

938.201



PATENT SPECIFICATION

NO DRAWINGS

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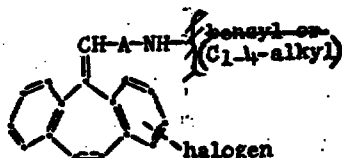
COMPLETE SPECIFICATION

Substituted Aminoalkylidene-Dibenzocyclohepta-Dienes and -Trienes and a process for the manufacture thereof

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

The present invention relates to novel substituted aminoalkylidene - dibenzocycloheptadienes and aminoalkylidene - dibenzocycloheptatrienes and salts thereof; more particularly, the invention is concerned with 5-[3² (benzyl - amino) - propylidene] - dibenzocycloheptadiene[1,5] and the corresponding 3 - (C₁₋₄ alkyl) amino compounds and their triene[1,3,5] analogues (all of which may contain a halogen substituent in a benzo ring) and with a process for the manufacture thereof.

The novel substances provided by the invention are compounds which may be formulated thus



wherein A stands for the ethylene radical or an ethylene radical containing a C₁₋₄-alkyl substituent and the broken lines denote optional bonds, and acid addition salts thereof.

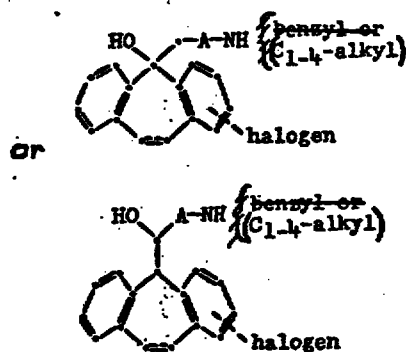
[Price 4s. 6d.]

The preferred salts are pharmaceutically acceptable acid addition salts with pharmaceutically acceptable organic and inorganic acids; for example, hydrochloric acid, hydrobromic acid, sulphuric acid, acetic acid, tartaric acid and lactic acid. The compounds and salts are distinguished by their manifold activity on the central nervous system. They have narcosis potentiation, adrenolytic, sedative, antihistaminic, antiemetic, antipyretic, local-anaesthetic and hypothermic activity. Especially remarkable is the rapid onset of action following the administration of these substances. They can be administered in conventional pharmaceutical form. Thus the compounds or their pharmaceutically acceptable acid addition salts can be admixed with suitable pharmaceutical organic or inorganic carrier materials adapted for parenteral or enteral application; such carriers as, for example, water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, petrolcum jelly or the like. The preparations can be in solid form (for example, tablets, suppositories, capsules, dragées and the like) or in liquid form (for example, solutions, suspensions, emulsions, and the like). If desired, they can be submitted to standard pharmaceutical processes, such as sterilization, and can contain conventional excipients such as preservatives, stabilizers, wetting agents, emulsifying agents, salts used for varying osmotic pressure, and buffers. The preparations can advantageously contain between about five and about 100 mg of the active material obtained according to this invention as well as other therapeutically active materials.

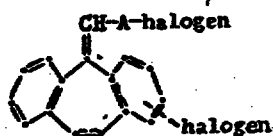
Illustrative of the C₁₋₄-alkyl substituents

which may be attached to the nitrogen atom and/or the adjoining ethylene radical are the groups methyl, ethyl, isopropyl. The optional halogen substituents are fluoro, chloro, bromo and iodo, chloro being preferred. The preferred substances are 5 - (3' - methylamino-propylidene) - dibenzo[a,e]cycloheptadiene-[1,5], 5 - (3' - ethylamino - propylidene) - dibenzo[a,e]cycloheptadiene[1,5], 5 - (3' - isopropylamino - propylidene) - dibenzo[a,e]cycloheptadiene [1,5], 3 - chloro - 5 - (3' - methylamino - propylidene) - dibenzo[a,e]cycloheptadiene [1,5], 5 - (2' - methyl - 3' - methylamino - propylidene) - dibenzo[a,e]cycloheptadiene [1,5], 5 - (3' - benzylamino - propylidene) - dibenzo[a,e]cycloheptadiene [1,5] and 5 - (3' - methylamino - propylidene) - dibenzo[a,e]cycloheptatriene [1,3,5] and their hydrochlorides.

According to the process provided by the invention the novel substances aforesaid are manufactured by dehydrating a hydroxy compound of the formula



(wherein A and the broken lines have the significance given hereinbefore) in an organic solvent in the presence of a dehydrating agent or reacting a halogeno-alkylidene compound of the formula



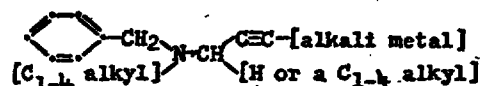
(wherein A and the broken lines have the significance given hereinbefore) with benzyl amine or a C₁₋₄-alkyl amine and, if desired, converting the dehydration or reaction product into an acid addition salt.

