

PATENT SPECIFICATION

NO DRAWINGS

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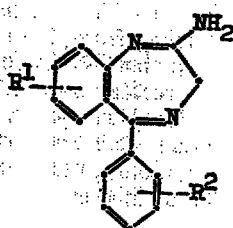
COMPLETE SPECIFICATION

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:—

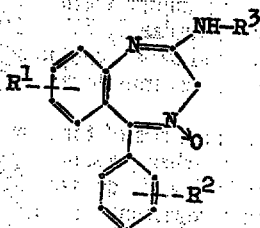
The present invention is concerned with a process for the manufacture of benzdiaz[1,4]-epine derivatives. The invention is also concerned with novel carbonitriles useful in said process.

The benzdiaz[1,4]epine derivatives obtained by carrying out the process of this invention are 2-amino compounds of the general formula



(I)

and 2-alkylamino compounds of the general formula



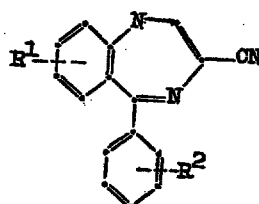
(II)

[Price 4s. 6d.]

wherein R¹ and R² each represent a halogen atom or a trifluoromethyl, nitro or cyano group and R³ represents a lower-alkyl group and wherein the broken lines denote that the atoms or groups attached thereby are optional.

It will be appreciated that the term 'lower alkyl' is used in this description and in the accompanying claims to mean alkyl groups containing from 1 to 7 (preferably from 1 to 4) carbon atoms.

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



(III)

wherein R¹, R² and the broken lines have the significance given earlier, with alkali and, if desired, transforming the resulting 2-amino compound of formula I hereinbefore into a corresponding 2-alkylamino compound of formula II hereinbefore.

The process provided by the invention is illustrated in greater detail by the following formula scheme in which R¹, R², R³ and the broken lines have the significance given earlier and R⁴ represents a lower-alkyl, phenyl or benzyl group. When R¹ is present in the following formulae, it is preferably in the 7-position.

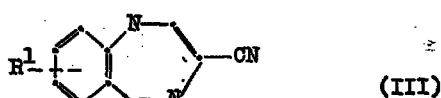
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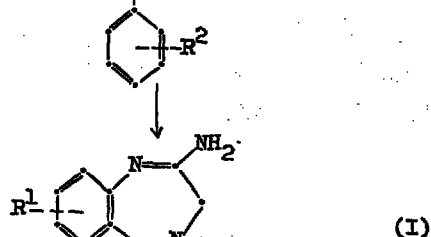
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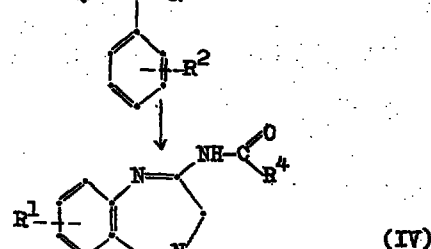
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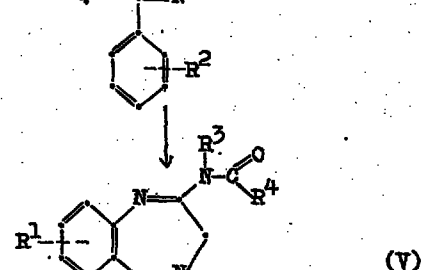
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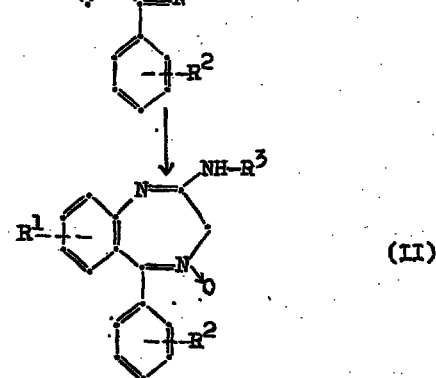
(I)



