

# PATENT SPECIFICATION

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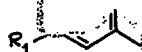
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## (54) A PROCESS FOR THE MANUFACTURE OF BENZODIAZEPINE DERIVATIVES

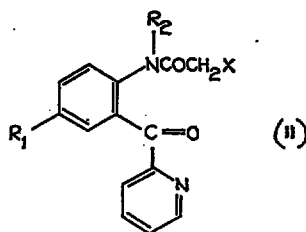
(71) We, P. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124-184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described and by the following statement:—  
 The present invention is concerned with a process for the manufacture of benzodiazepine derivatives.  
 The benzodiazepine derivatives are manufactured according to the following process:

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wherein R<sub>1</sub> represents a hydrogen or halogen atom or an alkyl group.  
 The benzodiazepine derivatives of formula I are known and anticonvulsants. In accordance with the present invention, these pharmaceutical desirable benzodiazepine derivatives are manufactured in a facile manner.

25 According to the present invention, the benzodiazepine derivatives of formula I are manufactured by reacting a haloacetamidobenzoyl-pyridine of the general formula



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, wherein R<sub>1</sub> and R<sub>2</sub> have the significance given earlier and X represents a chlorine, bromine or iodine atom, with hexamethyleneamine.

The term "low" is used in this description and in any claims to mean straight-chain alkyl groups such as ethyl, propyl, butyl and the like. The term "lower alkyl group" represents a lower alkyl group, this term includes the methyl group. The term "halogen" means chlorine, bromine, fluorine and iodine. When R<sub>1</sub> represents a halogen atom, chlorine and bromine are preferred with bromine being especially preferred. The most preferred benzodiazepine derivative of formula I manufactured in accordance with this invention is 7-bromo-1,3-dimethyl-5-(2-pyridyl)-2H-1,4-benzodiazepine.  
 The reaction of a haloacetamidobenzoyl-pyridine of formula II with hexamethyleneamine to give a benzodiazepine derivative of formula I is suitably carried out in the presence of an inert organic solvent. Among the many inert organic solvents which are suitable for use in this reaction there may be mentioned such as methanol, ethanol and acetone, tetrahydrofuran and the like, and other inert organic solvents. All that is required of the solvent is that the starting materials be soluble in the presence thereof and that it does not interfere with the reaction. While temperature and pressure are not critical to a successful performance of the reaction, it is preferred to carry out the reaction at a temperature of from about room temperature to about the reflux temperature of the reaction mixture. Most preferably, the reaction is carried out at an elevated temperature most suitably at a temperature of about the reflux temperature of the reaction mixture.

The foregoing reaction is preferably carried out using a haloacetamidobenzoyl-pyridine of formula II in the form of a salt thereof with any conventionally available non-oxidizing acid; for example a non-oxidizing mineral acid such as a hydrochloric acid (hydro-

bromic acid, hydrochloric acid, hydriodic acid and the like) or a non-oxidizing organic acid such as a C<sub>1</sub>-C<sub>4</sub> alcanoic acid (acetic acid, propionic acid, butyric acid and the like), toluenesulfonic acid and the like.

The following Examples illustrate the present invention:

#### Example 1

69.3 g of 2 - (2 - amino - 5 - bromo - benzoyl) - pyridine in 200 ml of toluene are reacted with 23.3 ml of bromoacetyl bromide. The 2 - (2 - bromoacetamido - 5 - bromo - benzoyl) - pyridine hydrobromide which forms is separated from the reaction solvent and, without drying, is added to 1.8 litres of ethanol containing 78 g of hexamethylenetetramine. The reaction mixture is heated under reflux for 10 hours and the solvent is then removed by distillation under reduced pressure from a steam-bath. The obtained is triturated with 250 ml of water while sufficient aqueous ammonia is added to bring the pH to 7-8. The crystalline product is obtained is filtered and the product is washed with water and dried to yield 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one of melting point 225°-235°C (uncorrected) with decomposition. Crystallization from dimethylformamide/ethanol gives the product with a melting point of 243°-245°C (uncorrected) with decomposition.

In a similar manner, 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one of melting point 230°-231°C with decomposition can be manufactured from 2 - (2 - bromoacetamido - 5 - bromo - benzoyl) - pyridine; 2 - (2 - chloro - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one of melting point 224°-225°C with decomposition can be manufactured from 2 - (2 - bromoacetamido - 5 - chloro - benzoyl) - pyridine; 1,3 - dihydro - 5 - (2 - pyridyl) - 7 - bromo - 2H - 1,4 - benzodiazepin - 2 - one can be manufactured from 2 - (2 - bromo - benzoyl) - pyridine or from 2 - (2 - iodoacetamido - 5 - bromo - benzoyl) - pyridine and 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one of melting point 135.5°-137°C with decomposition can be manufactured from 2 - (2 - chloro - N - methylacetamido - 5 - bromobenzoyl) - pyridine.