The compounds of formula II used as starting materials can be prepared, for example, by the following methods:

a) Dibenzo[a,e]cycloheptadiene [1,5] one-(5) or dibenzo[a,e]cycloheptatriene [1,3,5]

one-(5) or the appropriate halogeno derivative is reacted by means of a magnesium, lithium, or zinc metal-organic reaction with the appropriate N-alkyl-N-benzyl-aminoalkyl halide and the reaction product hydrolyzed and then debenzylated by hydrogenolysis. Preferably the magnesium compound of the chosen N - alkyl - N - benzyl - aminoalkyl halide is used and can, for example, be prepared by the reaction of activated magnesium [for example, magnesium in the form of a finely divided copper-magnesium alloy such as that of GILMAN (Recueil des Travaux Chimiques des Pays-Bas, 1928, 47, 19)] with an ether solution of the halide. In a preferred embodiment, the reaction is initiated by the addition of a suitable alkyl halide; for example, methyl iodide or ethyl bromide. The subsequent hydrolysis of the metal-organic complex is suitably effected under practically neutral conditions; for example, by means of ammonium chloride. The debenzylation can suitably be effected by hydrogenation in the presence of a noble metal catalyst, preferably in a lower aliphatic alcohol solvent at an elevated pressure and temperature in the presence of palladium/carbon. During this treatment, the multiple bonds in the ring skeleton are unattacked.

b) Dibenzo [a,e]cycloheptadiene[1,5] one-(5) or dibenzo[a,e]cycloheptatriene[1,3,5] one-(5) or the appropriate halogeno derivative is reacted with an alkali metal compound of the formula



and subsequently hydrolyzed and the hydrolysis product reduced at the triple bond and debenzylated by hydrogenation. This reaction is advantageously effected by the use of a sodium, potassium or lithium compound. The ketone, either in a finely powdered form or dissolved in an inert solvent (for example, absolute ether, benzene, or tetrahydrofuran), is suitably added to a suspension of the alkali-metal organic compound of Formula IV in liquid ammonia. The hydrolysis of the resultant metal-organic compound is advantageously effected under practically neutral conditions; for example, hydrolysis with solid ammonium chloride or an aqueous ammonium chloride solution. The resultant disubstituted-amino compound is obtained directly in free form and can be separated from side products and isolated by treatment with a suitable water-immiscible organic solvent such as, for example, ether, ethyl acetate, chloroform, methylene chloride or the like. The isolated

product is then hydrogenated in order to saturate the triple bond and debenzylate. The hydrogenation can suitably be effected under the conditions described earlier under (a).

- 5 c) The ketones mentioned in (a) and (b) are reacted with an ethyl-magnesium halide and the resulting carbinols converted by dehydration into ethylidene compounds. By the action of an oxidizing agent the ethylidene group is then converted into an acetyl group and the resulting 5-acetyl compounds are then reacted in the presence of a benzyl amine or a C₁₋₄-alkyl amine or a benzyl alkyl amine in which the alkyl group contains from 1 to 4 carbon atoms, with formaldehyde or a C₁₋₃-aliphatic aldehyde under the conditions of a MAN-NICH reaction and subsequently the resulting ketone is catalytically reduced according to the method described under (a).

- 20 The compounds of formula III used as starting materials can be obtained for example by the following method:

- (1) Dibenzo[a,e]cycloheptadiene[1,5]one-(5) or dibenzo[a,e]cycloheptatriene[1,3,5]one-(5) or the appropriate halogeno derivative is reacted by means of an organo-magnesium reaction with a suitable etherified 3(or-2)-hydroxy-propyl halide (e.g. a 3(or-2)-alkoxy-propyl halide) or a propenyl halide or a C₁₋₄-alkyl substituted derivative thereof. The reaction conditions are analogous to those described for the preparation of the starting material II under (a). Examples of etherified hydroxy-propyl halides and propenyl halides used as reactants are 1-chloro-2-methyl-3-methoxy-propane; 1-chloro-2-methyl-propene-(2); 1-chloro-3-methoxy-propane and 1-bromo-propene-(2). The ether function is preferably a lower-alkoxy group such as methoxy, ethoxy, propoxy or butoxy and is preferably in the terminal position of the alkyl halide. The (3-methoxy-propyl)-magnesium compounds are preferred materials. The ether function can however be aralkoxy such as benzyloxy or phenethoxy or even tetrahydro-pyranyloxy.

- (2) The reaction products obtained by the reaction of the ketone with the organo-magnesium compound which contains the ether function or unsaturated group in the terminal position are converted by hydrolysis as described in (a) into tertiary carbinols which, in turn, can be separated from side products and isolated by treatment with suitable water-immiscible organic solvents such as, for example, ether, ethyl acetate, chloroform, methylene chloride or the like. The tertiary carbinols are solid, for the most part easily crystallizable, compounds.

- 60 (3) In a further step the ether function is, simultaneously with the dehydration of the carbinol, replaced by halogen. The same reaction product is obtained from compounds which bear a terminally unsaturated propenyl group by a simultaneous dehydration and

halogenation—which can be effected, for example, by addition of hydrochloric acid. These reactions are advantageously conducted as described below:

- (i) The hydrolysis product is treated with hydrobromic acid (suitably with a concentrated aqueous solution of hydrobromic acid at the boil or with a solution of hydrobromic acid in acetic acid at room temperature), whereby the corresponding 5-(3'-bromopropylidene)-derivative is obtained.

- (ii) The hydrolysis product is treated with phosphorus oxychloride, preferably at reflux temperature. There is thus obtained the corresponding 5-(3'-chloro-propylidene)-derivative. The 5-(3'-halogeno-propylidene)-derivatives are mostly viscous, in part crystallizable, substances which can be distilled in high vacuum without decomposition.

According to the embodiment of the invention in which compounds of Formulae II are dehydrated, the dehydration is especially advantageously executed by warming the compound in an alcoholic solution of hydrochloric acid. The dehydration, however, also takes place with the other usual dehydrating agents (for example, phosphorus oxychloride, *parat*-tosyl chloride, sulphuric acid, zinc chloride and potassium hydrogen sulphate) and in other conventional organic solvents (for example, chloroform or methylene chloride).

