

PATENT SPECIFICATION

NO DRAWINGS

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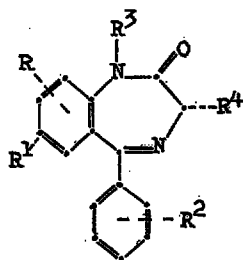
COMPLETE SPECIFICATION

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 process of the present invention may be formulated thus:



(I)

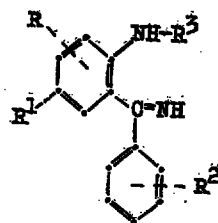
wherein R and R¹ each represent a halogen atom or the nitro or trifluoromethyl group or a lower-alkyl group, R² represents a halogen atom, R³ represents a lower-alkyl, C₃—C₆ cycloalkyl or (C₃—C₆ cycloalkyl)-(lower alkyl) group and R⁴ represents a lower-alkyl group and wherein the broken lines denote that the substituents attached thereby are optional. They are medicinally valuable derivatives.

It will be appreciated that the term 'halogen' is used in this description and in the claims appended hereto to mean fluorine, chlorine, bromine and iodine. It will similarly be appreciated that the term 'lower

alkyl' is used to mean both straight-chain and branched-chain alkyl groups containing up to seven carbon atoms (e.g. methyl, ethyl and isopropyl). Examples of C₃—C₆ cycloalkyl groups are cyclopropyl, cyclopentyl and cyclohexyl, the cyclopropyl group being preferred.

One preferred class of benzdiaz[1,4]epine derivatives of formula I hereinbefore comprises those in which R¹ is present and represents a halogen atom (advantageously a chlorine atom) or the nitro group, particularly those in which R, R² and R⁴ are absent and R³ represents a lower-alkyl group. An especially preferred class of benzdiaz[1,4]epine derivatives of formula I hereinbefore comprises those in which R¹ is present and represents a halogen atom (advantageously a chlorine atom), R is absent and R³ represents the methyl group, particularly those in which R² and R⁴ are absent. When R² is present, it is preferably situated in the *ortho*-position of the 5-phenyl ring.

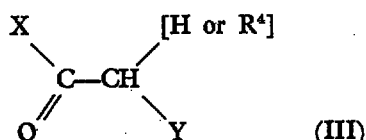
The benzdiaz[1,4]epine derivatives of formula I hereinbefore are manufactured in accordance with the present process by reacting a 2-amino-benzophenone imine of the general formula



(II)

[Price 4s. 6d.]

wherein R, R¹, R², R³ and the broken lines have the significance given earlier, with a halo-acyl halide of the general formula



5 wherein R⁴ has the significance given earlier and X and Y each represent a halogen atom, in the presence of a base.

The 2-amino-benzophenone imine starting materials of formula II hereinbefore can be prepared in accordance with the process described and claimed in the specification of our copending Application for Letters Patent No: 54952/66 (now Serial No: 1,164,498). One preferred class of 2-amino-benzophenone imine starting materials of formula II comprises those in which R¹ is present and represents a halogen atom (advantageously a chlorine atom) or the nitro group, particularly those in which R and R² are absent and R³ represents a lower-alkyl group. An especially preferred class of 2-amino-benzophenone imine starting materials of formula II comprises those in which R¹ is present and represents a halogen atom (advantageously a chlorine atom), R is absent and R³ represents the methyl group, particularly those in which R² is absent. The especially preferred 2-amino-benzophenone imine starting materials of formula II are 2-methylamino-5-(chloro or nitro)-benzophenone imine.

It will be appreciated that X and Y in the halo-acyl halide starting materials of formula III hereinbefore can represent the same or different halogen atoms. The preferred halo-acyl halides are those in which X and Y each represent a chlorine, bromine or iodine atom and those in which R⁴ is absent. Examples of useful halo-acyl halides are bromo-acetyl bromide, chloro-acetyl bromide and chloro-acetyl iodide.

The reaction of a 2-amino-benzophenone imine of formula II hereinbefore with a halo-acyl halide of formula III hereinbefore to give a benz Diaz[1,4]epine derivative of formula I hereinbefore is carried out in the presence of a base. Included among the many bases which may suitably be used in the present process are alkali-metal hydroxides (e.g. sodium hydroxide) and alkaline-earth-metal hydroxides. In a particularly advantageous aspect of the present process, aqueous solutions of alkali-metal hydroxides are used.

