

PATENT SPECIFICATION

NO DRAWINGS

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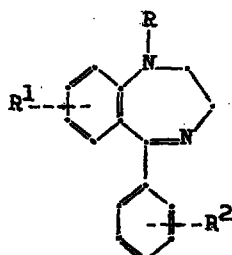
COMPLETE SPECIFICATION

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



(I)

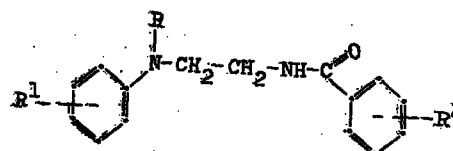
, wherein R represents a lower-alkyl group, R¹ represents a chlorine or bromine atom or the nitro or trifluoromethyl group and R² represents a halogen atom and wherein the broken lines denote that the atom or group attached thereby is optional, and acid addition salts thereof.

It will be appreciated that the term 'halogen' is used in this description and in the claims appended hereto to mean chlorine, bromine, iodine and fluorine. The term 'lower alkyl' is used to mean a straight-chain or branched-chain alkyl group containing from 1 to 7 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl and isobutyl. The preferred lower-alkyl groups are those containing from 1 to 4 carbon atoms.

[Price 4s. 6d.]

An especially valuable class of benzdiaz[1,4]epine products aforesaid comprises compounds of formula I in which R¹ is present and represents a chlorine or bromine atom and R² is absent. An especially preferred compound of formula I is that in which R represents the methyl group, R¹ is present in the 7-position and represents a chlorine atom and R² is absent; that is to say, 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epine.

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



(II)

, wherein R, R¹, R² and the broken lines have the significance given earlier, in the presence of a dehydrating system and, if desired, converting the cyclisation product into an acid addition salt.

In the present process, the starting materials of formula II are dehydrated whereby cyclisation to a compound of formula I occurs. The cyclisation can be carried out in the presence of any dehydrating agent which is capable of achieving this end. Among the many suitable dehydrating agents there may be named phosphorus pentoxide, phosphorus oxychloride and polyphosphoric acid as well as mixtures thereof. In a particularly advantageous embodiment of the process, a dehydrating system consisting essentially of phosphorus oxychloride and phosphorus pent-

SEE ERRATA SLIP ATTACHED

oxide (preferably containing the former in a molar amount greater than 50% of the total molar amount of the two ingredients) is used. The cyclisation is preferably carried out at elevated temperatures (e.g. at a temperature within the approximate range of from 50°C to 120°C).

The starting materials of formula II hereinbefore in which R¹ is present are claimed *per se* in the specification of our copending Application for Letters Patent No. 29740/68 (now Serial No. 1,153,102) and can be prepared as described therein.

The present invention provides a process which is eminently well suited for commercial application since the desired compounds of formula I and their acid addition salts are obtained in good yields and high quality. Furthermore, the various reactants employed are readily available and are inexpensive or can easily be prepared from commercially available materials.

The compounds of formula I hereinbefore and their acid addition salts are claimed *per se* in the specification of our Letters Patent No. 1,017,276.

The following Examples illustrate the present invention.

EXAMPLE 1

288 mg (1 mmol) of N - (4 - chlorophenyl) - N' - methyl - N' - benzoyl - ethylenediamine, [prepared as described in the specification of our copending Application No. 29740/68 (now Serial No. 1,153,102)], 1.42 g. (10 mmol) of phosphorus oxychloride were stirred at 110°C for 17 hours. The reaction mixture was cooled and treated with 25 g of ice and 25 ml of 4-N hydrochloric acid. The solution was extracted with ether and made basic with 10-N sodium hydroxide. The organic free base was then extracted with methylene chloride and the extract dried. Removal of the solvent gave 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H-benzdiaz[1,4]epine as a yellow oil which was dissolved in 2 ml. of methanol. 0.7 ml of methanol containing 1.05 mmol of hydrogen chloride were added and crystallization was induced by adding ether. This yielded 7-chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride of melting point 250°—252°C.

