

PATENT SPECIFICATION

NO DRAWINGS

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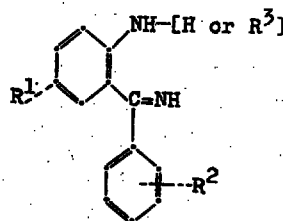
COMPLETE SPECIFICATION

A Process for the manufacture of Benzdiaz[1,4]Epine 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:—

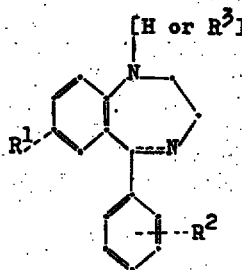
The present invention is concerned with a process for the manufacture of benzdiaz[1,4]-epine derivatives.

The benzdiaz[1,4]epine derivatives obtained by carrying out the present process are compounds of the general formula



(IIa)

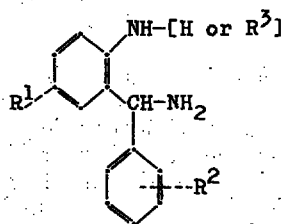
(wherein R^1 , R^2 , R^3 and the broken lines have the significance given earlier) or a benzhydrol amine of the general formula



(I)

wherein R^1 and R^2 each represent a halogen atom and R^3 represents a lower-alkyl group and wherein the broken lines denote optional bonds, and acid addition salts thereof.

According to the present invention, the benzdiaz[1,4]epine derivatives aforesaid are manufactured by reacting a benzophenone imine of the general formula



(IIb)

(wherein R^1 , R^2 , R^3 and the broken lines have the significance given earlier) with a compound of the general formula



(wherein X and X^1 each represent a leaving atom or group) and isolating the desired compound of formula I from the reaction mixture.

Compounds of formula I have been synthesized heretofore by a wide variety of methods. It has now unexpectedly been found

[Price 4s. 6d.]

in accordance with the present invention that compounds of formula III react with benzophenone imines of formula IIa or benzohydril amines of formula IIb and that compounds of formula I can be isolated from the resulting reaction mixture. Thus, by a single step reaction which involves the use of inexpensive starting materials, a facile and novel route to the known benzodiaz[1,4]epine compounds can be provided.

According to one advantageous embodiment of the present process, compounds of formula I hereinbefore in which a double-bond is present in the 4,5-position are manufactured by reacting a benzophenone imine of formula IIa with a compound of formula III.

In a particularly preferred aspect of this embodiment there is used a benzophenone imine starting material of formula IIa in which R^1 is present (advantageously as a chlorine atom) and R^2 is absent. In a more preferred aspect there is used a benzophenone imine starting material of formula IIa in which R^1 is present and represents a halogen atom, R^2 is absent and R^3 is present and represents the methyl group, whereby there is obtained as the reaction product of compound of formula I in which a double-bond is present in the 4,5-position, R^1 is present and represents a chlorine atom, R^2 is absent and R^3 is present and represents the methyl group.

The leaving atoms or groups X and X^1 in the compounds of formula III can be any suitable leaving atoms or groups provided they are capable of functioning efficaciously in the present process. Preferably X and X^1 represent halogen, arylsulphonyl (e.g. benzene-sulphonyl and tosyl) or lower-alkylsulphonyl (e.g. mesyl).

The reaction between a benzophenone imine of formula IIa and a compound of formula III can be carried out using an excess amount of a compound of formula III whereby it serves the two-fold purpose of being a participant in the reaction as well as the medium in which the reaction is carried out. Thus by the convenient step of providing a compound of formula III in excess amounts, both the solvent medium and a reaction partner are provided. Alternatively, the reaction can be carried out in the presence of any suitable inert organic solvent such as an aromatic hydrocarbon (e.g. toluene or benzene), a halogenated hydrocarbon (e.g. a chlorobenzene), an ether (e.g. ethyl ether or dibutyl ether), a lower-alkanol (e.g. methanol or 2-ethoxy-ethanol) and the like. If desired, the reaction can be carried out in the presence of an acid acceptor such as pyridine or triethyl amine, tributyl amine and the like whereby the acid acceptor serves to accept any hydrogen halide formed. However, an acid acceptor is not essential to a successful performance of the reaction since any hydrogen halide

formed would join to a compound of formula I hereinbefore to yield the same in salt form. While temperature and pressure are not critical aspects of this embodiment of the process, it is preferred to carry out the reaction at elevated temperatures, preferably at from about 50° C. to about the reflux temperature of the reaction medium and most preferably under reflux conditions. The desired compound of formula I is then isolated from the reaction mixture.