Temperature and pressure are not critical features of the present process. Thus, the

reaction will proceed at room temperature and at atmospheric pressure or at temperatures above or below room temperature and/or under pressure. Preferably the reaction is carried out at a temperature below room temperature. In one particularly preferred aspect of the present process, the reaction is carried out at a temperature within the range of from 0°C to 20°C (most suitably at a temperature within the range of from 5°C to 15°C). The reaction is preferably carried out in the presence of an inert organic solvent; for example, aromatic hydrocarbons such as benzene, toluene and xylenes, chlorinated aromatic hydrocarbons such as chloro-benzene, or any other suitable inert organic solvent.

The benz Diaz[1,4]epine derivatives of formula I hereinbefore in which R, R¹, R² and R⁴ have the significance given earlier (provided that both R and R¹ do not represent a trifluoromethyl group) and R³ represents a lower-alkyl group are claimed *per se* in the specification of our Letters Patent No: 972,968.

The following Example illustrates the invention:

EXAMPLE

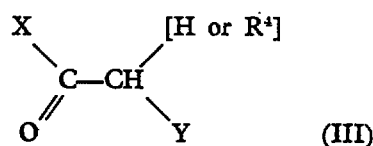
A solution of 5 g (20.7 mmol) of 5-chloro-2-methylamino-benzophenone imine in 50 ml of benzene was cooled in an ice-bath and treated with 50 ml of 0.5-N sodium hydroxide and then with a solution of 4.6 g (22.7 mmol) of bromo-acetyl bromide in 10 ml of benzene. The resulting mixture was vigorously stirred for 0.25 hour, then 23 ml of 1-N sodium hydroxide were added thereto and stirring was continued for an additional 2 hours. The layers which formed were subsequently separated and the organic layer was washed, dried, concentrated and chromatographed over 100 g of silica. 2-Amino-5-chloro-benzophenone was eluted with benzene and discarded. When no further 2-amino-5-chloro-benzophenone was isolated (still utilizing benzene as the eluant), the eluant was changed to ether. Evaporation of the ether eluate gave 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-benz Diaz[1,4]epinone-(2) as white prisms which melted at 128°-130°C after recrystallization from ether.

Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to the claims of Patents Nos. 1,029,741 and 1,117,062.

WHAT WE CLAIM IS:—

1. A process for the manufacture of benz Diaz[1,4]epine derivatives of the general formula

wherein R, R¹, R², R³ and the broken lines have the significance given earlier, with a halo-acyl halide of the general formula



- 5 wherein R⁴ has the significance given earlier and X and Y each represent a halogen atom, in the presence of a base.

The 2-amino-benzophenone imine starting materials of formula II hereinbefore can be prepared in accordance with the process described and claimed in the specification of our copending Application for Letters Patent No: 54952/66 (now Serial No: 1,164,498). One preferred class of 2-amino-benzophenone imine starting materials of formula II comprises those in which R¹ is present and represents a halogen atom (advantageously a chlorine atom) or the nitro group, particularly those in which R and R² are absent and R³ represents a lower-alkyl group. An especially preferred class of 2-amino-benzophenone imine starting materials of formula II comprises those in which R¹ is present and represents a halogen atom (advantageously a chlorine atom), R is absent and R³ represents the methyl group, particularly those in which R² is absent. The especially preferred 2-amino-benzophenone imine starting materials of formula II are 2-methylamino-5-(chloro or nitro)-benzophenone imine.

It will be appreciated that X and Y in the halo-acyl halide starting materials of formula III hereinbefore can represent the same or different halogen atoms. The preferred halo-acyl halides are those in which X and Y each represent a chlorine, bromine or iodine atom and those in which R⁴ is absent. Examples of useful halo-acyl halides are bromo-acetyl bromide, chloro-acetyl bromide and chloro-acetyl iodide.

The reaction of a 2-amino-benzophenone imine of formula II hereinbefore with a halo-acyl halide of formula III hereinbefore to give a benzdiaz[1,4]epine derivative of formula I hereinbefore is carried out in the presence of a base. Included among the many bases which may suitably be used in the present process are alkali-metal hydroxides (e.g. sodium hydroxide) and alkaline-earth-metal hydroxides. In a particularly advantageous aspect of the present process, aqueous solutions of alkali-metal hydroxides are used.