The reaction of compounds of formula III with the listed amines is advantageously conducted in an inert organic solvent; for example, benzene or toluene. It is preferably conducted at an elevated temperature (for example, at or near the boiling point of the mixture or, in the case of an easily volatilizable amine, in a sealed tube at a temperature between about 80° C. and about 140° C.—preferably about 100° C.). The reaction is suitably effected in the presence of an inorganic or organic acid binding agent. As inorganic acid binding agents, there can be employed, for example, anhydrous calcium carbonate; as an organic acid binding agent, there can advantageously be used the same amine which is used to react with the halogen compound. A suitable embodiment thus consists in employing one mol of the halide of formula III and two mols of the amine. As amines, there are advantageously employed methyl amine, ethyl amine, *isopropyl* amine, and benzyl amine.

When the amino-alkylidene compound obtained by the process contains a halogeno-substituent, it is obtained as a stereoisomeric mixture. This mixture can be separated by methods known *per se*; for example, by fractional crystallization based on the different solubilities of the compounds themselves or of their acid addition salts.

The following examples are illustrative of the preparation of the starting materials and of the process of the invention.

EXAMPLE 1

A) Preparation of the Starting Material:

The 5 - (3' - bromo - propylidene) - dibenzo[a,e]cycloheptadiene[1,5] used as the starting material can be prepared as follows:—

(i) In a two-litre, three-necked flask, equipped with stirrer, dropping funnel and condenser, 15 g of magnesium shavings were covered with 60 ml of anhydrous ether and then reacted with 0.5 ml of methyl iodide. After the active reaction had subsided somewhat, a solution of 54.6 g of 1-chloro-3-methoxy-propane in 300 ml of anhydrous ether was added in such a way that the reaction mixture was maintained at the boil. It was then heated under reflux for 5 hours at 45° C. The reaction mixture was then cooled with ice-water. In the course of 1 hour a solution of 50 g of dibenzo[a,e]cycloheptadiene[1,5]one-(5) in 600 ml of anhydrous ether was added thereto and the resulting mixture heated under reflux with stirring for 17 hours at 40° C. After *ca* 16 hours, the reaction mixture was once more cooled with ice-water and then mixed with a cold saturated ammonium chloride solution. The organic layer was separated, the aqueous phase extracted twice, each time with 150 ml of ether and the combined ether portions dried over sodium sulphate and concentrated. The residue, after recrystallization from a mixture of high boiling and low boiling petroleum ether, yielded colourless crystals of 5-hydroxy-5-(3'-methoxy - propyl) - dibenzo[a,e]cycloheptadiene[1,5], melting at 88°—89° C.

20 g of the foregoing 5-hydroxy-5-(3'-methoxy - propyl) - dibenzo[a,e]cycloheptadiene[1,5] and 50 ml of a 48% aqueous solution of hydrobromic acid were heated under reflux for 12 hours with strong agitation. After cooling down, the reaction mixture was extracted twice, each time with 100 ml of ether, and the combined ether portions washed neutral with water, sodium carbonate solution and water, and then concentrated. The residue, after distillation in high vacuum, yielded 5 - (3' - bromo - propylidene) - dibenzo[a,e]cycloheptadiene[1,5] in the form of an oil which promptly congealed and which boiled at 145°—150° C./0.07 mm Hg. Upon recrystallization from a mixture of high boiling and low boiling petroleum ether it formed colourless crystals which melted at 74°—76° C.

(ii) In a 1-litre three-necked flask, fitted with stirrer, dropping funnel and condenser, 18 g of magnesium turnings were covered with 50 ml of ether and treated, in the course of 2 hours, while stirring, with a solution of 30 g of 1-bromo-propene-(2). Stirring was continued at 20° C. for a further 5 hours. Then the reaction mixture, which still contained some magnesium in excess, was cooled with ice-water, to it was added dropwise

within 1 hour, a solution of 52 g of dibenzo[a,e]cycloheptadiene[1,5]one-(5) in 100 ml of dry ether, whereupon the whole mixture was stirred for a further 2 hours at 20° C. and allowed to stand for 16 hours. Then, the mixture was again cooled with ice-water and treated with a cold saturated ammonium chloride solution. The organic layer was separated, the aqueous phase shaken twice with 100 ml portions of ether and the combined ether portions dried over sodium sulphate. On concentrating, there was obtained the 5 - hydroxy - 5 - (propen - (2 - yl) - dibenzo[a,e]cycloheptadiene[1,5] as thick yellow oil. 30 g of this compound were dissolved in 200 ml of dry chloroform and the solution obtained was saturated with dry hydrobromic acid while cooling with ice. The solution was concentrated under reduced pressure and the residue again dissolved in 200 ml of chloroform and saturated at 0° C. with dry hydrobromic acid. After several hours standing, the mixture was concentrated under reduced pressure, the residue dissolved in ether and the ethereal solution washed with water, with a sodium hydrogen carbonate solution again with water, dried over sodium sulphate and concentrated. The residue thus obtained consisted of 5 - (3' - bromo - propylidene) - dibenzo[a,e]cycloheptadiene[1,5].

B) The Process:

(1) 10 g of 5 - (3' - bromo - propylidene) - dibenzo[a,e]cycloheptadiene[1,5] and 25 ml of a 20% alcoholic methyl amine solution were warmed for 8 hours in a sealed tube at 100° C. After cooling, the alcohol was distilled off under reduced pressure, the residue taken up in ether, the ether solution washed with water and shaken with dilute hydrochloric acid. The aqueous acid solution was treated with excess potassium carbonate, the oil extracted with ether, dried and concentrated, yielding 5 - (3' - methylamino-propylidene) - dibenzo[a,e]cycloheptadiene[1,5] which boiled at 150°—160° C./0.03 mm Hg. The hydrochloride of the foregoing product was crystallized from alcohol/ether and melted at 218°—220° C.

