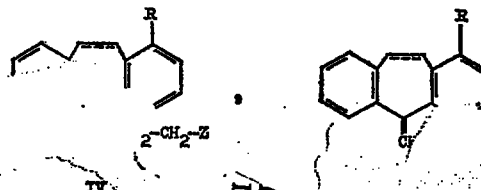


III

15

wherein R and the dotted bond have the significance given in claim 1, one of the symbols Y₁ and Y₂ represents a hydrogen atom and the other represents a hydroxy group, or an acid addition salt thereof, or treating a compound of the general formula

15

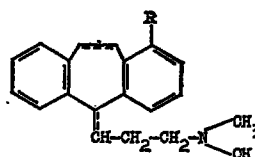


IV

20

wherein R and the dotted bonds have the significance given in claim 1, Z represents a hydrogen atom or a substituted sulphonyloxy residue and A represents the oxylamine, or treating a compound of the general formula

20



VII

wherein R and the dotted bond

have the significance given in claim 1,



* C L M S *

29

16

1,188,107

16

with a methylating agent, whereupon, in optional sequence, if desired, the isomers are isolated from an isomer mixture obtained and, if desired, a base obtained is converted into an acid addition salt.

5 9) A process according to claim 8, wherein a starting compound in which R represents a chlorine atom is used.

10) A process according to claim 8 or claim 9, wherein 1 - chloro - 5 - (3-dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene is oxidized or 1 - chloro - 5 - (3 - dimethylaminopropyl) - 5 - hydroxy - 5H - dibenzo[a,d]cycloheptene - N-oxide or an acid addition salt thereof is dehydrated, if desired, the geometric isomers are isolated from an isomer mixture obtained, and, if desired, a base obtained is converted into an acid addition salt.

11) A process according to claim 8 or claim 9, wherein 1 - chloro - 10,11-dihydro - 5 - (3 - dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene is oxidized or 1 - chloro - 10,11 - dihydro - 5 - (3 - dimethylaminopropyl) - 5 - hydroxy-5H-dibenzo[a,d]cycloheptene-N-oxide or an acid addition salt thereof is dehydrated, if desired, the geometric isomers are isolated from an isomer mixture obtained and, if desired, a base obtained is converted into an acid addition salt.

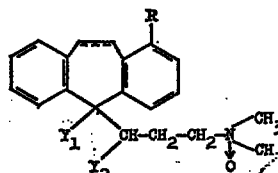
12) A process according to claim 8 or claim 9, wherein 1 - chloro - 5 - (3-dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene is oxidized, if desired, the geometric isomers are isolated from an isomer mixture obtained and, if desired, a base obtained is converted into an acid addition salt.

13) A process according to claim 8 or claim 9, wherein 1 - chloro - 10,11-dihydro - 5 - (3 - dimethylaminopropyl) - 5H - dibenzo[a,d]cycloheptene is oxidized and, if desired, the base obtained is converted into an acid addition salt.

14) A process for the manufacture of the dibenzocycloheptene compounds formulated in claim 1, isomers thereof and acid addition salts of said compounds and isomers, substantially as hereinbefore described with reference to the Examples.

15) Dibenzocycloheptene compounds as formulated in claim 1, isomers thereof and acid addition salts of said compounds and isomers, when manufactured by the process claimed in any one of claims 8 to 14 inclusive.

16) Carbinols of the general formula



III

where R represents a hydroxyl group or a fluorine atom or a chlorine atom or a hydroxyl group and the

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