

1082,164



PATENT SPECIFICATION

NO DRAWINGS

1082,164

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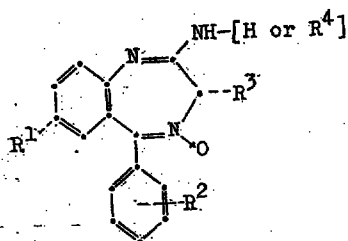
COMPLETE SPECIFICATION

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 derivaives obtained by carrying out the process of the present invention are compounds of the general formula



I

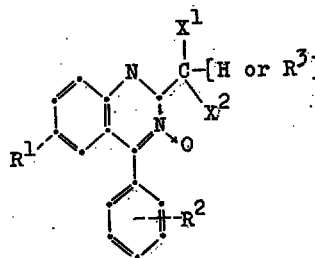
wherein R¹ represents a halogen atom or the trifluoromethyl, nitro or cyano group or an alkyl, alkoxy or alkylthio group containing from one to seven carbon atoms, R² represents a halogen atom, R³ represents an alkyl group containing from one to six carbon atoms and R⁴ represents an alkyl group containing from one to seven carbon atoms or an alkenyl group containing from two to seven carbon atoms and wherein the broken lines denote that the substituents attached thereby are optional.

One interesting class of derivative obtained by carrying out the present process comprises

[Price 4s. 6d.]

those compounds of formula I hereinbefore in which R¹ (when present) represents a halogen atom or the nitro, trifluoromethyl or cyano group or an alkyl thio group containing from one to seven carbon atoms, R³ is absent and R⁴ (when present) represents an alkyl group containing from one to seven carbon atoms. An especially interesting compound within the foregoing class is 7-chloro - 2 - methylamino - 5 - phenyl - 3H - benzdiaz[1,4]epine 4 - oxide.

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



II

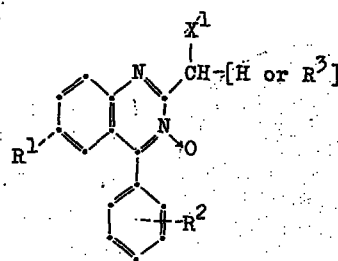
(wherein R¹, R², R³ and the broken lines have the significance given earlier and X¹ and X² each represent a halogen atom) with ammonia, an alkyl amine containing from one to seven carbon atoms or an alkenyl amine containing from two to seven carbon atoms.

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 R³ is absent are claimed *per se* in the specification of our copending

application for Letters Patent No. 14884/65 (now serial no: 1082163) and may be obtained according to the process described and claimed therein.

5 The reaction of a quinazoline derivative of formula II hereinbefore with ammonia, an alkyl amine containing from one to seven carbon atoms or an alkenyl amine containing from two to seven carbon atoms can be carried out by using one of the reactants (i.e. liquid ammonia or a liquid amine) as a solvent. In this case, the reaction is carried out by simply mixing the reactants. The reaction begins immediately upon mixing the reactants and is normally completed in about 3 to 4 hours. Alternatively, the reaction can be carried out in an inert organic solvent such as an alcohol containing up to seven carbon atoms (e.g. methanol, ethanol or propanol), ethers, dioxan, tetrahydrofuran or a hydrocarbon (e.g. benzene or toluene). When a solvent is used, the reaction can be carried out by first forming a suspension of the quinazoline derivative in the solvent and treating the suspension with gaseous ammonia or amine. The suspension of the quinazoline derivative is formed by simply stirring a mixture of the quinazoline derivative and the solvent. Alternatively, ammonia or an appropriate amine can be dissolved in a suitable solvent and the quinazoline derivative added to said solution. The reactants can be used in any molar ratio, but it has been found preferable to use at least about 3 mol of ammonia or the amine per mol of the quinazoline derivative. The reaction of the quinazoline derivative with ammonia or the amine can be carried out at the boiling temperature of ammonia or the amine, at room temperature or at a temperature above or below room temperature. A preferred temperature range is between *ca* -70°C and 80°C. One interesting aspect of the process comprises reacting a quinazoline derivative of formula II in which R¹ (when present) represents a halogen atom or the trifluoromethyl, nitro or cyano group or an alkylthio group containing from one to seven carbon atoms and R² is absent with ammonia or an alkyl amine containing from one to seven carbon atoms. An especially interesting aspect of the process comprises reacting 6 - chloro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide with methyl amine.

55 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 R¹, R², R³, X¹ and the broken lines have the significance given earlier, and reacting this compound with ammonia, an alkyl amine containing from one to seven carbon atoms or an alkenyl amine containing from two to seven carbon atoms.

The compounds of formula III hereinbefore in which R¹ (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 R² is absent and R¹ 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 alcoholates (preferably alkyl alcoholates 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°C. The reaction of a compound of formula III with ammonia or an alkyl or alkenyl amine as hereinbefore defined to give a compound of

formula I can be carried out according to known methods.

- One interesting aspect of the variant process aforesaid 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 methyl amine.

- 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.

