

PATENT SPECIFICATION

NO DRAWINGS

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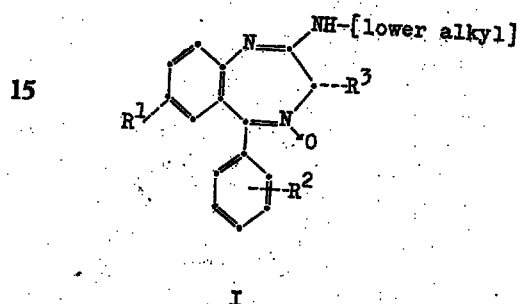
COMPLETE SPECIFICATION

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:



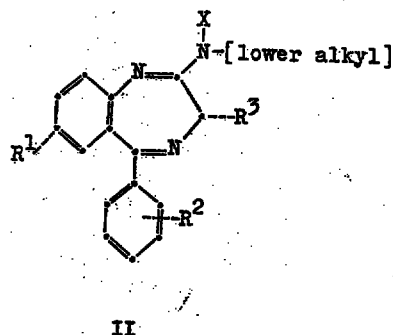
wherein R¹ and R² each represent a halogen atom or a trifluoromethyl, cyano or nitro group and R³ represents a lower-alkyl group and wherein the broken lines denote that the substituents attached thereby are optional.

Those compounds of formula I hereinbefore in which R² (when present) represents a halogen atom or a nitro group and R¹ (when present) represents a halogen atom are claimed *per se* in the specification of our Letters Patent No. 864,824. Those compounds of formula I hereinbefore in which R² is absent and R¹ is present and represents a trifluoromethyl group are claimed *per se* in the specification of our Letters Patent No. 972,969. Those compounds of formula I hereinbefore

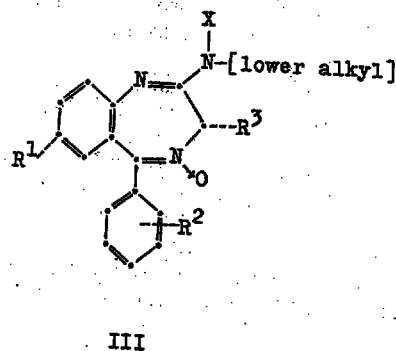
[Price 4s. 6d.]

in which R³ is absent, R² (when present) represents a halogen atom and R¹ is present and represents a nitro group are claimed *per se* in the specification of our Letters Patent No. 986,903.

According to the invention, the compounds of formula I hereinbefore are manufactured by treating a compound of the formula



(wherein R¹, R², R³ and the broken lines have the significance given earlier and X represents a carboxylic acyl group or the tosyl, mesyl or benzenesulphonyl group) with an oxidising agent to yield an N-oxide of the formula



(wherein R¹, R², R³, X and the broken lines have the significance given earlier) and hydrolysing this N-oxide.

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

The compounds of formula III hereinbefore in which R² (when present) represents a halogen atom or the trifluoromethyl group and R¹ (when present) represents a halogen atom or the trifluoromethyl or nitro group are claimed *per se* in the specification of our Letters Patent No. 932,496.

The oxidation of compounds of formula II to the N-oxides of formula III can be effected with any suitable oxidising agent (for example, hydrogen peroxide or peracids). Examples of suitable peracids are peracetic acid, trifluoroperacetic acid, perphthalic acid and persulphuric acid.

The oxidation can be accomplished in a variety of ways. In one embodiment, the compound of formula II is added to an acidic medium and hydrogen peroxide is then added thereto. In another embodiment, a peracid is prepared *in situ* and the compound of formula II to be oxidised is then added to the mixture. The peracid is prepared by mixing hydrogen peroxide with a straight-chain alkanolic acid containing up to four carbon atoms (preferably up to three carbon atoms) or a functional derivative thereof (for example, acetic anhydride). The temperature at which the oxidation is carried out is not critical. Thus, it can be effected at room temperature or at a temperature above or below room temperature.

The protecting group represented by X in formulae II and III is a carboxylic acyl group (for example, an alkanoyl group containing up to seven carbon atoms such as acetyl or propionyl or a benzoyl or substituted-benzoyl group) or a tosyl, mesyl or benzenesulphonyl group. In a preferred aspect, X represents a carboxylic acyl group, preferably an alkanoyl group containing up to seven carbon atoms and most preferably the acetyl group.

The hydrolysis of N-oxides of formula III can be achieved using any suitable hydrolysing agent. For example, N-oxides of formula III can be treated with an alkaline agent such as, for example, sodium hydroxide or basic alumina (that is to say, alumina which contains some water such as WOELM grade I alumina). The manner in which the hydrolysis is effected is not critical and, accordingly,

it may be carried out in any suitable solvent, at room temperature or at a temperature above or below room temperature.