(IV)



(V)

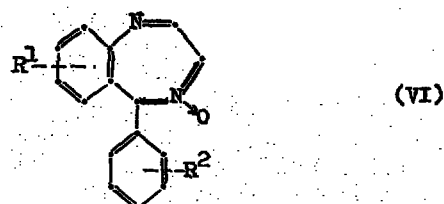


(II)

The carbonitrile starting materials of formula III hereinbefore can be readily converted into the 2-amino compounds of formula I hereinbefore by reaction with alkali. This reaction can be carried out using any of the conventional bases, although a strong base such as sodium hydroxide or potassium hydroxide is preferred. The reaction is conveniently carried out in the presence of a water-miscible organic solvent such as an alcohol (e.g. methanol or ethanol), and is preferably carried out at an elevated temperature, suitably at a temperature between about room temperature and the reflux temperature of the reaction mixture.

The 2-amino compounds of formula I can be readily acylated by any of the usual techniques such as treatment with an alkanolic acid anhydride (e.g. acetic anhydride) to give the N-acylamino compounds of formula IV which, upon alkylation by any of the usual alkylation techniques (e.g. treatment with an alkyl halide) yield the known benzdiaz[1,4]-epines of formula V. These benzdiaz[1,4]-epines of formula V can, in turn, be converted into the pharmaceutically useful benzdiaz[1,4]epine N-oxides of formula II (e.g. chlordiazepoxide) by oxidation and hydrolysis according to known techniques.

The carbonitrile starting materials of formula III hereinbefore are novel and it will be appreciated that they also form part of this invention. They can be prepared by reacting a 5H-benzdiaz[1,4]epine 4-oxide of the general formula



(VI)

wherein R¹, R² and the broken lines have the significance given earlier, with an alkali-metal cyanide such as sodium cyanide or potassium cyanide. The carbonitriles of formula III are isolated from the reaction mixture by treating it with any suitable acid to neutralise the excess base and then separating the product by any of the usual techniques (e.g. filtration or evaporation). The reaction is conveniently carried out in the presence of an inert organic solvent, preferably a solvent which will dissolve the cyanide reactant such as an alkanol containing from 1 to 7 (preferably from 1 to 4) carbon atoms (e.g. methanol or ethanol). It is preferred to carry out the reaction at a reduced temperature, preferably at a temperature between about 0°C and room temperature, although temperatures up to about 50°C or higher can be employed if desired.

The 5H-benzdiaz[1,4]epine 4-oxides of formula VI are known compounds or analogues of known compounds and can be obtained in accordance with known methods.

The compounds of formulae I, IV and V are pharmaceutically valuable compounds. They are useful as sedatives, muscle relaxants or anticonvulsants.

The 2-alkylamino compounds of formula II hereinbefore in which R¹ (when present) represents a halogen atom in the 7- or 8-position and R² (when present) represents a halogen atom or a nitro group are claimed *per se* in the specification of our Letters Patent No. 864,824. The 2-alkylamino compounds of

formula II in which R¹ is present and represents a trifluoromethyl group in the 7- or 8-position and R² is absent are claimed *per se* in the specification of our Letters Patent No. 972,969. The 2-alkylamino compounds of formula II in which R¹ is present and represents a nitro group in the 7-position and R² (when present) represents a halogen atom are claimed *per se* in the specification of our Letters Patent No. 986,903.

The compounds of formula I, IV and V hereinbefore in which R¹ (when present) represents a halogen atom or a trifluoromethyl or nitro group and R² (when present) represents a halogen atom or a trifluoromethyl group are claimed *per se* in the specification of our Letters Patent No. 932,495.