- Those compounds of formula I in which R¹ (when present) represents a halogen atom or an alkyl group containing up to seven carbon atoms and the second step of the aforesaid variant process leading thereto are claimed in the specification of our Letters Patent No. 864824. Those compounds of formula I in which R² is absent, R³ is present and represents a trifluoromethyl group and R⁴ (when present) represents an alkyl group containing from one to seven carbon atoms and the second step of the aforesaid variant process leading thereto are claimed in the specification of our Letters Patent No. 972,969. Those compounds of formula I in which R¹ is present and represents the nitro group, R³ is absent and R⁴ (when present) represents an alkyl group containing not more than three carbon atoms and the second step of the aforesaid variant process leading thereto are claimed in the specification of our Letters Patent No. 986,903.

The following Example illustrates the process and variant process provided by the invention:

EXAMPLE

- A) The process:
i) A solution of 3.4 g (10 mmol) of 6-chloro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide [prepared as described in the specification of our copending application for Letters Patent No. 14884/65 (now Serial No. 1082163)] in 100 ml of liquid methyl amine was stirred under a dry ice condenser for 2.5 hours. The methyl amine was then allowed to evaporate slowly overnight and the residue was dissolved in 200 ml of methylene chloride. The solution was washed with a mixture of 50 ml of 10% sodium carbonate solution and 50 ml of ice and dried over sodium sulphate. The solvent was removed *in vacuo* to give a yellow oil from which, on addition of ether, there was obtained 7 - chloro - 2 - methylamino - 5 - phenyl - 3H - benz[diaz[1,4]epine 4 - oxide of

melting point 220°—230°C (sintering at 190°C).

Recrystallization from *ca* 15 ml of ethanol gave pure material of melting point 236°—241°C.

ii) Gaseous methyl amine was bubbled for 5 hours into a suspension of 10 g (29 mmol) of 6 - chloro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide in 250 ml of methanol; the heat of reaction caused the methanol to reflux. The clear solution which formed was allowed to stand at room temperature for 11 hours and then concentrated *in vacuo*. The residue was partitioned between 250 ml of methylene chloride and 250 ml of 10% sodium carbonate solution. The methylene chloride phase was dried over sodium sulphate and concentrated *in vacuo* to give 11.9 g of an orange solid which was treated with ether to give 7 - chloro - 2 - methylamino - 5 - phenyl - 3H - benz[diaz[1,4]epine 4 - oxide. Recrystallization from ethanol gave pure material of melting point 236°—236.5°C.

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 - dichloromethyl - 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 crystallised from ether and then from cyclohexane to give 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3 - oxide of melting point 109°—112°C.

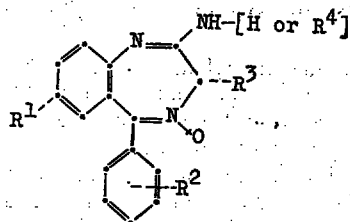
The resulting 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3 - oxide was treated in known manner with methyl amine to yield 7 - chloro - 2 - methylamino - 5 - phenyl - 3H - benz[diaz[1,4]epine 4 - oxide.

It will be appreciated that the alkyl, alkenyl, alkoxy and alkylthio groups referred to in the foregoing description and in the claims appended hereto include both straight-chain and branched-chain groups (e.g. methyl, ethyl, *isopropyl* and *allyl*). 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 or different halogen atoms. Chlorine or bromine are the preferred halogen values of X¹, X² and R¹ and fluorine or chloride are the preferred halogen values for R².

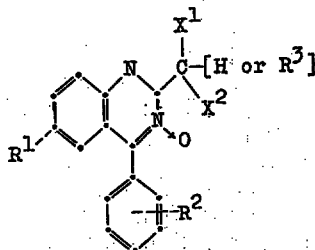


WHAT WE CLAIM IS:—

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



- 5 , 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, R³ represents an alkyl group containing from one to six carbon atoms and R⁴ represents an alkyl group containing from one to seven carbon atoms or an alkenyl group containing from two to seven carbon atoms and wherein the broken lines denote that the substituents attached thereby are optional,
- 10 which process comprises reacting a quinazoline derivative of the general formula

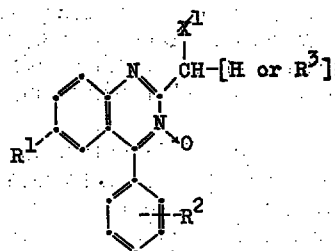


- 20 , wherein R¹, R², R³ and the broken lines have the significance given earlier in this claim and X¹ and X² each represent a halogen atom, with ammonia, an alkyl amine containing from one to seven carbon atoms or an alkenyl amine containing from two to seven carbon atoms.

- 25 2) A process as set forth in claim 1, wherein a quinazoline derivative of the second formula given in that claim in which R¹ (when present) represents a halogen atom or the trifluoromethyl, nitro or cyano group or an alkylthio group containing from one to seven carbon atoms and R² is absent is reacted with
- 30 ammonia or an alkyl amine containing from one to seven carbon atoms.

3) A process as set forth in claim 2, wherein 6 - chloro - 2 - dichloromethyl - 4 - phenyl - 1,2 - dihydro - quinazoline 3 - oxide is reacted with methyl amine.

- 4) 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 ammonia, an alkyl amine containing from one to seven carbon atoms or an alkenyl amine containing from two to seven carbon atoms.

- 5) A process as set forth in claim 4, 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 methyl amine.

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

- 7) 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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