

PATENT SPECIFICATION

(11) 1390277

1390277

- (21) Application No. 31894/72 (22) Filed 8 July 1971
 (62) Divided out of No. 1383647
 (23) Complete Specification filed 7 July 1972
 (44) Complete Specification published 9 April 1975
 (51) INT CL² C07D 243/24 (C07D 243/24 243/30)
 (52) Index at acceptance

C2C 1530 213 215 21X 246 247 250 251 252 25Y 28X
 305 314 31Y 337 351 352 386 40Y 625 670 761 762
 790 TR

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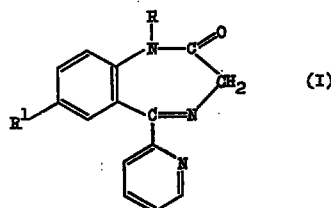


(54) A PROCESS FOR THE MANUFACTURE OF BENZODIAZEPINE DERIVATIVES

(71) We, ROCHE PRODUCTS LIMITED, a British Company of Broadwater Road, Welwyn Garden City, Hertfordshire, 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:—

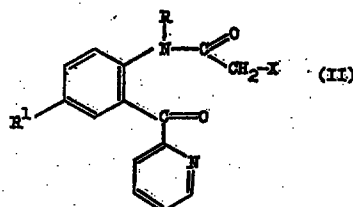
The present invention is concerned with a process for the manufacture of benzodiazepine derivatives.

The benzodiazepine derivatives obtained according to the present invention are benzodiazepine-2-ones of the general formula



wherein R represents a hydrogen atom or a methyl group and R¹ represents a hydrogen, chlorine, bromine or iodine atom.

According to the present invention, the benzodiazepine-2-ones of formula I hereinbefore are manufactured by reacting a (2-haloacetamido-benzoyl)-pyridine of the general formula



wherein R and R¹ have the significance given earlier and X stands for a chlorine, bromine or iodine atom, with hexamethylenetetramine under weak acidic conditions in the

presence of a water-containing hydroxylic solvent.

The reaction of a (2-haloacetamido-benzoyl)-pyridine of formula II with hexamethylenetetramine is carried out under weak acidic conditions. Such conditions can be provided by carrying out the reaction in the presence of an organic acid such as formic acid, acetic acid, pivalic acid, chloroacetic acid or trifluoroacetic acid or, preferably, in the presence of a strong inorganic acid, especially hydrochloric acid. The reaction is also carried out in a water-containing hydroxylic solvent, preferably an aqueous alkanol (especially an aqueous lower alkanol such as aqueous methanol, ethanol, n-propanol, n-butanol and amyl alcohol). A preferred solvent is aqueous methanol or aqueous ethanol. The proportion of water present in the solvent is preferably that which ensures a homogeneous reaction mixture under reflux conditions. The reaction is expediently carried out at an elevated temperature, preferably at the reflux temperature of the reaction mixture. When the reaction is carried out at reflux temperature, the reaction time can vary between about 2 hours and about 20 hours depending on the solvent employed. The reaction is preferably carried out for a period of about 7 to about 16 hours at reflux when aqueous methanol or aqueous ethanol is used as the solvent.

The reaction can also be carried out using part of the hexamethylenetetramine in the form of an acid addition salt thereof, preferably the hydrochloride. Thus, for example, the reaction can be carried out using, per mol of a (2-haloacetamido-benzoyl)-pyridine of formula II, 1 to 1.5 moles of hexamethylene tetramine and from 0.5 to 1.0 mol of hexamethylenetetramine hydrochloride, the reaction mixture having a pH of from about 4.5 to 6.0 under the previously described reaction conditions.

According to a further embodiment of the present process, the hexamethylenetetramine can be formed *in situ* from formaldehyde and ammonia. Thus, for example, a mixture of a (2 - haloacetamido - benzoyl) - pyridine of formula II and a hydroxylic solvent can first be prepared, the calculated amount of formaldehyde and ammonia can be introduced into the mixture and then hydrochloric acid can be added thereto.

The desired benzodiazepin - 2 - ones of formula I hereinbefore described can be obtained from the reaction mixture in crystalline form with a high degree of purity in a simple manner by merely cooling the reaction mixture. Further, they are obtained in a remarkably increased yield compared with the well-known process of treating a (2 - haloacetamido - benzoyl) - pyridine with ammonia.

The (2 - haloacetamido - benzoyl) - pyridine starting materials of formula II hereinbefore can be prepared by reacting an appropriately substituted (2-amino - benzoyl) - pyridine with an appropriate haloacetyl halide such as chloroacetyl chloride or bromoacetyl bromide.

The (2 - iodoacetamido - benzoyl) - pyridine starting materials of formula II can also be prepared by reacting a (2 - chloroacetamido - benzoyl) - pyridine or (2 - bromoacetamido - benzoyl) - pyridine of formula II, preferably a (2 - chloroacetamido - benzoyl) - pyridine, with an equivalent amount of an alkali metal iodide or alkaline earth metal iodide (e.g. sodium iodide, potassium iodide and the like). Alternatively, the reaction between a (2 - chloroacetamido - benzoyl) - pyridine of formula II and hexamethylenetetramine can be carried out in the presence of major amounts of an alkali metal iodide or alkaline earth metal iodide (e.g. sodium iodide, potassium iodide and the like) whereby a (2 - iodoacetamido - benzoyl) - pyridine is prepared *in situ* and then reacts with the hexamethylenetetramine to form a benzodiazepin - 2 - one of formula I.