The following Example, which includes the preparation of the starting material, illustrates the invention:

EXAMPLE

A) The preparation of the starting material:

A mixture of 13.5 g (50 mmol) of 7-chloro - 5 - phenyl - 5H - benz[diaz][1,4]epine 4-oxide and 100 ml of methanol was cooled in an ice-bath. 2.5 g (51 mmol) of sodium cyanide were added to the cooled mixture. After the mixture had been stirred for 10 minutes, 3 ml of acetic acid were added. After the mixture had been stirred for a further 30 minutes, the solid was collected and washed with methanol to give 7 - chloro - 5 - phenyl - 1H - benz[diaz][1,4]epine - 3 - carbonitrile of melting point 205°—208°C. Recrystallization from methanol gave dark red prisms of melting point 211°—213°C.

B) The process:

3 ml of 3-N sodium hydroxide were added to a mixture of 2.8 g (10 mmol) of 7 - chloro - 5 - phenyl - 1H - benz[diaz][1,4]epine - 3 - carbonitrile in 50 ml of methanol maintained under reflux. After 25 minutes, a further 6 ml of 3-N sodium hydroxide were added and heating was continued for 35 minutes. The reaction mixture was kept in the refrigerator overnight and the product having a melting point of 238°—247°C (decomposition) was collected. Recrystallization from aqueous methanol and from acetone gave 2 - amino - 7 - chloro - 5 - phenyl - 3H - benz[diaz][1,4]epine of melting point 236°—240°C which was undepressed on addition of authentic material.

10 ml of acetic anhydride were added to suspension of 1.7 g (6.3 mmol) of 2 - amino - 7 - chloro - 5 - phenyl - 3H - benz[diaz][1,4]epine in 10 ml of pyridine. This mixture was stirred for a short time in order to bring about solution and was then allowed to stand for 18 hours at room temperature and then concentrated *in vacuo*. The crystalline residue

was collected and washed with ether to give 2 - acetamido - 7 - chloro - 5 - phenyl - 3H - benz[diaz][1,4]epine of melting point 193°—197°C (decomposition). Recrystallization from ethyl acetate gave colourless needles of melting point 200°—204°C (decomposition).

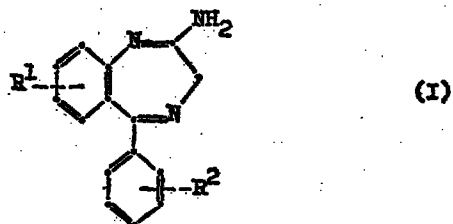
A solution of 1.5 g (4.8 mmol) of 2 - acetamido - 7 - chloro - 5 - phenyl - 3H - benz[diaz][1,4]epine in 50 ml of N,N - dimethyl - formamide (which had been dried by distillation therefrom of 20 ml of benzene) was treated with 365 mg (ca 7.6 mmol) of a 50 per cent dispersion of sodium hydride in oil. This mixture was stirred for 10 minutes at room temperature and 0.5 ml (ca 8 mmol) of methyl iodide were added. After this mixture had been stirred for 3 hours, it was diluted with 200 ml of ice-water and extracted with three 100 ml portions of methylene chloride. The methylene chloride extracts were combined, washed with two 100 ml portions of water and dried over sodium sulphate. The residue remaining after removal of the methylene chloride *in vacuo* was diluted with 250 ml of water and extracted with 250 ml of cyclohexane. The residue (2.1 g) remaining after removal of the cyclohexane *in vacuo* was crystallized from hexane/ether to give 7 - chloro - 2 - (N - methyl - acetamido) - 5 - phenyl - 3H - benz[diaz][1,4]epine of melting point 140°—150°C. Two recrystallizations in the presence of charcoal raised the melting point to 155°—160°C and it was undepressed on admixture with authentic material of melting point 160°—164°C. The infrared spectrum and the thin-layer chromatographic behaviour were identical with the authentic material.