#### Example 2

69.3 g of 2 - (2 - amino - 5 - bromo - benzoyl) - pyridine are converted into 2 - (2 - bromoacetamido - 5 - bromo - benzoyl) - pyridine hydrobromide as described in Example 1. The hydrobromide is separated from the reaction solvent and, without drying, is added to 1.8 litres of methanol containing 101.1 g of hexamethylenetetramine. The reaction mixture is stirred under reflux for 6 hours and the reaction solvent is then removed by dis-

tillation from a steam-bath under reduced pressure. The crystalline residue thus obtained is suspended in 250 ml of water, filtered, washed and dried to yield 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one melting at 225°-235°C with decomposition (uncorrected). Crystallization from dimethylformamide/ethanol gives pure material melting at 243°-245°C with decomposition (uncorrected).

#### Example 3

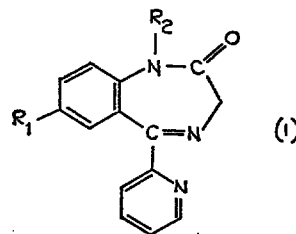
99.5 g of 2 - (2 - bromoacetamido - 5 - bromo - benzoyl) - pyridine and 78 g of hexamethylenetetramine are heated under reflux in 1.2 litres of ethanol for 10 hours. The solvent is removed by distillation under reduced pressure from a steam-bath. The residue in the still is suspended, with stirring, in 500 ml of water, isolated by filtration and dried to yield 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one melting point 225°-235°C with decomposition. Upon crystallization from dimethylformamide/ethanol, the product melts at 243°-245°C with decomposition (uncorrected).

2 - (2 - bromoacetamido - 5 - bromo - benzoyl) - pyridine and 78 g of hexamethylenetetramine are heated under reflux in 1.2 litres of ethanol for 10 hours. The solvent is removed by distillation under reduced pressure from a steam-bath. The residue in the still is suspended, with stirring, in 500 ml of water, isolated by filtration and dried to yield 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one, melts at 220°-230°C with decomposition (uncorrected). Crystallization from dimethylformamide/ethanol gives the product melting at 243°-245°C with decomposition (uncorrected). The above process makes no claim to the manufacture of general formula (I) wherein R<sub>1</sub> is hydrogen or methyl, R<sub>2</sub> is hydrogen or iodine, and the reaction is carried out under weak acidic conditions in a water-containing hydroalcoholic solvent.

Subject to the foregoing disclaimer,

WHAT WE CLAIM IS:-

1. A process for the manufacture of benzodiazepine derivative of the general formula



, wherein R<sub>1</sub> represents a hydrogen or halo-



bromic acid, hydrochloric acid, hydriodic acid and the like) or a non-oxidizing organic acid such as a C<sub>1</sub>-C<sub>4</sub> alkanic acid (acetic acid, propionic acid, butyric acid and the like), toluenesulfonic acid and the like.

The following Examples illustrate the present invention:

### Example 1

69.3 g of 2 - (2 - amino - 5 - bromo - benzoyl) - pyridine in 200 ml of toluene are reacted with 23.3 ml of bromoacetyl bromide. The 2 - (2 - bromoacetamido - 5 - bromo - benzoyl) - pyridine hydrobromide which forms is separated from the reaction solvent and, without drying, is added to 1.8 litres of ethanol containing 78 g of hexamethylenetetramine. The reaction mixture is heated under reflux for 10 hours and the solvent is then removed by distillation under reduced pressure from a steam-bath. The residue obtained is triturated with 250 ml of water while sufficient aqueous ammonia is added to bring the pH to 7-8. The crystalline product is obtained by filtration and the product is dried with water and dried to yield 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - benzodiazepin - 2 - one of melting point 225°-235°C (uncorrected) with decomposition. Crystallization from dimethylformamide/ethanol gives the product with a melting point of 243°-245°C (uncorrected) with decomposition.

In a similar manner, 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one of melting point 230°-231°C with decomposition can be manufactured from 2 - (2 - bromoacetamido - 5 - bromo - benzoyl) - pyridine; 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one of melting point 224°-225°C with decomposition can be manufactured from 2 - (2 - bromoacetamido - 5 - chloro - benzoyl) - pyridine; 1,3 - dihydro - 5 - (2 - pyridyl) - 7 - bromo - 2H - 1,4 - benzodiazepin - 2 - one can be manufactured from 2 - (2 - bromoacetamido - 5 - chloro - benzoyl) - pyridine or from 2 - (2 - iodoacetamido - 5 - bromo - benzoyl) - pyridine and 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one of melting point 135.5°-137°C with decomposition can be manufactured from 2 - (2 - chloro - N - methylacetamido - 5 - bromobenzoyl) - pyridine.