According to another embodiment of the present process, compounds of formula I hereinbefore in which a single-bond is present in the 4,5 - position are manufactured by reacting a benzohydril amine of formula IIb with a compound of formula III.

The reaction conditions described hereinbefore in connection with the reaction of a benzophenone imine of formula IIa with a compound of formula III are equally applicable in this embodiment of the process involving the reaction of a benzohydril amine of formula IIb with a compound of formula III. The desired compound of formula I in which a single-bond is present in the 4,5-position is then isolated from the reaction mixture.

X and X^1 in the compounds of formula III hereinbefore may be the same or different radicals. All that is required of them is that they are suitable for the purposes of the present invention. Hence, there is contemplated the use of any leaving atom or group which can be employed in the reaction sequence to effect the desired end. A particularly preferred class of compounds of formula III for use in the present process comprises those in which X and X^1 each represent a halogen atom. Examples of such compounds are ethylene dibromide, 1 - chloro - 2 - bromo - ethane, ethylene dichloride, 1 - iodo - 2 - bromo - ethane and the like. A compound of formula III above which is most advantageous for the purposes of the present process is ethylene dibromide. Other compounds of formula III which are suitable for the purposes of the present process are ethylene ditosylate, ethylene dibenzenesulphonate and ethylene dimesylate.

The following Examples illustrate the invention:

EXAMPLE 1.

A) The preparation of the starting material:
A mixture of 97 g of 5 - chloro - 2 - methylaminobenzophenone, 200 ml of ammonia, 2 g of zinc chloride and 200 ml of methanol was placed in an autoclave which was then charged with an over-pressure of 15 atmospheres of nitrogen and heated for 24 hours at 145° C. The resulting solution was then evaporated. The residue was taken up in 300 ml of dichloro-methane and the resulting medium was washed, dried and evaporated. Recrystallization of the residue from methanol gave 2 - methylamino - 5 - chloro -

benzophenone imine as yellow prisms melting at 95°—97° C.

B) The process:

1 g (4.08 mmol) of 2 - methylamino - 5 - chloro - benzophenone imine in 10 ml (21.7 g, 115 mmol) of ethylene dibromide were stirred and heated at reflux for 17 hours. The colour of the medium became deep orange. The resulting mixture was evaporated and the residue was partitioned between dilute hydrochloric acid and ether. The resulting mixture was left overnight to hydrolyse any unchanged imine starting material and then the acid layer was made basic with dilute sodium hydroxide. 7 - Chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine was recovered by extraction of the acid layer with ether, and was obtained as a yellow-brown gum. It was further purified by filtration of a benzene solution through 2 g of alumina (WOELM, neutral, activity III). Evaporation of the eluates and crystallization from hexane gave 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine as pale yellow prisms of melting point 97°—99° C.

EXAMPLE 2.

In a similar manner to that described in Example 1B, 2 - amino - 5 - chloro - benzophenone imine was reacted with ethylene dibromide to give 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine.

EXAMPLE 3.

A) The preparation of the starting material: A mixture of 90 g (0.346 mol) of 2 - methylamino - 5 - chloro - benzophenone oxime, 1 litre of ethanol, 135 ml (0.81 mol) of 6 - N hydrochloric acid and 15 g of 10% palladium-on-carbon catalyst was hydrogenated at 50°—60° C in a rocking autoclave until 2 mols of hydrogen had been absorbed. The filtrate was concentrated to dryness *in vacuo*. The resulting oil was dissolved in 700 ml of water and extracted with three 300 ml portions of dichloro-methane. The aqueous solution was alkalisied with 40% (w/v) sodium hydroxide solution and then extracted again with three 300 ml portions of dichloro-methane. The dichloro-methane extracts were combined, washed with two 200 ml portions of water, dried over sodium sulphate, filtered and concentrated to dryness *in vacuo* to give an oil. The oil, while still warm, was dissolved in 150 ml of ether. The resulting crystals were isolated and washed with ether to give 2 - methylamino - 5 - chloro - benzhydryl amine of melting point 108°—111° C. After recrystallization from ether, the product melted at 113°—115° C.