(2) A mixture of 20 g of 5 - (3' - bromo-propylidene) - dibenzo[a,e]cycloheptadiene[1,5], 100 ml of anhydrous toluene, and 50 g of isopropyl amine was warmed in a rocking autoclave for 7 hours at 100° C. under 20 atmospheres of nitrogen. The reaction mixture was then permitted to cool down and the toluene and excess isopropyl amine were distilled off under reduced pressure. The residue was shaken with ether and dilute sodium hydroxide, the ether solution separated, washed neutral with water, dried over sodium sulphate and concentrated. Distillation of the oily residue under a pressure of 0.05 mm Hg at 165° C. yielded 5-(3'-isopropylamino-propylidene) - dibenzo[a,e]cycloheptadiene[1,5]. The hydrochloride was recrystallized

is om alcohol/ether and melted at 239°—242° C.

- (3) 50 g of ethyl amine, 100 ml of anhydrous toluene and 20 g of 5-(3'-bromopropylidene) - dibenzo[a,e]cycloheptadiene- [1,5] were mixed at -15° C. and agitated for 7 hours at a temperature of 100°—110° C. in an autoclave under 20 atmospheres of nitrogen. After the reaction mixture had cooled down, the toluene and excess ethyl amine were distilled off, the residue shaken with ether and dilute sodium hydroxide, the ether solution separated, washed with water, dried over sodium sulphate and concentrated. Distillation under a pressure of 0.1 mm Hg at 160° C. yielded 5 - (3' - ethylamino-propylidene) - dibenzo[a,e]cycloheptadiene- [1,5]. The hydrochloride was recrystallized from ethanol/ether and melted at 262°—264° C.

- (4) 14 g of 5 - (3' - bromo - propylidene) - dibenzo[a,e]cycloheptadiene[1,5] and 50 g of benzyl amine were dissolved in 100 ml of anhydrous xylene and the resulting solution was heated under reflux for 5 hours. After it had cooled down, the reaction mixture was diluted with 200 ml of ether, washed several times with water, dried over sodium sulphate. Then, the ether and xylene were first distilled off under the vacuum of a water-jet vacuum pump, and then the excess benzyl amine was distilled off under a vacuum of 0.05 mm Hg at a bath temperature of 160° C. The product, 5 - (3' - benzylamino - propylidene) - dibenzo[a,e]cycloheptadiene[1,5], which remained as a thick oil, was converted into its hydrochloride, which upon crystallization from ethanol/ether melted at 174°—176° C.

EXAMPLE 2

40 A) Preparation of the Starting Material:

The 5 - (3' - bromo - propylidene) - dibenzo[a,e]cycloheptatriene[1,3,5] used as starting material can be prepared as follows:

- In a one-litre, three-necked flask, equipped with stirrer, dropping funnel and condenser, 7.5 g of magnesium shavings were covered with 30 ml of anhydrous ether and mixed with 10 drops of methyl iodide. After the active reaction had subsided somewhat, a solution of 27.3 g of 1-chloro-3-methoxy-propane and 150 ml of anhydrous ether was added thereto in the course of 1 hour. The resultant mixture was then heated under a reflux condenser for 3 hours at 45° C. A solution of 21 g of dibenzo[a,e]cycloheptatriene[1,3,5]one - (5) in 300 ml of anhydrous ether was then added in the course of 1 hour to the reaction mixture, which had been cooled with ice-water. After the addition, the resulting mixture was heated for 3 hours under the reflux condenser. After 16 hours, it was once again cooled with ice-water and then mixed with a cold saturated ammonium chloride solution. The organic layer was separated, the aqueous

phase extracted twice, each time with 100 ml of ether and the combined ether portions dried over sodium sulphate and concentrated. The residue, after crystallization from petroleum ether, yielded colourless crystals of 5-hydroxy-5 - (3' - methoxy - propyl) - dibenzo[a,e]cycloheptatriene[1,3,5], which melted at 90°—91° C. Another crystal form, which melted at 78°—79° C., occurred but this was easily converted into the high melting form by intimate trituration of a mixture of the two forms.

15 g of 5 - hydroxy - 5 - (3' - methoxy-propyl) - dibenzo[a,e]cycloheptatriene[1,3,5] and 40 ml of a 48% aqueous solution of hydrogen bromide were heated for 20 hours under reflux with strong agitation. After the reaction mixture had cooled down, it was extracted twice, each time with 100 ml of ether. The combined ether portions were then washed neutral with water, sodium hydrogen carbonate solution and again water, and then concentrated. The residue, after distillation in high vacuum, yielded 5 - (3' - bromopropylidene) - dibenzo[a,e]cycloheptatriene- [1,3,5] as a yellow oil which boiled at 150° C./0.1 mm Hg, and which soon became solid upon standing.

B) The Process:

20 g of 5 - (3' - bromo - propylidene) - dibenzo[a,e]cycloheptatriene[1,3,5] were added at -20° C. to a mixture of 100 ml of anhydrous toluene and 40 g of methyl amine. The reaction mixture was heated to 100° C. for 7 hours in an autoclave under 20 atmospheres of nitrogen. After the mixture had cooled down, the excess methyl amine and toluene were distilled off under reduced pressure and the residue was shaken with ether and potassium carbonate. The ether solution was separated, washed with water and dried over sodium sulphate. The residue, upon distillation in a high vacuum, yielded 5 - (3' - methylamino - propylidene) - dibenzo[a,e]cycloheptatriene[1,3,5] which boiled at 150° C./0.1 mm Hg. The hydrochloride was crystallized from ethanol/ether and melted at 181°—183° C.