Temperature and pressure are not critical features of the present process. Thus, the

reaction will proceed at room temperature and at atmospheric pressure or at temperatures above or below room temperature and/or under pressure. Preferably the reaction is carried out at a temperature below room temperature. In one particularly preferred aspect of the present process, the reaction is carried out at a temperature within the range of from 0°C to 20°C (most suitably at a temperature within the range of from 5°C to 15°C). The reaction is preferably carried out in the presence of an inert organic solvent; for example, aromatic hydrocarbons such as benzene, toluene and xylenes, chlorinated aromatic hydrocarbons such as chloro-benzene, or any other suitable inert organic solvent.

The benzdiaz[1,4]epine derivatives of formula I hereinbefore in which R, R¹, R² and R⁴ have the significance given earlier (provided that both R and R¹ do not represent a trifluoromethyl group) and R³ represents a lower-alkyl group are claimed *per se* in the specification of our Letters Patent No: 972,968.

The following Example illustrates the invention:

EXAMPLE

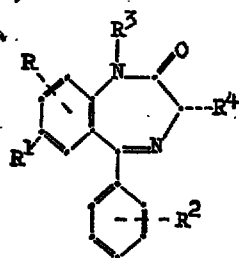
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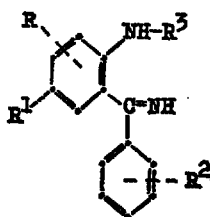
WHAT WE CLAIM IS:—

1. A process for the manufacture of benzdiaz[1,4]epine derivatives of the general formula

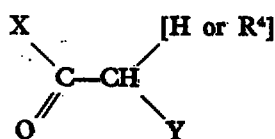




wherein R and R¹ each represent a halogen atom or the nitro or trifluoromethyl group or a lower-alkyl group, R² represents a halogen atom, R³ represents a lower-alkyl, C₃-C₆ cycloalkyl or (C₃-C₆ cycloalkyl)-(lower alkyl) group and R⁴ represents a lower-alkyl group and wherein the broken lines denote that the substituents attached thereby are optional, which process comprises reacting a 2-amino-benzophenone imine of the general formula



wherein R, R¹, R², R³ and the broken lines have the significance given earlier in this claim, with a halo-acyl halide of the general formula



wherein R⁴ has the significance given earlier in this claim and X and Y each represent a halogen atom, in the presence of a base.

2. A process as set forth in claim 1, wherein a 2-amino-benzophenone imine of the formula second written in that claim in which R¹ is

present and represents a halogen atom or the nitro group is used as the 2-amino-benzophenone imine starting material.

3. A process as set forth in claim 2, wherein said 2-amino-benzophenone imine R and R² are absent and R³ represents a lower-alkyl group.

4. A process as set forth in claim 2, wherein a 2-amino-benzophenone imine of the formula second written in claim 1 in which R¹ is present and represents a halogen atom, R is absent and R³ represents the methyl group is used as the 2-amino-benzophenone imine starting material.

5. A process as set forth in claim 4, wherein in said 2-amino-benzophenone imine R² is absent.

6. A process as set forth in claim 3, wherein 2-methylamino-5-chloro-benzophenone imine is used as the 2-amino-benzophenone imine starting material.

7. A process as set forth in claim 3, wherein 2-methylamino-5-nitro-benzophenone imine is used as the 2-amino-benzophenone imine starting material.

8. A process as set forth in any one of claims 1 to 7 inclusive, wherein a halo-acyl halide in which X and Y each represent a chlorine, bromine or iodine atom is used as the halo-acyl halide starting material.

9. A process as set forth in any one of claims 1 to 8 inclusive, wherein a halo-acyl halide in which R⁴ is absent is used.

10. A process as set forth in any one of claims 1 to 9 inclusive, wherein an alkali-metal hydroxide is used as the base.

11. A process as set forth in claim 10, wherein said alkali-metal hydroxide is sodium hydroxide.

12. A process as claimed in claim 1, substantially as described with reference to the foregoing Example.

13. Benzodiaz[1,4]epine derivatives of the formula first written in claim 1, when manufactured by the process claimed in any one of claims 1 to 12 inclusive.

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