

L124829



PATENT SPECIFICATION

NO DRAWINGS

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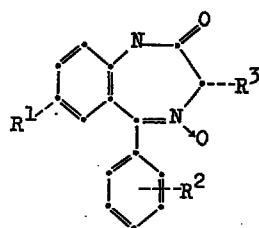
COMPLETE SPECIFICATION

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 are compounds of the general formula



I

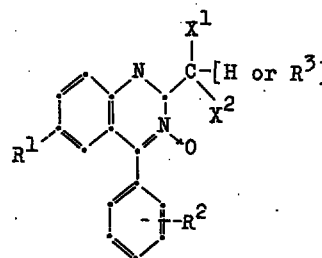
wherein R¹ represents a halogen atom or the trifluoromethyl, nitro or cyano group or an alkyl, alkoxy or alkylthio group containing from one to seven carbon atoms, R² represents a halogen atom and R³ represents an alkyl group containing from one to six carbon atoms and wherein the broken lines denote that the substituents attached thereby are optional.

Those compounds of formula I in which R¹ (when present) represents a halogen atom or the trifluoromethyl or nitro group or an alkyl, alkoxy or alkylthio group containing up to seven carbon atoms are claimed *per se* in

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the specification of our Letters Patent No. 972,968.

According to the process provided by the invention, the compounds of formula I hereinbefore are manufactured by reacting a quinazoline derivative of the general formula



II

wherein R¹, R², R³ and the broken lines have the significance given earlier and X¹ and X² each represent a halogen atom, with an aqueous alkali-metal hydroxide in the presence or absence of a solvent and, where the reaction product is not the desired benzdiaz[1,4] epine compound, acidifying same and heating the resulting product.

The quinazoline derivatives of formula II hereinbefore in which R¹ (when present) represents a halogen atom or the trifluoromethyl or nitro group or an alkyl group as hereinbefore defined and R² is absent are claimed *per se* in the specification of our copending application for Letters Patent No. 14884/65 (now serial no. 1,082,163) and may be obtained according to the process described and claimed therein.

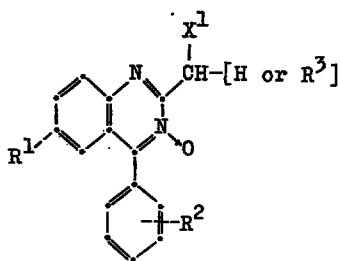
The reaction of a quinazoline derivative of formula II with an alkali-metal hydroxide

SEE ERRATA SLIP ATTACHED

is preferably carried out using an aqueous solution of sodium or potassium hydroxide. The reaction is preferably carried out in an inert organic solvent such as an alcohol (for example, ethanol or methanol). The reaction can be carried out at room temperature or at a temperature above or below room temperature, but it is preferably carried out at an elevated temperature. A suitable temperature is between about room temperature and the boiling point of the reaction mixture.

An interesting aspect of the foregoing process comprises reacting 6 - chloro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide or 6 - nitro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide with aqueous sodium hydroxide in the presence or absence of a solvent.

According to a variant process provided by the invention, the compounds of formula I hereinbefore are manufactured by treating a quinazoline derivative of formula II hereinbefore in an inert organic solvent with 1 mol of a non-nucleophilic strong base to give a compound of the formula



III

wherein R^1 , R^2 , R^3 , X^1 and the broken lines have the significance given earlier, and reacting this compound with an aqueous alkali-metal hydroxide in the presence or absence of a solvent.

The compounds of formula III hereinbefore in which R^1 (when present) represents a halogen atom or an alkyl group containing up to seven carbon atoms are claimed *per se* in the specification of our Letters Patent No. 864,825. The compounds of formula III hereinbefore in which R^2 is absent and R^1 is present and represents the trifluoromethyl group are claimed *per se* in the specification of our Letters Patent No. 972,970.

The treatment of a quinazoline derivative of formula II hereinbefore to give a compound of formula III is carried out in an inert organic solvent using 1 mol of a non-nucleophilic strong base. It will be appreciated that the term "non-nucleophilic" as used in this specification in relation to strong bases includes strong bases which are so weakly nucleophilic as to be substantially non-nucleophilic. Examples of suitable non-nucleophilic strong bases are alkali-metal tertiary alkoxides (pre-

ferably alkoxides containing up to seven carbon atoms such as sodium or potassium *tert*-butoxide or sodium or potassium *tert*-amylate) alkali-metal hydrides (e.g. sodium hydride), alkali-metal triphenyl methides (e.g. sodium triphenyl methide) or alkali-metal di(hydrocarbyl) amides such as dialkyl amides (e.g. sodium diethyl amide). Examples of suitable inert organic solvents which can be used are ethers, dioxan, tetrahydro-furan or a hydrocarbon such as benzene or toluene.

The treatment can be carried out at room temperature or at a temperature above or below room temperature. It is preferred, however, to carry out the treatment at a temperature between ca -30° and $+30^\circ\text{C}$.