### Example 2

69.3 g of 2 - (2 - amino - 5 - bromo - benzoyl) - pyridine are converted into 2 - (2 - bromoacetamido - 5 - bromo - benzoyl) - pyridine hydrobromide as described in Example 1. The hydrobromide is separated from the reaction solvent and, without drying, is added to 1.8 litres of methanol containing 101.1 g of hexamethylenetetramine. The reaction mixture is stirred under reflux for 6 hours and the reaction solvent is then removed by dis-

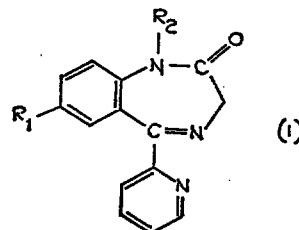
tillation from a steam-bath under reduced pressure. The crystalline residue thus obtained is suspended in 250 ml of water, filtered, washed and dried to yield 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one melting at 225°-235°C with decomposition (uncorrected). Crystallization from dimethylformamide/ethanol gives pure material melting at 243°-245°C with decomposition (uncorrected).

### Example C

99.5 g of 2 - (2 - bromoacetamido - 5 - bromo - benzoyl) - pyridine and 78 g of hexamethylenetetramine are heated under reflux in 1.2 litres of ethanol for 10 hours. The solvent is removed by distillation under reduced pressure from a steam-bath. The residue in the still is suspended, with stirring, in 500 ml of water, isolated by filtration and dried to yield 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one melting point 225°-235°C with decomposition. Upon crystallization from dimethylformamide/ethanol, the product melts at 243°-245°C with decomposition (uncorrected).

2 - (2 - bromoacetamido - 5 - bromo - benzoyl) - pyridine and 78 g of hexamethylenetetramine are heated under reflux in 1.2 litres of ethanol for 10 hours. The solvent is removed by distillation under reduced pressure from a steam-bath. The residue in the still is suspended, with stirring, in 500 ml of water, isolated by filtration and dried to yield 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one, melts at 220°-230°C with decomposition (uncorrected). Crystallization from dimethylformamide/ethanol gives the product melting at 243°-245°C (uncorrected). The above process can be used for the manufacture of general formula (I) wherein R<sub>1</sub> is hydrogen or halogen, R<sub>2</sub> is hydrogen or methyl, and the reaction is carried out under weak acidic conditions in a water-soluble solvent.

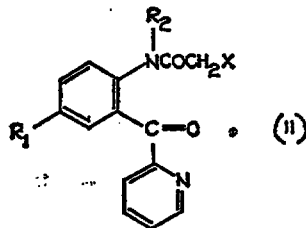
Subject to the foregoing disclaimer, WHAT WE CLAIM IS:—  
1. A process for the manufacture of benzodiazepine derivative of the general formula



, wherein R<sub>1</sub> represents a hydrogen or halo-



gen. atom and  $R_2$  represents a hydrogen atom or a lower ( $C_1-C_7$ ) alkyl group, which process comprises reacting a haloacetamidobenzoyl-pyridine of the general formula



, wherein  $R_1$  and  $R_2$  have the significance given earlier in this claim and X represents a chlorine, bromine or iodine atom, with hexamethylenetetramine.

10 2. A process according to claim 1, wherein  $R_1$  represents a bromine atom,  $R_2$  represents a hydrogen atom and X represents a bromine or chlorine atom.

15 3. A process according to claim 1, wherein  $R_1$  and  $R_2$  each represent a hydrogen atom

and X represents a bromine or chlorine atom.

4. A process according to claim 1, claim 2 or claim 3, wherein the haloacetamidobenzoyl-pyridine starting material of formula II is used in the form of a salt with a non-oxidizing mineral acid.

5. A process for the manufacture of the benzodiazepine derivatives of formula I in claim 1, substantially as hereinbefore described with reference to the foregoing Examples.

6. Benzodiazepine derivatives of formula I in claim 1, when manufactured by the process claimed in any one of claims 1 to 5 inclusive.

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Reference has been made in pursuance of section 9, sub-section (1) of the Patents Act 1949, to the specification of the Patents 1,388,892 and 1,388,893.

for Her Majesty's Stationery Office, by the Courier, Southampton Buildings, London, W.C.2A 1AY, from which copies may be obtained.