B) The process:

1 g (4.05 mmol) of 2 - methylamino - 5 -

chlorobenzhydryl amine in 10 ml (21.7 g, 115 mmol) of ethylene dibromide were stirred and heated at reflux for 24 hours. The resulting mixture was evaporated and the residue was partitioned between ether and dilute hydrochloric acid. The acid aqueous layer was made basic with dilute sodium hydroxide and the crude product was recovered by extraction of the acid layer with methylene chloride. Evaporation of the extract gave a yellow-brown gum which was dissolved in benzene and purified by chromatography on a column of 17 g of alumina (WOELM, neutral, activity III). Evaporation of the eluates gave 7 - chloro - 5 - phenyl - 1 - methyl - 2,3,4,5 - tetrahydro - 1H - benzdiaz[1,4]epine which was further purified by distillation in a straight tube at 130°—150° C/0.1 mm. The base was converted to the picrate, namely 7 - chloro - 5 - phenyl - 1 - methyl - 2,3,4,5 - tetrahydro - 1H - benzdiaz[1,4]epine picrate, by treatment of an ethereal solution thereof with 5% (w/v) picric acid in ethanol. Recrystallization of the picrate from ethanol gave bright yellow prisms of melting point 201°—203° C.

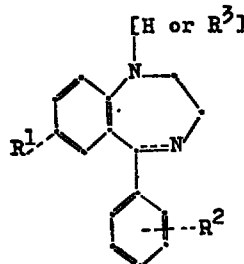
EXAMPLE 4.

In a similar manner to that described in Example 3B, 7 - chloro - 5 - phenyl - 2,3,4,5 - tetrahydro - 1H - benzdiaz[1,4]epine was obtained by reaction of 2 - amino - 5 - chloro - benzhydryl amine with ethylene dibromide.

The term "halogen" is used in this description and in the accompanying claims to mean all four halogens (i.e. bromine, chlorine, fluorine and iodine). The term "lower alkyl" means straight-chain and branched-chain alkyl groups containing from 1 to 7 carbon atoms in the chain (e.g. methyl, ethyl, propyl, isopropyl and the like).

WHAT WE CLAIM IS:—

1. A process for the manufacture of compounds of the general formula



wherein R¹ and R² each represent a halogen atom and R³ represents a lower-alkyl group and wherein the broken lines denote optional bonds, and acid addition salts thereof, which process comprises reacting a benzophenone imine of the general formula

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benzophenone imine as yellow prisms melting at 95°—97° C.

B) The process:

1 g (4.08 mmol) of 2 - methylamino - 5 - chloro - benzophenone imine in 10 ml (21.7 g, 115 mmol) of ethylene dibromide were stirred and heated at reflux for 17 hours. The colour of the medium became deep orange. The resulting mixture was evaporated and the residue was partitioned between dilute hydrochloric acid and ether. The resulting mixture was left overnight to hydrolyse any unchanged imine starting material and then the acid layer was made basic with dilute sodium hydroxide. 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine was recovered by extraction of the acid layer with ether, and was obtained as a yellow-brown gum. It was further purified by filtration of a benzene solution through 2 g of alumina (WOELM, neutral, activity III). Evaporation of the eluates and crystallization from hexane gave 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine as pale yellow prisms of melting point 97°—99° C.

EXAMPLE 2.

In a similar manner to that described in Example 1B, 2 - amino - 5 - chloro - benzophenone imine was reacted with ethylene dibromide to give 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine.

EXAMPLE 3.

A) The preparation of the starting material:

A mixture of 90 g (0.346 mol) of 2 - methylamino - 5 - chloro - benzophenone oxime, 1 litre of ethanol, 135 ml (0.81 mol) of 6 - N hydrochloric acid and 15 g of 10% palladium-on-carbon catalyst was hydrogenated at 50°—60° C in a rocking autoclave until 2 mols of hydrogen had been absorbed. The filtrate was concentrated to dryness *in vacuo*. The resulting oil was dissolved in 700 ml of water and extracted with three 300 ml portions of dichloro-methane. The aqueous solution was alkalisied with 40% (w/v) sodium hydroxide solution and then extracted again with three 300 ml portions of dichloro-methane. The dichloro-methane extracts were combined, washed with two 200 ml portions of water, dried over sodium sulphate, filtered and concentrated to dryness *in vacuo* to give an oil. The oil, while still warm, was dissolved in 150 ml of ether. The resulting crystals were isolated and washed with ether to give 2 - methylamino - 5 - chloro - benzhydryl amine of melting point 108°—111° C. After recrystallization from ether, the product melted at 113°—115° C.