The preferred (2 - haloacetamido - benzoyl) - pyridines of formula II are those in which X represents a chlorine atom. Examples of (2 - haloacetamido - benzoyl) - pyridines of formula II are 2 - [2 - (2 - chloro - acetamido) - 5 - bromo - benzoyl] - pyridine as well as the corresponding 2 - bromo and 2-iodo compounds.

The benzodiazepin-2-ones of formula I hereinbefore possess valuable therapeutic properties; for example, sedative, muscle relaxant and anticonvulsant properties. A preferred benzodiazepin - 2 - one of formula I is 7 - bromo - 5 - [pyridyl - (2)] - 2,3 - dihydro - 1H - 1,4 - benzodiazepin - 2 - one.

The following Example illustrates the invention:

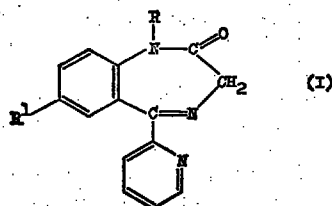
Example

A mixture of 10.0 g of 2 - [2 - (2 - chloro-

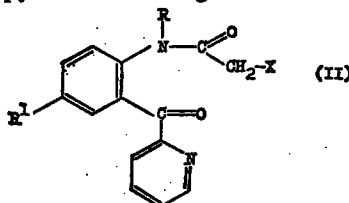
acetamido) - 5 - bromo - benzoyl] - pyridine, 8.1 g of hexamethylenetetramine, 12.75 ml of 2-N aqueous hydrochloric acid, 55 ml of methanol and 5.2 ml of water was heated under reflux for 7 hours. The mixture was then cooled and stirred at 0°C for 1 hour. The resulting crystals were filtered off and washed with 20 ml of aqueous methanol. After drying *in vacuo* at 60°C, 7.15 g (80% of theory) of pure crystalline 7 - bromo - 5 - [pyridyl - (2)] - 2,3 - dihydro - 1H - 1,4 - benzodiazepin - 2 - one of melting point 249°—251°C was obtained. Thin-layer chromatographic analysis of the mother liquors indicated the presence of a further 3—4% of the desired product.

WHAT WE CLAIM IS:—

1. A process for the manufacture of benzodiazepin - 2 - ones of the general formula



wherein R represents a hydrogen atom or a methyl group and R¹ represents a hydrogen, chlorine, bromine or iodine atom, which process comprises reacting a (2-haloacetamido - benzoyl) - pyridine of the general formula



wherein R and R¹ have the significance given earlier in this claim and X stands for a chlorine, bromine or iodine atom, with hexamethylene tetramine under weak acidic conditions in the presence of a water-containing hydroxylic solvent.

2. A process according to claim 1 wherein a (2 - chloroacetamido - benzoyl) - pyridine or (2 - bromoacetamido - benzoyl) - pyridine starting material of formula II is employed.

3. A process according to claim 2, wherein a (2 - chloroacetamido - benzoyl) - pyridine starting material of formula II is employed.

4. A process according to claim 3, wherein 2 - [2 - (2 - chloro - acetamido) - 5 - bromo - benzoyl] - pyridine is used as the starting material.

5. A process according to any one of claims 1 to 4 inclusive, wherein the weak acidic conditions are provided by carrying out the reaction in the presence of an organic acid or a strong inorganic acid.



According to a further embodiment of the present process, the hexamethylenetetramine can be formed *in situ* from formaldehyde and ammonia. Thus, for example, a mixture of a (2 - haloacetamido - benzoyl) - pyridine of formula II and a hydroxylic solvent can first be prepared, the calculated amount of formaldehyde and ammonia can be introduced into the mixture and then hydrochloric acid can be added thereto.

The desired benzodiazepin - 2 - ones of formula I hereinbefore described can be obtained from the reaction mixture in crystalline form with a high degree of purity in a simple manner by merely cooling the reaction mixture. Further, they are obtained in a remarkably increased yield compared with the well-known process of treating a (2 - haloacetamido - benzoyl) - pyridine with ammonia.

The (2 - haloacetamido - benzoyl) - pyridine starting materials of formula II hereinbefore can be prepared by reacting an appropriately substituted (2 - amino - benzoyl) - pyridine with an appropriate haloacetyl halide such as chloroacetyl chloride or bromoacetyl bromide.

