

L116,918



PATENT SPECIFICATION

NO DRAWINGS

L116,918

Date of Application and filing Complete Specification: 8 Dec., 1966.

No. 54956/66.

Application made in United States of America (No. 512,783) on 9 Dec., 1965.

Complete Specification Published: 12 June, 1968.

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Index at acceptance:—C2 C(1E7C1, 1E7F1, 1E7N5)

Int. Cl.:—C 07 d 53/06

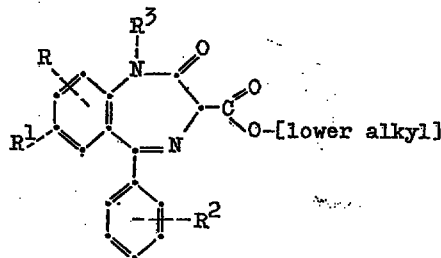
COMPLETE SPECIFICATION

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 this invention are compounds of the general formula



(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 and R³ represents a lower-alkyl group and wherein the broken lines denote that the substituents attached thereby are optional, and acid addition salts thereof.

Compounds of formula I hereinbefore and their pharmaceutically acceptable acid addition salts (formed with inorganic and organic acids such as hydrobromic acid, hydrochloric acid, sulphuric acid, citric acid and ascorbic acid) are useful as muscle relaxants, sedatives and anticonvulsants. They can be administered internally (for example, parenterally or enterally) in conventional pharmaceutical dosage forms with dosage adjusted to fit the exigencies of a particular therapeutic situation. The pharmaceutical dosage forms can be prepared by incorporating the active ingredient in liquid or solid vehicles to form elixirs, tablets, capsules, suspensions and suppositories.

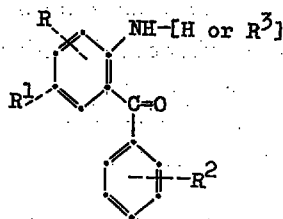
It will be appreciated that the term 'lower alkyl' is used in this description and in the claims appended hereto to mean both straight-chain and branch-chain alkyl groups containing up to seven carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl and pentyl). It will further be appreciated that the term 'halogen' is used to mean fluorine, chlorine, bromine or iodine.

The preferred compounds of formula I are those in which R¹ is present and represents a halogen atom, advantageously a chlorine atom. Further preferred compounds for formula I are those in which R¹ is present and represents a halogen atom (advantageously a chlorine atom) and R and R² are both absent. The especially preferred compounds of formula I are those in which R¹ is present and represents a halogen atom (advantageously a chlorine atom), R and R² are both absent and R³ (when present) represents the methyl group. The preferred lower-alkoxycarbonyl group present in the 3-position is the ethoxycarbonyl group. When R² is present, it is pre-

[Price 4s. 6d.]

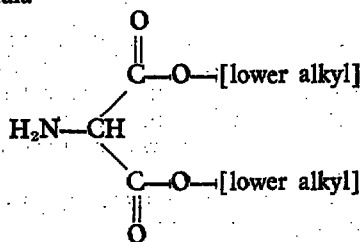
ferably situated in the *ortho*-position of the 5-phenyl ring.

The compounds of formula I hereinbefore and their acid addition salts are manufactured in accordance with the present invention by reacting a 2-amino-benzophenone of the general formula



(II)

wherein R, R¹, R², R³ and the broken lines have the significance given earlier, with a diester of the general formula



(III)

and, if desired, converting the reaction product into an acid addition salt.

The preferred 2-amino-benzophenone starting materials of formula II hereinbefore are those in which R¹ is present and represents a halogen atom (advantageously a chlorine atom). Especially preferred 2-amino-benzophenone starting materials of formula II hereinbefore are those in which R¹ is present and represents a halogen atom (advantageously a chlorine atom) and R and R² are both absent or R and R² are both absent and R³ (when present) represents the methyl group.

Examples of diester starting materials of formula III hereinbefore are dipropyl amino-malonate, dimethyl amino-malonate and, most preferably, diethyl amino-malonate. The diester starting materials are advantageously used in the reaction in the form of a salt.