The process described hereinbefore is particularly useful since it provides a valuable synthetic route for the manufacture of useful benzdiaz[1,4]epines of formula I. One particularly useful benzdiaz[1,4]epine of formula I is 7-chloro-2-methylamino-5-phenyl-3H-benzdiaz[1,4]epine 4-oxide, which is otherwise known as chlordiazepoxide. Accordingly, a particularly useful embodiment of the process is that leading to this compound which comprises treating 7-chloro-2-(N-methylacetamido)-5-phenyl-3H-benzdiaz[1,4]epine with an oxidising agent and hydrolysing the resulting 7-chloro-2-(N-methylacetamido)-5-phenyl-3H-benzdiaz[1,4]epine 4-oxide.

The following Example illustrates the invention:

EXAMPLE

3.35 g of acetic anhydride were added dropwise to a stirred cold suspension (ice-bath) of 0.75 ml of 90% hydrogen peroxide and one drop of concentrated sulphuric acid in 3 ml of methylene chloride. After stirring for 0.25 hour at 9° C, the solution was left at 25° C for 0.5 hour. The solution of peracetic acid thus obtained was added dropwise with stirring to an ice-cold solution of 3.0 g (0.0092 mol) of 7-chloro-2-(N-methylacetamido)-5-phenyl-3H-benzdiaz[1,4]epine in methylene chloride. The mixture was kept overnight at 25° C, washed with water and dilute aqueous ammonia, dried over sodium sulphate and concentrated. The crude 7-chloro-2-(N-methylacetamido)-5-phenyl-3H-benzdiaz[1,4]epine 4-oxide obtained was adsorbed on a column containing 90 g of aluminium oxide [basic, WOELM grade I (which contains some water)]. After elution with ethyl acetate and evaporation of the ethyl acetate, white prisms melting at 233°—237° C. were obtained. Recrystallisation from a mixture of methylene chloride and ether gave 7-chloro-2-methylamino-5-phenyl-3H-benzdiaz[1,4]epine 4-oxide as crystals melting at 235°—237° C.

The term 'halogen' is used in the foregoing description and in the claims appended hereto to mean fluorine, bromine, iodine and chlorine. Similarly, the term 'lower alkyl' is used to mean a straight-chain or branched-chain alkyl group containing up to seven carbon atoms (e.g. methyl, propyl and isobutyl).

WHAT WE CLAIM IS:—

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



(wherein R^1 , R^2 , R^3 , X and the broken lines have the significance given earlier) and hydrolysing this N-oxide.

5 The compounds of formula II hereinbefore in which R^2 (when present) represents a halogen atom or the trifluoromethyl group and R^1 (when present) represents a halogen atom or the trifluoromethyl or nitro group are claimed *per se* in the specification of our
10 Letter Patent No. 932,495.

The compounds of formula III hereinbefore in which R^2 (when present) represents a halogen atom or the trifluoromethyl group and R^1 (when present) represents a halogen atom or the trifluoromethyl or nitro group are claimed *per se* in the specification of our
15 Letters Patent No. 932,496.

The oxidation of compounds of formula II to the N-oxides of formula III can be effected with any suitable oxidising agent (for example, hydrogen peroxide or peracids). Examples of suitable peracids are peracetic acid, trifluoroperacetic acid, perphthalic acid and persulphuric acid.

25 The oxidation can be accomplished in a variety of ways. In one embodiment, the compound of formula II is added to an acidic medium and hydrogen peroxide is then added thereto. In another embodiment, a peracid is prepared *in situ* and the compound of formula II to be oxidised is then added to the mixture. The peracid is prepared by mixing
30 hydrogen peroxide with a straight-chain alkanolic acid containing up to four carbon atoms (preferably up to three carbon atoms) or a functional derivative thereof (for example, acetic anhydride). The temperature at which the oxidation is carried out is not critical. Thus, it can be effected at room temperature
40 or at a temperature above or below room temperature.

The protecting group represented by X in formulae II and III is a carboxylic acyl group (for example, an alkanoyl group containing up to seven carbon atoms such as acetyl or propionyl or a benzoyl or substituted-benzoyl group) or a tosyl, mesyl or benzenesulphonyl group. In a preferred aspect, X represents a carboxylic acyl group,
45 preferably an alkanoyl group containing up to seven carbon atoms and most preferably the acetyl group.

The hydrolysis of N-oxides of formula III can be achieved using any suitable hydrolysing agent. For example, N-oxides of formula III can be treated with an alkaline agent such as, for example, sodium hydroxide or basic alumina (that is to say, alumina which contains some water such as WOELM grade
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it may be carried out in any suitable solvent, at room temperature or at a temperature above or below room temperature.

