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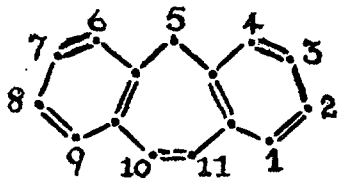
COMPLETE SPECIFICATION

Novel Dibenzoheptaenes and Salts thereof and a process for the Manufacture of same

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 dibenzoheptaenes and salts thereof and to a process for the manufacture of same.

The novel dibenzoheptaenes provided by the invention are derivatives of compounds which may be represented by the following structural formula:



in which the broken line denotes an optional double bond; that is to say, they are derivatives of 2,3; 6,7 - dibenz - *cyclo*heptadiene - (2,6) or of 2,3; 6,7 - dibenz - *cyclo*heptatriene - (2,4,6) [which will hereinafter be referred to as dibenz*cyclo*heptadiene and dibenz*cyclo*heptatriene and will bear the numbering given in the foregoing formula]. The class of derivative and salts provided are those substances derived from the compounds formulated by substitution at position - 5 with a hydroxyl group and an alkyl radical containing more than two carbon atoms and carrying one or more disubstituted - amino groups (including such compounds which contain in addition to the 5 - substitution one or more nuclear alkyl, alkoxy, and/or halogeno substituents) and acid addition and quaternary salts thereof.

[*Price 3s. 6d.*]

The foregoing derivatives and salts thereof are characterized by manifold activity upon the central nervous system and are useful as pharmacological and medicinal agents, particularly as narcosis - potentiating, adrenolytic, sedative, antihistaminic, antiemetic, antipyretic and hypothermic agents. They can also be dehydrated to give further active compounds [see the specification of our copending application No. 13814/60 (now Serial No. 858,187)] which, in turn, can be hydrogenated to give still further active compounds [see the specification of our copending application No. 13815/60 (now Serial No. 858,188)].

The basically substituted alkyl radical in the 5 - position is preferably a lower - alkyl radical which contains more than two carbon atoms and which contains a di(lower - alkyl) - amino radical in which the two lower - alkyl groups may be joined to form, together with the nitrogen atom to which they are attached, a five- or six - membered ring. If desired, the joining of the two lower - alkyl groups may take place through an oxygen or sulphur atom as in the morpholino or thiamorpholino radicals.

The process provided by the present invention comprises condensing dibenz*cyclo*heptadi[or tri] - enone - (5), or a substitution-derivative thereof which carries one or more nuclear alkyl, alkoxy, and/or halogeno substituents, with a saturated non - aromatic organo - metallic compound containing more than two carbon atoms and carrying one or more disubstituted - amino groups, hydrolyzing the condensation product and, if desired, transforming the product, if a salt, into a different salt or into the base or, if a base, into an acid addition or quaternary salt.

The preparation of the starting materials required for the practice of the invention can be effected according to procedures known *per se*. Thus, the dibenz*cyclo*heptadienone - (5) or its substitution - derivatives prepared,

for example, by reducing the corresponding benzal - phthalides and subsequently cyclizing the dibenzyl - *ortho*carboxylic acid compounds obtained. The dibenzo*cyclo*heptatrienone - (5)s may e.g. easily be obtained from the corresponding dibenzo*cyclo*heptadienone - (5)s by bromination and splitting off or hydrogen bromide [Berichte der deutschen chemischen Gesellschaft, 1951, *84*, 678]. The preparation of the saturated organo - metallic compounds containing one or more disubstituted - amino groups can likewise be prepared by methods known *per se*. In a preferred mode of execution, magnesium compounds of dialkylamino - alkyl halides are employed as the basically substituted non - aromatic organo - metallic compounds, and these can be prepared for example by direct reaction of metallic magnesium with an ethereal solution of the dialkylamino - alkyl halide. In such cases, an especially active form of metal is used; for example, a finely divided copper/magnesium alloy such as that of GILMAN [Recueil des Travaux Chimiques des Pays-Bas, 1928, *47*, 19] and the reaction is initiated by addition of a suitable alkyl halide, e.g. methyl iodide or ethyl bromide.

In the first step of the process according to the invention, magnesium-, lithium- and zinc-organic compounds can be employed. In a preferred procedure, the dibenzo*cyclo*heptadienone - (5)s or dibenzo*cyclo*heptatrienone - (5)s either in a solid finely divided form or in solution in an inert organic solvent such as absolute ether or benzene or tetrahydrofuran, are added to the magnesium compound of the (disubstituted - amino) - alkyl halide in the same or a similar inert organic liquid. In the second step of the process, the metal - containing condensation product is hydrolytically decomposed. It is especially advantageous to decompose the metal - containing condensation product under practically neutral conditions; for example, by hydrolysis in aqueous ammonium chloride solution. In this way the dibenzo*cyclo*heptadienes or dibenzo*cyclo*heptatrienes containing disubstituted - amino groups are obtained in the form of the free base and can be separated from the byproducts and isolated by treatment with suitable water - immiscible organic solvents such as, for example, diethyl ether, ethyl acetate, chloroform of methylene chloride.