The (2 - iodoacetamido - benzoyl) - pyridine starting materials of formula II can also be prepared by reacting a (2 - chloroacetamido - benzoyl) - pyridine or (2 - bromoacetamido - benzoyl) - pyridine of formula II, preferably a (2 - chloroacetamido - benzoyl) - pyridine, with an equivalent amount of an alkali metal iodide or alkaline earth metal iodide (e.g. sodium iodide, potassium iodide and the like). Alternatively, the reaction between a (2 - chloroacetamido - benzoyl) - pyridine of formula II and hexamethylenetetramine can be carried out in the presence of minor amounts of an alkali metal iodide or alkaline earth metal iodide (e.g. sodium iodide, potassium iodide and the like) whereby a (2 - iodoacetamido - benzoyl) - pyridine is prepared *in situ* and then reacts with the hexamethylenetetramine to form a benzodiazepin - one of formula I.

The preferred (2 - haloacetamido - benzoyl) - pyridines of formula II are those in which X represents a chlorine atom. Examples of (2 - haloacetamido - benzoyl) - pyridines of formula II are 2 - [2 - (2 - chloro - acetamido) - 5 - bromo - benzoyl] - pyridine as well as the corresponding 2-bromo and 2-iodo compounds.

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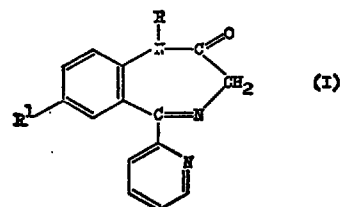
Example

A mixture of 10.0 g of 2 - [2 - (2 - chloro-

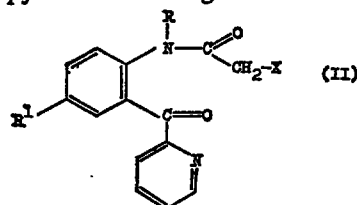
acetamido) - 5 - bromo - benzoyl] - pyridine, 8.1 g of hexamethylenetetramine, 12.75 ml of 2-N aqueous hydrochloric acid, 55 ml of methanol and 5.2 ml of water was heated under reflux for 7 hours. The mixture was then cooled and stirred at 0°C for 1 hour. The resulting crystals were filtered off and washed with 20 ml of aqueous methanol. After drying *in vacuo* at 60°C, 7.15 g (80% of theory) of pure crystalline 7 - bromo - 5 - [pyridyl - (2)] - 2,3 - dihydro - 1H - 1,4 - benzodiazepin - 2 - one of melting point 249°-251°C was obtained. Thin-layer chromatographic analysis of the mother liquors indicated the presence of a further 3-4% of the desired product.

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1. A process for the manufacture of benzodiazepin - 2 - ones of the general formula



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wherein R and R¹ have the significance given earlier in this claim and X stands for a chlorine, bromine or iodine atom, with hexamethylene tetramine under weak acidic conditions in the presence of a water-containing hydroxylic solvent.

2. A process according to claim 1 wherein a (2 - chloroacetamido - benzoyl) - pyridine or (2 - bromoacetamido - benzoyl) - pyridine starting material of formula II is employed.

3. A process according to claim 2, wherein a (2 - chloroacetamido - benzoyl) - pyridine starting material of formula II is employed.

4. A process according to claim 3, wherein 2 - [2 - (2 - chloro - acetamido) - 5 - bromo - benzoyl] - pyridine is used as the starting material.

5. A process according to any one of claims 1 to 4 inclusive, wherein the weak acidic conditions are provided by carrying out the reaction in the presence of an organic acid or a strong inorganic acid.



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6. A process according to claim 5, wherein a strong inorganic acid is used.
7. A process according to claim 6, wherein said strong inorganic acid is hydrochloric acid.
- 5 8. A process according to any one of claims 1 to 7 inclusive wherein the water-containing hydroxylic solvent is an aqueous alkanol.
- 10 9. A process according to claim 8, wherein an aqueous lower alkanol is used.
- 10 10. A process according to claim 9, wherein said aqueous lower alkanol is aqueous methanol or aqueous ethanol.
- 15 11. A process according to any one of claims 1 to 10 inclusive, wherein the proportion of water present in the water-containing hydroxylic solvent is that which ensures a homogeneous reaction mixture under reflux conditions.
- 20 12. A process according to any one of claims 1 to 11 inclusive, wherein the reaction is carried out at an elevated temperature.
- 25 13. A process according to claim 12, wherein the reaction is carried out at the reflux temperature of the reaction mixture.
14. A process according to any one of claims 1 to 13 inclusive, wherein part of the hexamethylenetetramine is used in the form of an acid addition salt thereof.
- 30 15. A process according to claim 14, wherein said acid addition salt is the hydrochloride.
16. A process according to claim 15, wherein there are used, per mol of a (2-haloacetamido - benzoyl) - pyridine starting material, 1 to 1.5 moles of hexamethylenetetramine and from 0.5 to 1.0 mol of hexamethylene tetramine hydrochloride.
- 35 17. A process according to any one of claims 1 to 16 inclusive, wherein the hexamethylene tetramine is formed *in situ* from formaldehyde.
18. A process according to claim 1, substantially as hereinbefore described with reference to the foregoing Example.
- 40 19. Benzodiazepin - 2 - ones of formula I in claim 1, when manufactured by the process claimed in any one of claims 1 to 18 inclusive.
- 45 50

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Reference has been directed in pursuance of section 9, subsection (1) of the Patent Act 1949, to patent No. 948,888.