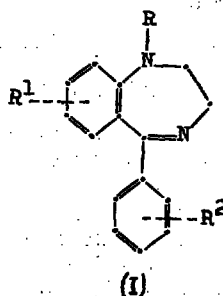
EXAMPLE 2

288 mg (1 mmol) of N - (4 - chlorophenyl) - N' - methyl - N' - benzoyl - ethylenediamine were heated under reflux with 1 ml of phosphorus oxychloride for 7 hours. The reaction mixture was then evaporated to dryness *in vacuo* and the residue dissolved in ice-cold 3-N hydrochloric acid. The acidic solution was extracted once with ether, made basic with 5-N sodium hydroxide and the product extracted 3 times with methylene

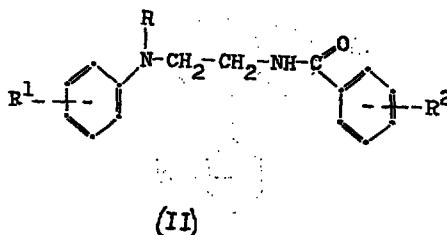
chloride. After drying the extracts followed by evaporation in order to remove the solvent, the residue was dissolved in 5 ml of methanol. 0.4 ml of methanol containing 0.64 mmol of hydrogen chloride were added to the solution. Upon the addition of ether, 7 - chloro - 1 - methyl - 5 - phenyl - 2,3-dihydro - 1H - benzdiaz[1,4]epine hydrochloride of melting point 250°—252°C precipitated.

WHAT WE CLAIM IS:—

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



, wherein R represents a lower-alkyl group, R¹ represents a chlorine or bromine atom or the nitro or trifluoromethyl group and R² represents a halogen atom and wherein the broken lines denote that the atom or group attached thereby is optional, and acid addition salts thereof, which process comprises cyclising a compound of the general formula



, wherein R, R¹, R² and the broken lines have the significance given earlier in this claim, in the presence of a dehydrating system and, if desired, converting the cyclisation product into an acid addition salt.

2. A process as set forth in claim 1, wherein the dehydrating system consists essentially of phosphorus pentoxide and phosphorus oxychloride.

3. A process as set forth in claim 1 or claim 2, wherein N - (4 - chloro - phenyl) - N' - methyl - N' - benzoyl ethylenediamine is used as the starting material.

4. 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 foregoing Examples.

5. Compounds of the formula first written



oxide (preferably containing the former in a molar amount greater than 50% of the total molar amount of the two ingredients) is used. The cyclisation is preferably carried out at elevated temperatures (e.g. at a temperature within the approximate range of from 50°C to 120°C).

The starting materials of formula II hereinbefore in which R¹ is present are claimed *per se* in the specification of our copending Application for Letters Patent No. 29740/68 (now Serial No. 1,153,102) and can be prepared as described therein.

The present invention provides a process which is eminently well suited for commercial application since the desired compounds of formula I and their acid addition salts are obtained in good yields and high quality. Furthermore, the various reactants employed are readily available and are inexpensive or can easily be prepared from commercially available materials.

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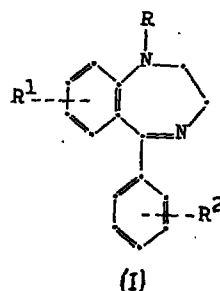
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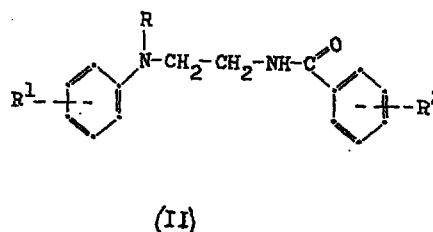
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, wherein R, R¹, R² and the broken lines have the significance given earlier in this claim, in the presence of a dehydrating system and, if desired, converting the cyclisation product into an acid addition salt.

2. A process as set forth in claim 1, wherein the dehydrating system consists essentially of phosphorus pentoxide and phosphorus oxychloride.

3. A process as set forth in claim 1 or claim 2, wherein N - (4 - chloro - phenyl) - N - methyl - N' - benzoyl - ethylenediamine is used as the starting material.

4. 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 foregoing Examples.

5. Compounds of the formula first written



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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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