From the foregoing it can be seen that the invention is particularly concerned with the manufacture of dibenzo*cyclo*heptadi[or tri]ene bases having a (disubstituted - amino) - alkyl group attached at the 5 - position, the alkyl radical of which contains from three to seven carbon atoms. Preferred groups are: dialkylamino - propyl groups such as dimethylamino-propyl, morpholino - propyl, pyrrolidino - propyl or piperidino - propyl. The substituent in 5 - position may also contain several disubstituted - amino groups.

The invention is also concerned with the manufacture of acid addition salts of said bases with pharmacologically acceptable acids and of quaternary salts of said bases with pharmacologically acceptable quaternizing agents. Exemplary of pharmacologically acceptable acids that are suitable for the practice of the invention are common mineral acids such as hydrochloric acid, hydrobromic acid, phosphoric acid and sulphuric acid and common organic acids such as acetic acid, tartaric acid, maleic acid, citric acid, ethanesulphonic acid, oxalic acid and lactic acid. Exemplary of pharmacologically acceptable quaternizing agents such as alkyl halides (e.g., methyl bromide, ethyl bromide, ethyl iodide), dialkyl sulphates (e.g., dimethyl sulphate) and aralkyl halides (e.g., benzyl bromide).

The invention is further disclosed in the following examples, which are illustrative but not limitative thereof:

EXAMPLE 1

In a one-litre, three-necked flask, fitted with a stirrer, dropping funnel and condenser, 2.5 g of GILMAN - alloy (*op. cit. supra*) were covered with 10 ml of dry diethyl ether and reacted with 0.5 ml of methyl iodide.

After the vigorous reaction subsided somewhat, 7.5 g of magnesium shavings were added in one portion and a solution of 40 g of freshly distilled ω - dimethylamino - propyl chloride in 180 ml of dry ether was added dropwise over a period of one hour. The reaction mixture was heated under reflux at 40°C for five hours longer, and then was stirred for 16 hours at *ca* 20°C.

A solution of 21.2 g of dibenzo*cyclo*heptadienone - (5) in 400 ml of dry diethyl ether was added little by little while stirring. The whole was then stirred 20 hours longer at 20°—25°C. Then the reaction mixture was cooled with ice-water and mixed with a cold saturated ammonium chloride solution. The organic layer was separated, the aqueous phase was extracted twice with 100 ml portions of diethyl ether, and the combined ether layers were dried over sodium sulphate and evaporated. The residue, upon recrystallization from high boiling petroleum ether, yielded colourless crystals of 5 - hydroxy - 5 - (ω - dimethylamino - propyl) - dibenzo*cyclo*heptadiene, melting at 118°—119°C.

EXAMPLE 2

In a one-litre, three-necked flask fitted with a stirrer, dropping funnel and condenser, 2.5 g of GILMAN - alloy were covered with 10 ml of dry diethyl ether and reacted with 0.5 ml of methyl iodide.

After vigorous reaction had subsided somewhat, 7.5 g of magnesium shavings were added in a single portion, and a solution of 40 g of freshly distilled ω - dimethylamino - propyl chloride in 180 ml of dry ether was added dropwise over a period of 1 hour. The reaction mixture was heated under reflux at

40°C for 5 hours longer and then was stirred for 16 hours at *ca* 20°C.

A solution of 24.75 g of 3 - chloro - dibenzo*cyclo*heptadienone - (5) in 400 ml of dry diethyl ether was slowly added, dropwise, while stirring. The whole was stirred for an additional period of 20 hours at 20°—25°C. Then, the reaction mixture was cooled with ice-water and mixed with an ammonium chloride solution (saturated in the cold). The organic layer was separated, the aqueous layer was extracted twice with 100 ml portions of diethyl ether, and the combined ethereal portions were dried over sodium sulphate and evaporated. The residue, upon recrystallization from high boiling petroleum ether, yielded colourless crystals of 3 - chloro - 5 - hydroxy - 5 - (ω - dimethylamino - propyl) - dibenzo*cyclo*heptadiene which melted at 127°—128°C.

The starting material, 3 - chloro - dibenzo*cyclo*heptadienone - (5), can be prepared as follows:

100 g of phthalic anhydride, 137 g of (4 - chloro - phenyl) - acetic acid and 2.6 g of freshly molten sodium acetate were mixed well in a 500 ml round bottomed flask, and the mixture was quickly heated in a sand bath to 230°C and was then slowly heated over a period of two hours to 240°C and was finally kept at 240°C until water no longer distilled off. The mixture was cooled, whereupon it became solid. It was then recrystallized from a large quantity of absolute alcohol, whereupon 4 - chloro - benzal phthalide of melting point 151°—152°C was obtained.