EXAMPLE 3

A) Preparation of the Starting Material:

The 3 - chloro - 5 - (3' - bromo - propylidene) - dibenzo[a,e]cycloheptadiene[1,5] used as the starting material can be prepared as follows:

In a two-litre, three-necked flask, equipped with stirrer, dropping funnel and condenser, 15 g of magnesium shavings were covered with 60 ml of anhydrous ether and mixed with 0.5 ml of methyl iodide. After the active reaction had subsided somewhat, a solution of 41 g of 1-chloro-3-methoxy-propane and 300 ml of anhydrous ether was added in such a manner that the reaction mixture was held at

the boil. It was then heated under reflux for 5 hours at 45° C. The reaction mixture was then cooled with ice-water. In the course of 1 hour, a solution of 47.8 g of 3-chloro-dibenzo[a,e]cycloheptadiene[1,5]one - (5) and 600 ml of anhydrous ether was added thereto, and the resulting mixture agitated at 40° C. under reflux for 17 hours. After 16 hours, it was once again cooled with ice-water and then mixed with a cold saturated solution of ammonium chloride. The organic layer was separated, the aqueous phase extracted twice, each time with 150 ml of ether, and the combined ether portions dried over sodium sulphate and concentrated. The residue, upon crystallization from high boiling petroleum ether, yielded colourless crystals of 3-chloro-5-hydroxy-5-(3'-methoxy-propyl)-dibenzo[a,e]cycloheptadiene[1,5], melting at 67°—69° C.

30 g of the foregoing 3-chloro-5-hydroxy-5-(3'-methoxy-propyl)-dibenzo[a,e]cycloheptadiene[1,5] were then added portionwise to 100 ml of a cold saturated solution of hydrogen bromide in acetic acid. With stirring, the temperature of the reaction mixture was permitted to slowly rise to 25° C. and then it was permitted to stand for 16 hours at this temperature. After 16 hours, the reaction mixture was cooled with ice-water, once again saturated with anhydrous hydrogen bromide and permitted to stand for 20 hours at ca 20° C. It was then diluted with two litres of ice-water, the oil once more extracted with ether, the combined ether portions washed with water, sodium hydrogen carbonate, and water, dried over sodium sulphate and concentrated. The residue yielded 3-chloro-5-(3'-bromo-propylidene)-dibenzo[a,e]cycloheptadiene[1,5] which boiled at 195° C./0.04 mm Hg.

B) The Process:

20 g of 3-chloro-5-(3'-bromo-propylidene)-dibenzo[a,e]cycloheptadiene[1,5] were added at -10° C. to -20° C. to a mixture of 30 ml of anhydrous toluene and 40 g of methyl amine and the resultant mixture heated in an autoclave for 7 hours at 100° C. After the reaction mixture had cooled down, the excess methyl amine and toluene were distilled off under reduced pressure. The residue was shaken with ether and dilute sodium hydroxide, the ether solution separated, washed with water, dried over sodium sulphate and concentrated. The product 3-chloro-5-(3'-methylamino-propylidene)-dibenzo[a,e]cycloheptadiene[1,5], remained behind as a thick oil, and was converted into its hydrochloride which, after crystallization from ethanol, melted at 260°—262° C.

EXAMPLE 4

A) Preparation of the Starting Material:

The 5-(3'-chloro-propylidene)-dibenzo[a,e]cycloheptadiene[1,5] used as the

starting material can be prepared as follows:

10 g of 5-hydroxy-5-(3'-methoxy-propyl)-dibenzo[a,e]cycloheptadiene[1,5] were dissolved in 25 ml of phosphorus oxychloride and the resulting solution heated under reflux for 3 hours. Thereafter, the phosphorus oxychloride was removed under reduced pressure, the resinous residue shaken with ether and ice-water until all of it had gone into solution. The ether solution was separated washed with water, sodium hydrogen carbonate solution, again with water, dried and concentrated. By distillation of the residue under a pressure of 0.1 mm Hg at a bath temperature of 200—230° C., there was obtained 5-(3'-chloro-propylidene)-dibenzo[a,e]cycloheptadiene[1,5] which, upon crystallization from a mixture of high boiling and low boiling petroleum ether, formed colourless crystals melting at 83°—85° C.

B) The Process:

10 g of 5-(3'-chloro-propylidene)-dibenzo[a,e]cycloheptadiene[1,5] and 30 ml of a 20% alcoholic methyl amine solution were heated at 100° C. for 8 hours in a sealed tube. After the reaction mixture had cooled off, the alcohol was distilled off under reduced pressure, the residue shaken with ether and aqueous potassium carbonate and the ether solution washed with water, dried over sodium sulphate and concentrated. There was thus obtained the compound described in Example 1 B) (1), namely, 5-(3'-methylamino-propylidene)-dibenzo[a,e]cycloheptadiene[1,5], with a boiling point of 150°—160° C./0.03 mm Hg. The hydrochloride melted at 218—220° C.