Peracetic acid was prepared by the dropwise addition of 3.35 g of acetic anhydride to a stirred cold suspension (ice-bath) of 0.75 ml of 90 per cent hydrogen peroxide and one drop of concentrated sulphuric acid in 3 ml of methylene chloride. After stirring for 15 minutes at 0°C, the solution was left at 25°C for 30 minutes. The solution was then added dropwise with stirring to an ice-cold solution of 3.0 g (0.0092 mmol) of 7 - chloro - 2 - (N - methyl - acetamido) - 5 - phenyl - 3H - benz[diaz][1,4]epine in methylene chloride. The so-formed mixture was kept at 25°C overnight, washed with water and dilute aqueous ammonia and then concentrated after drying over sodium sulphate. Crude 7 - chloro - 2 - (N - methyl - acetamido) - 5 - phenyl - 3H - benz[diaz][1,4]epine 4 - oxide was obtained. The so-formed crude product was placed on a column containing 90 g of aluminium oxide (basic, grade 1). Elution with ethyl acetate gave white prisms melting at 233°—237°C. After recrystallization from a mixture of methylene chloride and ether, 7 - chloro - 2 - methylamino - 5 - phenyl - 3H - benz[diaz][1,4]epine 4 - oxide was obtained as crystals melting at 235°—237°C.

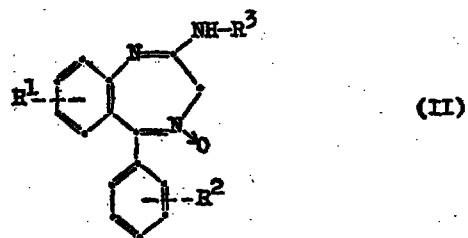


WHAT WE CLAIM IS:—

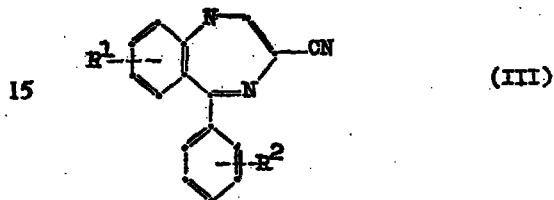
1) A process for the manufacture of 2-amino compounds of the general formula



5 and 2-alkylamino compounds of the general formula



10 wherein R¹ and R² each represent a halogen atom or a trifluoromethyl, nitro or cyano group and R³ represents a lower-alkyl group and wherein the broken lines denote that the atoms or groups attached thereby are optional, which process comprises reacting a carbonitrile of the general formula



15 wherein R¹, R² and the broken lines have the significance given earlier in this claim,

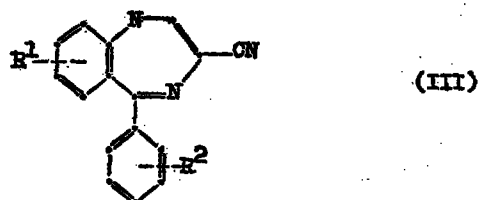
with alkali and, if desired, transforming the resulting 2-amino compound of the formula first written in this claim into a corresponding 2-alkylamino compound of the formula second written in this claim.

2) A process as set forth in claim 1, wherein 7-chloro-5-phenyl-1H-benzdiaz[1,4]epine-3-carbonitrile is reacted with alkali and, if desired, the resulting 2-amino-7-chloro-5-phenyl-3H-benzdiaz[1,4]epine is transformed into 7-chloro-2-methylamino-5-phenyl-3H-benzdiaz[1,4]epine 4-oxide.

3) A process for the manufacture of the 2-amino and 2-alkylamino compounds formulated in claim 1, substantially as described with reference to part B of the foregoing Example.

4) 2-Amino and 2-alkylamino compounds as formulated in claim 1, when manufactured by the process claimed in claim 1, claim 2 or claim 3.

5) A carbonitrile of the general formula



wherein R¹, R² and the broken lines have the significance given in claim 1.

6) 7-Chloro-5-phenyl-1H-benzdiaz[1,4]epine-3-carbonitrile.

W. D. Whitaker,
Patent Agent

for F. HOFFMANN-LA ROCHE & CO.,
Aktiengesellschaft.