The process described hereinbefore is particularly useful since it provides a valuable synthetic route for the manufacture of useful benzodiaz[1,4]epines of formula I. One particularly useful benzodiaz[1,4]epine of formula I is 7-chloro-2-methylamino-5-phenyl-3H-benzodiaz[1,4]epine 4-oxide, which is otherwise known as chlordiazepoxide. Accordingly, a particularly useful embodiment of the process is that leading to this compound which comprises treating 7-chloro-2-(N-methylacetamido)-5-phenyl-3H-benzodiaz[1,4]epine with an oxidising agent and hydrolysing the resulting 7-chloro-2-(N-methylacetamido)-5-phenyl-3H-benzodiaz[1,4]epine 4-oxide.

The following Example illustrates the invention:

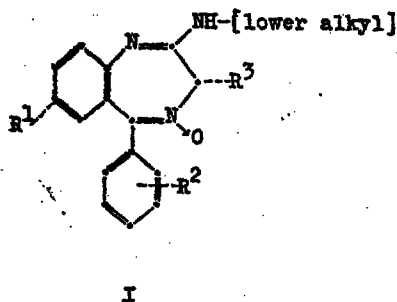
EXAMPLE.

3.35 g of acetic anhydride were added dropwise to a stirred cold suspension (ice-bath) of 0.75 ml of 90% hydrogen peroxide and one drop of concentrated sulphuric acid in 3 ml of methylene chloride. After stirring for 0.25 hour at 9° C, the solution was left at 25° C for 0.5 hour. The solution of peracetic acid thus obtained was added dropwise with stirring to an ice-cold solution of 3.0 g (0.0092 mol) of 7-chloro-2-(N-methylacetamido)-5-phenyl-3H-benzodiaz[1,4]epine in methylene chloride. The mixture was kept overnight at 25° C, washed with water and dilute aqueous ammonia, dried over sodium sulphate and concentrated. The crude 7-chloro-2-(N-methylacetamido)-5-phenyl-3H-benzodiaz[1,4]epine 4-oxide obtained was adsorbed on a column containing 90 g of aluminium oxide [basic, WOELM grade I (which contains some water)]. After elution with ethyl acetate and evaporation of the ethyl acetate, white prisms melting at 233°—237° C. were obtained. Recrystallisation from a mixture of methylene chloride and ether gave 7-chloro-2-methylamino-5-phenyl-3H-benzodiaz[1,4]epine 4-oxide as crystals melting at 235°—237° C.

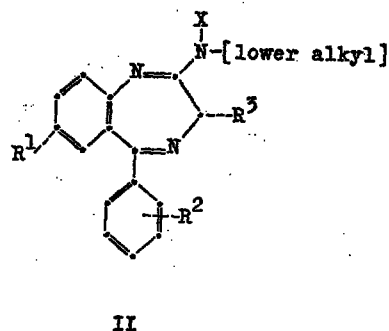
The term 'halogen' is used in the foregoing description and in the claims appended hereto to mean fluorine, bromine, iodine and chlorine. Similarly, the term 'lower alkyl' is used to mean a straight-chain or branched-chain alkyl group containing up to seven carbon atoms (e.g. methyl, propyl and isobutyl).

WHAT WE CLAIM IS:—

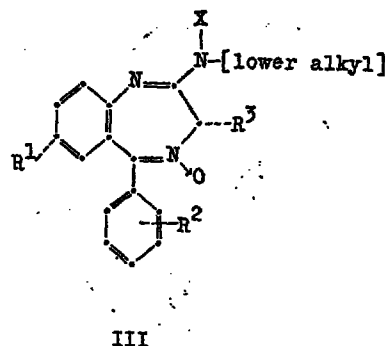
1) A process for the manufacture of compounds of the formula



(wherein R^1 and R^2 each represent a halogen atom or a trifluoromethyl, cyano or nitro group and R^3 represents a lower-alkyl group and wherein the broken lines denote that the substituents attached thereby are optional), which process comprises treating a compound of the formula



- 10 (wherein R^1 , R^2 , R^3 and the broken lines have the significance given earlier in this claim and X represents a carboxylic acyl group or the tosyl, mesyl or benzenesulphonyl group) with an oxidising agent to yield an N-oxide
- 15 of the formula



(wherein R^1 , R^2 , R^3 , X and the broken lines have the significance given earlier in this claim) and hydrolysing this N-oxide.

2) A process as set forth in claim 1, wherein X represents an a carboxylic acyl group. 20

3) A process as set forth in claim 1 or claim 2, wherein 7-chloro-2-(N-methyl-acetamido)-5-phenyl-3H-benzdiaz[1,4]epine is treated with an oxidising agent and the resulting 7-chloro-2-(N-methyl-acetamido)-5-phenyl-3H-benzdiaz[1,4]epine 4-oxide is hydrolysed to give 7-chloro-2-methylamino-5-phenyl-3H-benzdiaz[1,4]epine 4-oxide. 25

4) A process as set forth in claim 1, substantially as described with reference to the Example. 30

5) Compounds of the first formula written in claim 1, when manufactured by the process claimed in any one of claims 1 to 4 inclusive. 35

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Patent Agent

for F. Hoffmann-La Roche & Co., A.-G.