The reaction of a 2-amino-benzophenone of formula II with a diester of formula III or a salt thereof is preferably carried out in the presence of an inert organic solvent. Examples of suitable inert organic solvents are tetrahydro-furan, N,N-dimethyl-formamide, an alkanol containing up to seven carbon atoms or an organic base such as pyridine, picoline or quinoline. When the diester of formula III is present in its salt form, an organic base (particularly pyridine) is advantageously used due to the capability thereof to serve both as a neutralizing agent and as the reaction medium.

The temperature and pressure at which the reaction is carried out are not critical. Thus, the reaction can be carried out at room temperature and atmospheric pressure or at temperatures above room temperature. Advantageously, the reaction is carried out at elevated temperatures, most suitably at about the reflux temperature of the reaction medium.

The 2-amino-benzophenone starting material of formula II hereinbefore in which R, R² and R³ are absent and R¹ is present and represents the trifluoromethyl group is claimed *per se* in the specification of our Letters Patent No. 972,973. The benzophenone starting material of formula II hereinbefore in which R and R² are absent, R¹ is present and represents a chlorine atom and R³ is present and represents the methyl group is claimed *per se* in the specification of our Letters Patent No. 972,975.

The following Examples illustrate the invention.

EXAMPLE 1

A solution of 5 g (21.5 mmol) of 2-amino-5-chloro-benzophenone and 13.7 g (64.5 mmol) of diethyl amino-malonate hydrochloride in 30 ml of pyridine was heated under reflux for 20 hours. Pyridine was then removed under reduced pressure and the residue was dissolved in 50 ml of methylene chloride. The resulting solution was washed, dried and concentrated to give an oil which was dissolved in a small volume of benzene and chromatographed over a column of 100 g of silica gel using benzene

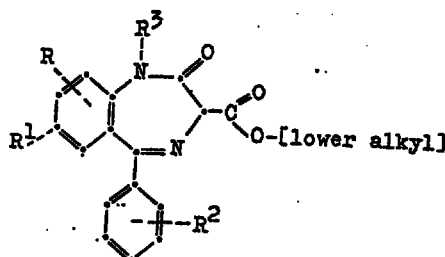
as the eluant. The benzene fraction was discarded and the eluant was changed to ether. Concentration of the ether fractions gave 7-chloro-3-ethoxycarbonyl-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]-epinone-(2) as white prisms; the product was recrystallized from a mixture of methylene chloride and ethanol.

EXAMPLE 2

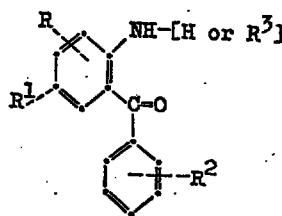
A solution of 2.5 g (10 mmol) of 5-chloro-2-methylamino-benzophenone and 6.3 g (30 mmol) of diethyl amino-malonate hydrochloride in 30 ml of pyridine was heated under reflux for 20 hours. Pyridine was then removed under reduced pressure and the residue was dissolved in 50 ml of methylene chloride. The resulting solution was washed, dried and evaporated to give an oil which was treated with two 100 ml portions of boiling hexane; the hexane fractions were discarded. The oil was next dissolved in a small amount of benzene and chromatographed over 100 g of silica using benzene as the eluant. The benzene fractions were discarded and the eluant changed to ether. Removal of solvent from the ether fractions by evaporation and recrystallization of the residue from methanol gave 7-chloro-1-methyl-3-ethoxycarbonyl-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]-epinone-(2).

WHAT WE CLAIM IS:—

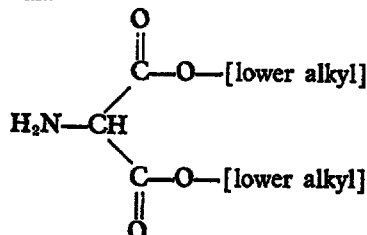
1) A process for the manufacture of compounds of the general formula



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 and R³ represents a lower-alkyl group and wherein the broken lines denote that the substituents attached thereby are optional, and acid addition salts thereof, which process comprises reacting a 2-amino-benzophenone of the general formula



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



and, if desired, converting the reaction product into an acid addition salt.