A mixture of 51.3 g of 4 - chloro - benzal phthalide, 100 ml of hydriodic acid (d=1.7) and 18 g of red phosphorus was heated under reflux for 15 hours. The reaction mixture was cooled and then mixed with sufficient water and methylene chloride to ensure that all the material, with the exception of the red phosphorus went into solution. The methylene chloride layer was separated, washed with water, and then extracted several times with 5% aqueous sodium carbonate solution. Upon acidification of the combined aqueous phases with hydrochloric acid, 4 - chloro - dibenzyl - (2^1) - carboxylic acid precipitated and was extracted with methylene chloride. Upon drying and evaporation of the methylene chloride solution, the residual 4 - chloro - dibenzyl - (2^1) - carboxylic acid obtained was recrystallized from high boiling petroleum ether and then had a melting point of 129°—130°C.

To 270 g of well stirred polyphosphoric acid, heated to 170°C, were added portionwise over a period of two hours 57.6 g of 4 - chloro - dibenzyl - (2^1) - carboxylic acid. The reaction mixture was stirred at 170°C for three hours longer, then poured on to ice and the reaction product was extracted by shaking with diethyl ether. The ethereal solution was washed with aqueous sodium carbonate solution, then with water and then dried over sodium sulphate and evaporated. The product, 3 - chloro - dibenzo*cyclo*heptadienone - (5) was purified by distillation (b.p.=150°—155°C/0.05 mm) and then by recrystallization from high boiling petroleum ether, whereupon it had a melting point of 64°—65°C.

EXAMPLE 3

In a one-litre, three-necked flask fitted with stirrer, dropping funnel and condenser, 2.5 g of GILMAN - alloy were covered with 10 ml of dry diethyl ether and reacted with 0.5 ml of methyl iodide.

After the vigorous reaction had subsided somewhat, 7.5 g of magnesium shavings were added in a single portion and a solution of 40 g of freshly distilled ω - dimethylamino - propyl chloride in 180 ml of dry ether was added dropwise over a period of one hour. The reaction mixture was heated under reflux at 40°C for an additional period of 5 hours and was then stirred for 16 hours at *ca* 20°C.

A solution of 21 g of dibenzo*cyclo*heptatrienone - (5) [prepared from dibenzo*cyclo*heptadienone - (5) by bromination and distillation of the bromination product, according to Ber. deutsch. chem. Ges., 1951, *84*, 678] in 400 ml of dry diethyl ether was slowly added dropwise while stirring. The whole was then stirred for an additional period of 20 hours at 20°—25°C. Then, the reaction mixture was cooled with ice-water and mixed with a cold saturated ammonium chloride solution. The organic layer was separated, the aqueous phase was extracted twice with 100 ml portions of diethyl ether and the combined ethereal portions were dried over sodium sulphate and evaporated. The residue, upon recrystallisation from high boiling petroleum ether, yielded colourless crystals of 5 - hydroxy - 5 - (ω - dimethylamino - propyl) - dibenzo*cyclo*heptatriene; melting point 139°—140°C.

EXAMPLE 4

In a two-litre, three-necked flask fitted with stirrer, dropping funnel and condenser, 5 g of GILMAN - alloy were covered with 20 ml of dry diethyl ether and reacted with 1 ml of methyl iodide.

After the vigorous reaction had subsided somewhat, 15 g of magnesium shavings were added in a single portion and a solution of 70 g of freshly distilled ω - piperidino - propyl chloride in 360 ml of dry ether was added dropwise over a period of one hour. The reaction mixture was heated under reflux at 40°C for an additional period of six hours and then stirred for 16 hours at *ca* 20°C.

On the following day, a solution of 42.4 g of dibenzo*cyclo*heptadienone - (5) in 600 ml of dry diethyl ether was slowly added dropwise. The whole was then stirred for an additional period of 18 hours at 20°—25°C. Then, the reaction mixture was cooled with

ice - water, mixed with an ammonium chloride solution (saturated in the cold) and filtered. The main fraction of the reaction product was extracted with methylene chloride from the solid residue and a little additional substance was obtained by concentrating the organic layer.

After recrystallization from absolute ethanol, the 5 - hydroxy - 5 - (ω - piperidino - propyl) - dibenzo*cyclo*heptadiene was obtained as colourless crystals melting at 167°—168°C.