EXAMPLE 5

A) Preparation of the Starting Material:

(i) The 5-hydroxy-5-(3'-methylamino-propyl)-dibenzo[a,e]cycloheptadiene[1,5] used as the starting material can be prepared as follows:

In a one-litre, three-necked flask, equipped with stirrer, dropping funnel and condenser, 10 g of a finely divided copper/magnesium alloy (GILMAN *op. cit. supra*) were covered with 20 ml of anhydrous ether and mixed with 0.5 ml of methyl iodide. After the active reaction had subsided somewhat, a solution of 60 g of 1-chloro-3-(N-methyl-N-benzyl-amino)-propane in 180 ml of anhydrous ether was added thereto in such a manner as to hold the reaction mixture at the boil. The mixture was then heated under reflux for 4 hours at 45° C. The reaction mixture was then cooled with ice-water, a solution of 21.2 g of dibenzo[a,e]cycloheptadiene-[1,5]one - (5) and 250 ml of anhydrous ether added thereto in the course of 1 hour and the resulting mixture stirred under reflux for 17 hours at 40° C. Then the mixture was again cooled with ice-water and

mixed with a cold, saturated solution of ammonium chloride. The organic layer was separated, the aqueous phase extracted twice, each time with 150 ml of ether and the combined ether portions were dried over sodium sulphate and concentrated. The residue, upon crystallization from high boiling petroleum ether, formed colourless crystals of 5-hydroxy-5 - [3' - (N - methyl - N - benzyl - amino) - propyl] - dibenzo[a,e]cycloheptadiene[1,5], melting at 123°—124° C.

11.1 g of 5 - hydroxy - 5 - [3' - (N - methyl - N - benzyl - amino) - propyl] - dibenzo[a,e]cycloheptadiene[1,5] were dissolved in 90 ml of methanol and hydrogenated for 8 hours in the presence of 3 g of palladium/carbon at 100° C. under 100 atmospheres pressure. When the hydrogenation had finished, the solution was filtered free of catalyst and concentrated to dryness. The residue was crystallized from high boiling petroleum ether and yielded colourless crystals of 5 - hydroxy - 5 - (3' - methylamino - propyl) - dibenzo[a,e]cycloheptadiene[1,5], melting at 94°—96° C.

(ii) In a two-litre, three-necked flask, equipped with stirrer, dropping funnel and ammonia condenser, 500 ml of liquid ammonia were placed and dried by the introduction of sodium chips until the appearance of a constant blue colour. Then, 7.25 g of sodium were introduced in small parts and the resulting mixture stirred for a further 0.25 hour. The resulting solution was mixed dropwise with 54.2 g of 3-(N-methyl-N-benzyl-amino) - propyne (1), whereupon the blue colour disappeared. To this mixture were then added dropwise 67.5 g of dibenzo[a,e]cycloheptadiene[1,5]one - (5) and the resulting mixture stirred for 5 hours, treated portionwise with 50 g of ammonium chloride, diluted with 400 ml of ether, and, after the ammonia condenser had been replaced with a water condenser, the ammonia was permitted to evaporate for 16 hours. Then, the solution was treated with water and the ether layer separated and dried. After distilling off the ether, the residue was crystallized from high boiling petroleum ether, yielding 5 - hydroxy-5 - [3' - (N - methyl - N - benzyl - amino) - propyn - (1) - yl] - dibenzo[a,e]cycloheptadiene[1,5] melting at 98°—100° C.

7.34 g of 5 - hydroxy - 5 - [3' - (N - methyl - N - benzyl - amino) - propyn - (1) - yl] - dibenzo[a,e]cycloheptadiene[1,5] were hydrogenated in the presence of 0.8 g of platinum oxide in 250 ml of isopropanol at atmospheric pressure and ca 20° C. After the calculated amount of hydrogen had been absorbed, the solution was filtered free of catalyst, concentrated, and the residue crystallized from petroleum ether, yielding the compound obtained by method (i) of this example, namely 5 - hydroxy - 5 - [3' - (N - methyl - N - benzyl - amino) - propyl] - di-

benzo - [a,e]cycloheptadiene[1,5] melting at 122°—124° C.

This compound can be debenzylated according to the method set forth in (i) (i.e. by hydrogenation) so as to form 5 - hydroxy-5 - (3' - methylamino - propyl) - dibenzo[a,e]cycloheptadiene[1,5].

B) The Process:

2 g of 5 - hydroxy - 5 - (3' - methylamino - propyl) - dibenzo[a,e]cycloheptadiene[1,5], 20 ml of absolute alcohol and 2 ml of a 20% hydrogen chloride solution in alcohol were warmed on a steam bath under a reflux condenser for 3 hours. The solution was then concentrated to dryness under reduced pressure. The residue, upon recrystallization from ethanol/ether, yielded the compound described in Example 1,B)(1), namely, 5 - (3' - methylamino - propylidene) - dibenzo[a,e]cycloheptadiene[1,5] hydrochloride, which melted at 220°—222° C.

EXAMPLE 6

A) Preparation of the Starting Material:

The starting diene compound can be obtained as follows:

In a 1-litre, 3-necked flask, fitted with stirrer, dropping funnel and condenser, 10 g of GILMAN alloy are covered by 20 ml of dry ether and treated with 0.5 ml of methyl iodide. Once the vigorous reaction has subsided somewhat a solution of 60 g of 1-chloro-2 - methyl - 3 - (N - methyl - N - benzyl-amino) - propane (prepared from 1 - chloro-2 - methyl - 3 - bromo - propane and N-benzyl - N - methyl - amine; boiling point 114°—116° C./0.5 mm) in 180 ml of dry ether was added dropwise in such a way that the reaction mixture was kept at the boil. Heating under reflux was then continued for a further 5 hours at 45° C. Then the reaction mixture was cooled down with ice-water and to it was added dropwise, within 1 hour, a solution of 21.2 g of dibenzo[a,e]cycloheptadiene[1,5]one-(5) in 250 ml of dry ether, whereupon the whole mixture was heated under reflux for a further 20 hours at 40° C. Then, the mixture was again cooled with ice-water and treated with a cold saturated ammonium chloride solution. The organic layer was separated, the aqueous phase shaken twice with 200 ml portions of ether and the combined ether extracts dried over sodium sulphate and concentrated. The residue was recrystallized from high boiling petroleum ether and gave colourless crystals of 5-hydroxy - 5 - [2' - methyl - 3' - (N - methyl - N - benzyl - amino) - propyl] - dibenzo[a,e]cycloheptadiene - [1,5] of melting point 99°—100° C.