2) A process as set forth in claim 1, wherein a 2-amino-benzophenone in which R¹ is present and represents a halogen atom is used as the 2-amino-benzophenone starting material.

3) A process as set forth in claim 1, wherein a 2-amino-benzophenone in which R¹ is present and represents a halogen atom and R and R² are both absent is used as the 2-amino-benzophenone starting material.



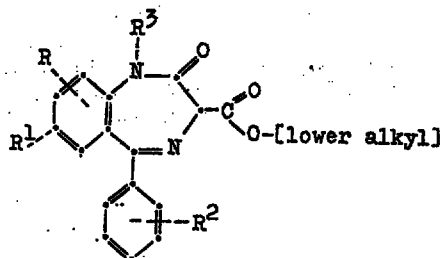
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EXAMPLE 2

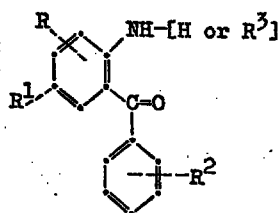
A solution of 2.5 g (10 mmol) of 5-chloro-2-methylamino-benzophenone and 6.3 g (30 mmol) of diethyl amino-malonate hydrochloride in 30 ml of pyridine was heated under reflux for 20 hours. Pyridine was then removed under reduced pressure and the residue was dissolved in 50 ml of methylene chloride. The resulting solution was washed, dried and evaporated to give an oil which was treated with two 100 ml portions of boiling hexane; the hexane fractions were discarded. The oil was next dissolved in a small amount of benzene and chromatographed over 100 g of silica using benzene as the eluant. The benzene fractions were discarded and the eluant changed to ether. Removal of solvent from the ether fractions by evaporation and recrystallization of the residue from methanol gave 7-chloro-1-methyl-3-ethoxycarbonyl-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]-epinone-(2).

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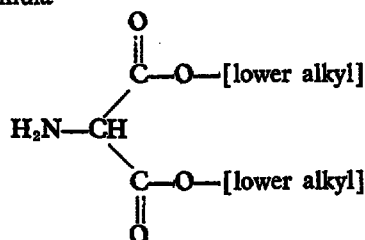
1) A process for the manufacture of compounds of the general formula



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



and, if desired, converting the reaction product into an acid addition salt.

2) A process as set forth in claim 1, wherein a 2-amino-benzophenone in which R¹ is present and represents a halogen atom is used as the 2-amino-benzophenone starting material.

3) A process as set forth in claim 1, wherein a 2-amino-benzophenone in which R¹ is present and represents a halogen atom and R and R² are both absent is used as the 2-amino-benzophenone starting material.



4) A process as set forth in claim 1, wherein a 2-amino-benzophenone in which R^1 is present and represents a halogen atom, R and R^2 are both absent and R^3 (when present) represents the methyl group is used as the 2-amino-benzophenone starting material.

5) A process as set forth in any one of claims 2 to 4 inclusive, wherein R^1 represents a chlorine atom. 5

6) A process as set forth in any one of claims 1 to 5 inclusive, wherein diethyl amino-malonate is used as the diester starting material.

7) A process as set forth in any one of claims 1 to 6 inclusive, wherein the diester is used in the form of a salt. 10

8) A process as set forth in any one of claims 1 to 7 inclusive, wherein the reaction is carried out in the presence of an inert organic solvent.

9) A process as set forth in claim 8, wherein said inert organic solvent is an organic base.

10) A process as claimed in claim 1, substantially as described with reference to the foregoing Examples. 15

11) Compounds of the formula first written in claim 1, and acid addition salts thereof, when manufactured by the process claimed in any one of the preceding claims.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1968.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which
copies may be obtained.