Compounds of formula II are base-labile and can be converted into compounds of formula I using a large molar excess of an aqueous alkali-metal hydroxide. The reaction of a compound of formula III with an aqueous alkali-metal hydroxide can be carried out according to known methods. One interesting aspect of this variant process comprises treating 6 - chloro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide in an inert organic solvent with 1 mol of potassium *tert*-butoxide and reacting the resulting 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3 - oxide with aqueous sodium hydroxide in the presence or absence of a solvent.

The step of the variant process aforesaid involving the reaction of a compound of formula III in which R^1 (when present) represents a halogen atom or the trifluoromethyl or nitro group or an alkyl, alkoxy or alkylthio group containing up to seven carbon atoms with an alkali-metal hydroxide is claimed in the specification of our Letters Patent No. 972,962.

It has been found in accordance with the present invention that the process and variant process described hereinbefore make it possible to readily manufacture the compounds of formula I hereinbefore from low-cost, readily available starting materials using easily prepared, non-corrosive and non-irritating reactants.

The following Examples illustrate the process and variant process provided by the invention:

EXAMPLE 1

A) The process:

A suspension of 10 g (29.2 mmol) of 6-chloro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide [prepared as described in the specification of our co-pending application for Letters Patent No. 14884/65 (now Serial No. 1,082,163)] in 300 ml of refluxing ethanol was treated with 60 ml of 1-N aqueous sodium hydroxide. The mixture obtained was heated under reflux for 35 minutes, cooled on ice and concentrated

in *vacuo*. The residue was partitioned between 200 ml of methylene chloride and 200 ml of water. After the mixture had been acidified with acetic acid, the phases were separated and the aqueous phase was washed with 50 ml of methylene chloride. The methylene chloride washings were combined with the methylene chloride phase, washed with 200 ml of water and dried over sodium sulphate. Evaporation of the solvent *in vacuo* gave 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) 4 - oxide of melting point 225°—230°C (with decomposition).

15 B) The variant process:

4.48 g (40 mmol) of potassium *tert*-butoxide were added to a solution of 13.6 g (40 mmol) of 6 - chloro - 2 - dichloro - methyl - 4 - phenyl - 1,2 dihydro - quinazoline 3 - oxide in 500 ml of dry tetrahydro-furan cooled in a bath of (dry ice)/acetone. The mixture was removed from the cooling bath, allowed to stand overnight at room temperature and then filtered through kieselguhr. The filtrate was concentrated *in vacuo* to give a yellow oil which was dissolved in methylene chloride, washed three times with water and then with brine, dried over sodium sulphate and filtered through alumina. The filtrate was concentrated *in vacuo* and the residue was crystallized from ether and then from cyclohexane to give 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3 - oxide of melting point 109°—112°C.

The resulting 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3 - oxide was reacted in a known manner with aqueous sodium hydroxide to yield 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) 4 - oxide.

EXAMPLE 2.

The Process:

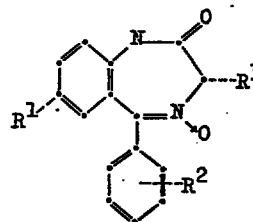
A mixture of 40 g (0.114 mol) of 6 - nitro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide [prepared as described in the specification of our co-pending application for Letters Patent No. 14884/65 (now serial no: 1,082,163)], 112 ml of 3-N aqueous sodium hydroxide and 1.2 litres of ethanol was stirred overnight at room temperature. The mixture was then diluted with 1.2 litres of water and acidified with 38 ml of 3-N hydrochloric acid. The precipitate was collected, dried and heated under reflux with 250 ml of ethanol for 4 hours. The mixture was cooled and 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) 4 - oxide of melting point 208°—218°C (with decomposition) was collected.

It will be appreciated that the alkyl, alkoxy and alkylthio groups referred to in the fore-

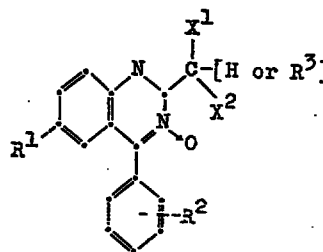
going description and in the claims appended hereto include both straight-chain and branched-chain groups (e.g. methyl, ethyl and isopropyl). Similarly, it will be appreciated the term 'halogen' means fluorine, chlorine, bromine and iodine and that where more than one halogen atom is present in any particular compound they can be the same of different halogen atoms. Chlorine or bromine are the preferred halogen values of X¹, X² and R¹ and fluorine or chlorine are the preferred halogen values for R².

WHAT WE CLAIM IS:—

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



wherein R¹ represents a halogen atom or the trifluoromethyl, nitro or cyano group or an alkyl, alkoxy or alkylthio group containing from one to seven carbon atoms, R² represents a halogen atom and R³ represents an alkyl group containing from one to six carbon atoms and wherein the broken lines denote that the substituents attached thereby are optional, which process comprises reacting a quinazoline derivative of the general formula



wherein R¹, R², R³ and the broken lines have the significance given earlier in this claim and X¹ and X² each represent a halogen atom, with an aqueous alkali-metal hydroxide in the presence or absence of a solvent and, where the reaction product is not the desired benzdiaz[1,4]epine compound, acidifying same and heating the resulting product.