7.71 g of the foregoing compound were dissolved in 60 ml of methanol and hydrogenated for 8 hours at 100° C. in the presence of 2 g of palladium/carbon catalyst and under a

hydrogen pressure of 100 atmospheres. Then, the catalyst was filtered off and the filtrate concentrated to dryness. The residue was recrystallized from high boiling petroleum ether and gave colourless crystals of 5 - hydroxy-5 - (2' - methyl - 3' - methylamino - propyl)-dibenzo[a,e]cycloheptadiene[1,5] of melting point 103°—104° C.

B) The Process:

- 3 g of 5 - hydroxy - 5 - (2' - methyl - 3' - methylamino - propyl) - dibenzo[a,e]cycloheptadiene[1,5], 30 ml of absolute alcohol and 3 ml of 20% alcoholic hydrochloric acid were heated under reflux for 3 hours on a steam bath, whereupon the solution was concentrated under reduced pressure. The residue was recrystallized from ethanol/ether and gave the 5 - (2' - methyl - 3' - methylamino-propylidene) - dibenzo[a,e]cycloheptadiene-[1,5] hydrochloride of melting point 195°—196° C.

The following are examples of the manner in which the novel substances of the invention may be made up into pharmaceutical preparations.

EXAMPLE A

- 100 g of 3 - chloro - 5 - (3' - methylamino - propylidene) - dibenzo[a,e]cycloheptadiene[1,5] hydrochloride, 150 g of a mixture of 15% starch and 85% finely divided silicic acid, 420 g of corn starch, 300 mg of lactose and 50 g of talcum are intimately mixed together and pressed to tablets each weighing 100 mg.

EXAMPLE B

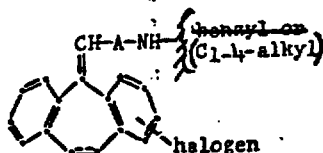
- 50 g of 5 - (3' - methylamino - propylidene) - dibenzo[a,e]cycloheptatriene[1,3,5] hydrochloride, 110 g of corn starch, 120 g of lactose and 20 g of talcum are intimately mixed together and pressed to tablets each weighing 300 mg.

EXAMPLE C

- A solution of 0.8 g of 5 - (3' - methylamino - propylidene) - dibenzo[a,e]cycloheptadiene[1,5] hydrochloride in 100 ml of redistilled water, 0.08 g of methyl *p*-hydroxybenzoate and 0.01 g of propyl *p*-hydroxybenzoate are filled, under nitrogen, into 2.2 ml ampoules.

- WHAT WE CLAIM IS:—

1) Compounds of the formula

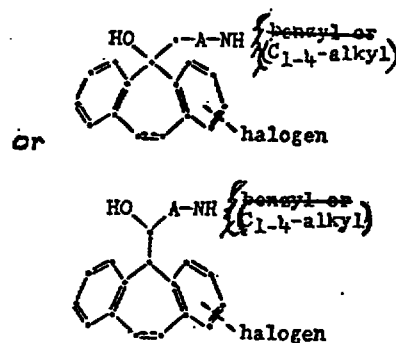


wherein A stands for the ethylene radical or

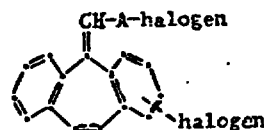
an ethylene radical containing a C_{1-4} -alkyl substituent and the broken lines denote optional bonds, and acid addition salts thereof.

- 2) 5 - (3' - methylamino - propylidene)-dibenzo[a,e] - cycloheptadiene [1,5], 5 - (3' - ethylamino - propylidene) - dibenzo[a,e] - cycloheptadiene [1,5], 5 - (3' - isopropylamino - propylidene) - dibenzo[a,e]cycloheptadiene [1,5], 3 - chloro - 5 - (3' - methylamino - propylidene) - dibenzo[a,e]cycloheptadiene [1,5], 5 - (2' - methyl - 3' - methylamino - propylidene) - dibenzo[a,e]cycloheptadiene [1,5], 5 - (3' - benzylamino-propylidene) - dibenzo[a,e]cycloheptadiene [1,5] and 5 - (3' - methylamino - propylidene) - dibenzo[a,e]cycloheptatriene [1,3,5] and their hydrochlorides.

3) A process for the manufacture of the substances claimed in claim 1, which process comprises dehydrating a hydroxy compound of the formula



(wherein A and the broken lines have the significance given in claim 1) in an organic solvent in the presence of a dehydrating agent or reacting a halogeno-alkylidene compound of the formula



(wherein A and the broken lines have the significance given in claim 1) with benzyl amine or a C_{1-4} -alkyl amine and, if desired, converting the dehydration or reaction product into an acid addition salt.

4) A process in accordance with claim 3, wherein the dehydration is carried out by warming the hydroxy compound in an alcoholic solution of hydrochloric acid.