B) The process:

1 g (4.05 mmol) of 2 - methylamino - 5 -

chlorobenzhydryl amine in 10 ml (21.7 g, 115 mmol) of ethylene dibromide were stirred and heated at reflux for 24 hours. The resulting mixture was evaporated and the residue was partitioned between ether and dilute hydrochloric acid. The acid aqueous layer was made basic with dilute sodium hydroxide and the crude product was recovered by extraction of the acid layer with methylene chloride. Evaporation of the extract gave a yellow-brown gum which was dissolved in benzene and purified by chromatography on a column of 17 g of alumina (WOELM, neutral, activity III). Evaporation of the eluates gave 7 - chloro - 5 - phenyl - 1 - methyl - 2,3,4,5 - tetrahydro - 1H - benzdiaz[1,4]epine which was further purified by distillation in a straight tube at 130°—150° C/0.1 mm. The base was converted to the picrate, namely 7 - chloro - 5 - phenyl - 1 - methyl - 2,3,4,5 - tetrahydro - 1H - benzdiaz[1,4]epine picrate, by treatment of an ethereal solution thereof with 5% (w/v) picric acid in ethanol. Recrystallization of the picrate from ethanol gave bright yellow prisms of melting point 201°—203° C.

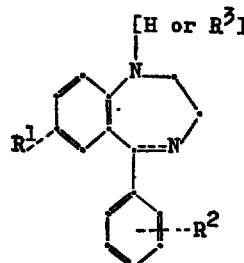
EXAMPLE 4.

In a similar manner to that described in Example 3B, 7 - chloro - 5 - phenyl - 2,3,4,5 - tetrahydro - 1H - benzdiaz[1,4]epine was obtained by reaction of 2 - amino - 5 - chloro - benzhydryl amine with ethylene dibromide.

The term "halogen" is used in this description and in the accompanying claims to mean all four halogens (i.e. bromine, chlorine, fluorine and iodine). The term "lower alkyl" means straight-chain and branched-chain alkyl groups containing from 1 to 7 carbon atoms in the chain (e.g. methyl, ethyl, propyl, isopropyl and the like).

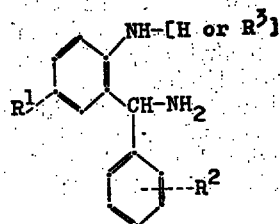
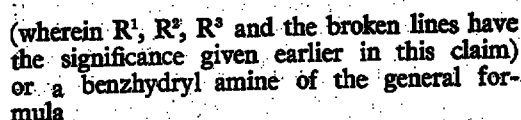
WHAT WE CLAIM IS:—

1. A process for the manufacture of compounds of the general formula



wherein R¹ and R² each represent a halogen atom and R³ represents a lower-alkyl group and wherein the broken lines denote optional bonds, and acid addition salts thereof, which process comprises reacting a benzophenone imine of the general formula





(wherein R¹, R², R³ and the broken lines have the significance given earlier in this claim) with a compound of the general formula



(wherein X and X¹ each represent a leaving atom or group) and isolating the desired compound of the formula first written in this claim from the reaction mixture.

2. A process as set forth in claim 1, wherein the reaction is carried out under reflux conditions.

3. A process as set forth in claim 1 or claim 2, wherein the benzophenone imine or benzhydryl amine starting material is reacted with a compound of the formula fourth written in claim 1 in which X and X¹ each represent a halogen atom.

4. A process as set forth in claim 3, wherein the benzophenone imine or benzhydryl amine starting material is reacted with ethylene dibromide.

5. A process as set forth in claim 1 or claim 2, wherein the benzophenone imine or benzhydriyl amine starting material is reacted with a compound of the formula fourth written in claim 1 in which X and X' represent arylsulphonyl or lower-alkylsulphonyl.

6. A process as set forth in any one of claims 1 to 5 inclusive, wherein 2-methylamino - 5 - chlorobenzophenone imine is used as the starting material.

7. A process as set forth in any one of claims 1 to 5 inclusive, wherein 2 - amino - 5 - chlorobenzophenone imine is used as the starting material.

8. A process as set forth in any one of claims 1 to 5 inclusive, wherein 2 - methyl-amino - 5 - chlorobenzhydryl amine is used as the starting material.

9. A process for the manufacture of the compounds of the formula first written in claim 1 and acid addition salts thereof substantially as described with reference to the Examples.

10. Compounds of the formula first written in claim 1, and acid addition salts thereof, when manufactured by the process claimed in any one of claims 1 to 9 inclusive.

W. D. WHITAKER,

Patent Agent,

For F. Hoffmann-la Roche & Co.,
Aktiengesellschaft.

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