2) A process as set forth in claim 1, wherein 6 - chloro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide or 6 - nitro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide is reacted with aqueous sodium hydroxide in the presence or absence of a solvent.

3) A variant process for the manufacture



in *vacuo*. The residue was partitioned between 200 ml of methylene chloride and 200 ml of water. After the mixture had been acidified with acetic acid, the phases were separated and the aqueous phase was washed with 50 ml of methylene chloride. The methylene chloride washings were combined with the methylene chloride phase, washed with 200 ml of water and dried over sodium sulphate. Evaporation of the solvent *in vacuo* gave 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) 4 - oxide of melting point 225°—230°C (with decomposition).

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4.48 g (40 mmol) of potassium *tert*-butoxide were added to a solution of 13.6 g (40 mmol) of 6 - chloro - 2 - dichloro - methyl - 4 - phenyl - 1,2 dihydro - quinazoline 3 - oxide in 500 ml of dry tetrahydro-furan cooled in a bath of (dry ice)/acetone. The mixture was removed from the cooling bath, allowed to stand overnight at room temperature and then filtered through kieselguhr. The filtrate was concentrated *in vacuo* to give a yellow oil which was dissolved in methylene chloride, washed three times with water and then with brine, dried over sodium sulphate and filtered through alumina. The filtrate was concentrated *in vacuo* and the residue was crystallized from ether and then from cyclohexane to give 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3 - oxide of melting point 109°—112°C.

35 The resulting 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3 - oxide was reacted in a known manner with aqueous sodium hydroxide to yield 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) 4 - oxide.

EXAMPLE 2.

The Process:

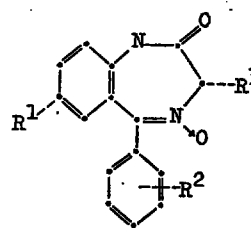
45 A mixture of 40 g (0.114 mol) of 6 - nitro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide [prepared as described in the specification of our co-pending application for Letters Patent No. 14884/65 (now serial no: 1,082,163)], 112 ml of 3-N aqueous sodium hydroxide and 1.2 litres of ethanol was stirred overnight at room temperature. The mixture was then diluted with 1.2 litres of water and acidified with 38 ml of 3-N hydrochloric acid. The precipitate was collected, dried and heated under reflux with 250 ml of ethanol for 4 hours. The mixture was cooled and 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) 4 - oxide of melting point 208°—218°C (with decomposition) was collected.

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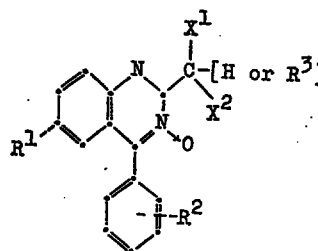
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WHAT WE CLAIM IS:—

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



wherein R¹ represents a halogen atom or the trifluoromethyl, nitro or cyano group or an alkyl, alkoxy or alkylthio group containing from one to seven carbon atoms, R² represents a halogen atom and R³ represents an alkyl group containing from one to six carbon atoms and wherein the broken lines denote that the substituents attached thereby are optional, which process comprises reacting a quinazoline derivative of the general formula

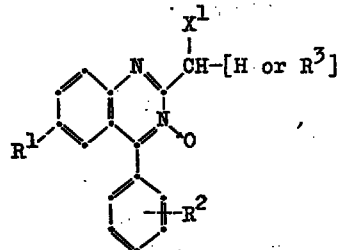


wherein R¹, R², R³ and the broken lines have the significance given earlier in this claim and X¹ and X² each represent a halogen atom, with an aqueous alkali-metal hydroxide in the presence or absence of a solvent and, where the reaction product is not the desired benzdiaz[1,4]epine compound, acidifying same and heating the resulting product.

2) A process as set forth in claim 1, wherein 6 - chloro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide or 6 - nitro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide is reacted with aqueous sodium hydroxide in the presence or absence of a solvent.

3) A variant process for the manufacture

- of the compounds of the first formula given in claim 1, which comprises treating a quinazoline derivative of the second formula given in that claim in an inert organic solvent with 1 mol of a non-nucleophilic strong base to give a compound of the formula



- wherein R¹, R², R³, X¹ and the broken lines have the significance given in claim 1, and reacting this compound with an aqueous alkali-metal hydroxide in the presence or absence of a solvent.

4) A process as set forth in claim 3, wherein 6-chloro-2-dichloromethyl-4-phenyl-1,2-dihydro-quinazoline 3-oxide is treated in an inert organic solvent with 1 mol of potassium *tert*-butoxide and the resulting 6-chloro-2-chloromethyl-4-phenyl-quinazoline 3-oxide is reacted with aqueous sodium hydroxide in the presence or absence of a solvent.

5) A process as set forth in claim 1 or in claim 3, substantially as described with reference to the Examples.

6) Compounds of the first formula given in claim 1, when manufactured by a process as claimed in any one of the preceding claims.

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