5) A process in accordance with claim 3, wherein the halogeno-alkylidene compound is reacted with methyl amine, ethyl amine, isopropyl amine, or benzyl amine.



hydrogen pressure of 100 atmospheres. Then, the catalyst was filtered off and the filtrate concentrated to dryness. The residue was recrystallized from high boiling petroleum ether and gave colourless crystals of 5 - hydroxy-5 - (2' - methyl - 3' - methylamino - propyl)-dibenzo[a,e]cycloheptadiene[1,5] of melting point 103°—104° C.

B) The Process:

- 3 g of 5 - hydroxy - 5 - (2' - methyl - 3' - methylamino - propyl) - dibenzo[a,e]cycloheptadiene[1,5], 30 ml of absolute alcohol and 3 ml of 20% alcoholic hydrochloric acid were heated under reflux for 3 hours on a steam bath, whereupon the solution was concentrated under reduced pressure. The residue was recrystallized from ethanol/ether and gave the 5 - (2' - methyl - 3' - methylamino-propylidene) - dibenzo[a,e]cycloheptadiene[1,5] hydrochloride of melting point 195°—196° C.

The following are examples of the manner in which the novel substances of the invention may be made up into pharmaceutical preparations.

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EXAMPLE B

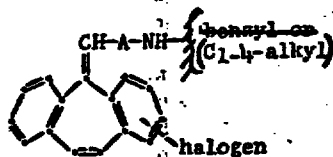
50 g of 5 - (3' - methylamino - propylidene) - dibenzo[a,e]cycloheptatriene[1,3,5] hydrochloride, 110 g of corn starch, 120 g of lactose and 20 g of talcum are intimately mixed together and pressed to tablets each weighing 300 mg.

EXAMPLE C

A solution of 0.8 g of 5 - (3' - methylamino - propylidene) - dibenzo[a,e]cycloheptadiene[1,5] hydrochloride in 100 ml of redistilled water, 0.08 g of methyl *p*-hydroxybenzoate and 0.01 g of propyl *p*-hydroxybenzoate are filled, under nitrogen, into 2.2 ml ampoules.

WHAT WE CLAIM IS:—

- 1) Compounds of the formula

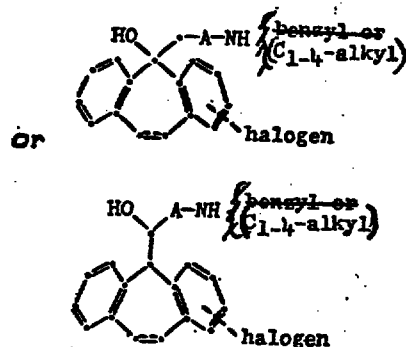


wherein A stands for the ethylene radical or

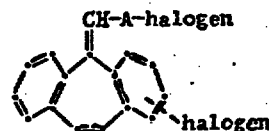
an ethylene radical containing a C_{1-4} -alkyl substituent and the broken lines denote optional bonds, and acid addition salts thereof.

- 2) 5 - (3' - methylamino - propylidene)-dibenzo[a,e] - cycloheptadiene [1,5], 5 - (3' - ethylamino - propylidene) - dibenzo[a,e] - cycloheptadiene [1,5], 5 - (3' - isopropylamino - propylidene) - dibenzo[a,e] - cycloheptadiene [1,5], 3 - chloro - 5 - (3' - methylamino - propylidene) - dibenzo[a,e] - cycloheptadiene [1,5], 5 - (2' - methyl - 3' - methylamino - propylidene) - dibenzo[a,e] - cycloheptadiene [1,5], 5 - (3' - benzylamino-propylidene) - dibenzo[a,e]cycloheptadiene [1,5] and 5 - (3' - methylamino - propylidene) - dibenzo[a,e]cycloheptatriene [1,3,5] and their hydrochlorides.

3) A process for the manufacture of the substances claimed in claim 1, which process comprises dehydrating a hydroxy compound of the formula



(wherein A and the broken lines have the significance given in claim 1) in an organic solvent in the presence of a dehydrating agent or reacting a halogeno-alkylidene compound of the formula



(wherein A and the broken lines have the significance given in claim 1) with benzyl amine or a C_{1-4} -alkyl amine and, if desired, converting the dehydration or reaction product into an acid addition salt.

4) A process in accordance with claim 3, wherein the dehydration is carried out by warming the hydroxy compound in an alcoholic solution of hydrochloric acid.

5) A process in accordance with claim 3, wherein the halogeno-alkylidene compound is reacted with methyl amine, ethyl amine, isopropyl amine, or benzyl amine.



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- 55 25) A process in accordance with claim 1, wherein the reaction is carried out in an inert organic solvent at an elevated temperature.
- 60 97) A process for the manufacture of the compounds formulated in claim 1 and acid addition salts thereof, substantially as described with reference to the examples.
- 65 108) Compounds as formulated in claim 1 hereof and acid addition salts thereof, when
- 70 10 manufactured by the process claimed in any one of claims 1⁵ to 1⁹ inclusive.
- 75 11 97) A composition having activity on the central nervous system, comprising a compound as formulated in claim 1, an acid addition salt thereof in association with a compatible pharmaceutical carrier.
- W. D. WHITAKER,
Patent Agent for
F. HOFFMANN—LA ROCHE & Co.,
Aktiengesellschaft.

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[Rider]

RIDER

3. 5 - (3'-isopropylamino - propylidene) - dibenzo [a,e] cycloheptadiene [1,5] and its hydrochloride.
4. 3 - chloro - 5 - (3'-methylamino - propylidene) - dibenzo [a,e] cycloheptadiene [1,5] and 5 - (2'-methyl - 3'-methylamino - propylidene) - dibenzo [a,e] cycloheptadiene [1,5] and their hydrochlorides.