WHAT WE CLAIM IS:—

1. 5 - hydroxy - 5 - substituted - dibenzo*cyclo*heptadienes and 5 - hydroxy - 5 - substituted - dibenzo*cyclo*heptatrienes in which the 5 - substituent is an alkyl radical containing more than two carbon atoms and carrying one or more disubstituted - amino groups and the corresponding compounds which contain one or more nuclear alkyl, alkoxy and/or halogeno substituents, and acid addition or quaternary salts thereof.

2. Substances as claimed in claim 1, wherein said substituent is a dialkylamino - alkyl group in which the alkylene moiety contains more than two carbon atoms.

3. Substances as claimed in claim 2, wherein said dialkylamino - alkyl group is a dialkylamino - propyl group.

4. 5 - hydroxy - 5 - (ω - dimethylamino - propyl) - dibenzo*cyclo*heptadiene.

5. 3 - chloro - 5 - hydroxy - 5 - (ω - dimethylamino - propyl) - dibenzo*cyclo*heptadiene.

6. 5 - hydroxy - 5 - (ω - dimethylamino - propyl) - dibenzo*cyclo*heptatriene.

7. 5 - hydroxy - 5 - (ω - piperidino - propyl) - dibenzo*cyclo*heptadiene.

8. A process for the manufacture of the substances claimed in claim 1 hereof, which process comprises condensing dibenzo*cyclo*heptadi[or tri]enone - (5), or a substitution - derivative thereof which carries one or more nuclear alkyl, ~~aloxy~~ alkoxy and/or halogeno, substituents, with a saturated non-aromatic organo - metallic compound containing more than two carbon atoms and carrying one or more disubstituted - amino groups, hydrolysing the condensation product and, if desired, transforming the product, if a salt, into a different salt or into the base or, if a base, into an acid addition or quaternary salt.

9. A process in accordance with claim 8, wherein said organo - metal compound is a magnesium-, lithium- or zinc - organic compound.

10. A process in accordance with claim 8 or claim 9, wherein the condensation is carried out in an inert solvent or diluent.

11. A process in accordance with any one of claims 8 to 10 inclusive, wherein the hydrolysis of the condensation product is carried out under practically neutral conditions.

12. A process for the manufacture of the substances claimed in claim 1 hereof, substantially as described with reference to the examples.

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ice - water, mixed with an ammonium chloride solution (saturated in the cold) and filtered. The main fraction of the reaction product was extracted with methylene chloride from the solid residue and a little additional substance was obtained by concentrating the organic layer.

After recrystallization from absolute ethanol, the 5 - hydroxy - 5 - (ω - piperidino - propyl) - dibenzo*cyclo*heptadiene was obtained as colourless crystals melting at 167°—168°C.

WHAT WE CLAIM IS:—

1. 5 - hydroxy - 5 - substituted - dibenzo*cyclo*heptadienes and 5 - hydroxy - 5 - substituted - dibenzo*cyclo*heptatrienes in which the 5 - substituent is an alkyl radical containing more than two carbon atoms and carrying one or more disubstituted - amino groups and the corresponding compounds which contain one or more nuclear alkyl, alkoxy and/or halogeno substituents, and acid addition or quaternary salts thereof.

2. Substances as claimed in claim 1, wherein said substituent is a dialkylamino - alkyl group in which the alkylene moiety contains more than two carbon atoms.

3. Substances as claimed in claim 2, wherein said dialkylamino - alkyl group is a dialkylamino - propyl group.

4. 5 - hydroxy - 5 - (ω - dimethylamino - propyl) - dibenzo*cyclo*heptadiene.

5. 3 - chloro - 5 - hydroxy - 5 - (ω - dimethylamino - propyl) - dibenzo*cyclo*heptadiene.

6. 5 - hydroxy - 5 - (ω - dimethylamino - propyl) - dibenzo*cyclo*heptatriene.

7. 5 - hydroxy - 5 - (ω - piperidino - propyl) - dibenzo*cyclo*heptadiene.

8. A process for the manufacture of the substances claimed in claim 1 hereof, which process comprises condensing dibenzo*cyclo*heptadi[or tri]enone - (5), or a substitution - derivative thereof which carries one or more nuclear alkyl, ~~aloxy~~ alkoxy and/or halogeno, substituents, with a saturated non-aromatic organo - metallic compound containing more than two carbon atoms and carrying one or more disubstituted - amino groups, hydrolysing the condensation product and, if desired, transforming the product, if a salt, into a different salt or into the base or, if a base, into an acid addition or quaternary salt.

9. A process in accordance with claim 8, wherein said organo - metal compound is a magnesium-, lithium- or zinc - organic compound.

10. A process in accordance with claim 8 or claim 9, wherein the condensation is carried out in an inert solvent or diluent.

11. A process in accordance with any one of claims 8 to 10 inclusive, wherein the hydrolysis of the condensation product is carried out under practically neutral conditions.

12. A process for the manufacture of the substances claimed in claim 1 hereof, substantially as described with reference to the examples.

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