

PATENT SPECIFICATION

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Inventors: CTIRAD PODESVA and ERNEST CULLEN

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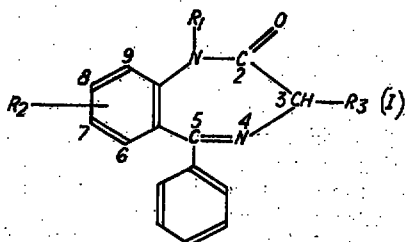
COMPLETE SPECIFICATION

Method for Preparation of Benzodiazepinones

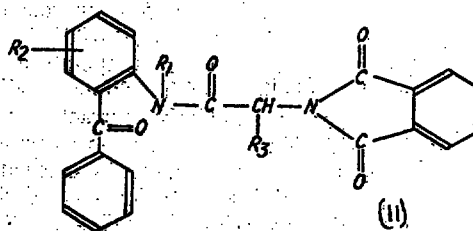
We, DELMAR CHEMICALS LIMITED, a Canadian Body Corporate, of 9321 Airlie Street, Ville la Salle, Province of Quebec, Canada, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a method for the production of 5-phenyl-1,4-3H-benzodiazepin-2(1H)-ones. It further relates to a method for the production of substituted 5-phenyl-1,4-3H-benzodiazepin-2(1H)-ones and more particularly to the production of the above 5-phenyl-1,4-3H-benzodiazepin-2(1H)-ones substituted on the fused aromatic ring. It also refers to a method for the preparation of the above mentioned substances substituted on the amido N atom, and/or in position 3.

The diazepinones corresponding to the following general formula I:



in which R_1 represents a hydrogen atom, a methyl group or an ethyl group, R_2 represents a halogen atom and R_3 represents a hydrogen atom or a lower alkyl, phenyl or *p*-hydroxybenzyl group, are, according to the present invention, prepared easily and in excellent yields by removing by hydrazinolysis in the presence of an inert solvent the phthaloyl group from a phthalimidoacetamide represented by the general formula II:



where R_1 , R_2 and R_3 are the same as in general formula I. The removal of the phthaloyl group is effected by reacting, preferably by refluxing, the phthalimidoacetamide with more than one mol equivalent of hydrazine hydrate. This method has the advantage over the previously known hydrolytic methods for removing phthaloyl groups in that only the phthalimido group is affected while the second amido group present in the molecule remains untouched. Moreover, excellent yields of the final product are obtained by this method.

Certain of the intermediate phthalimidoacetamides and their preparation are described and claimed in our co-pending application No. 1693/64 (Serial No. 1,056,289).

The diazepinones conforming to the general formula I are useful as chemotherapeutics, especially for the treatment of some nervous disorders. Those compounds *per se* are claimed in Specification No. 972,968. Especially useful is 7-chloro-1-methyl-5-phenyl-1,4-3H-benzodiazepin-2(1H)-one.

The object of this invention is, therefore, to provide an economical and easy method for the preparation of benzodiazepinones corresponding to the above shown general formula I, in high yields after a short processing time.

The reaction may be carried out in a number of common solvents, in which both

[Price 4s. 6d.]

the starting material and hydrazine hydrate are soluble and which are inert to the reactants. Preferred as easily available solvents are lower aliphatic alcohols, e.g. ethanol. The reaction may be satisfactorily completed in about two hours.

In this specification the word "lower" as applied to alkyl groups and aliphatic alcohols means such groups and alcohols containing not more than 3 carbon atoms.

In order that the invention may be well understood the following examples are given by way of illustration only:—

EXAMPLE I

A solution of 2-(N-methylphthalimidoacetamido)-5-chlorobenzophenone (0.5 g) in 95% ethanol (25 ml) containing hydrazine hydrate (0.174 g) was heated under reflux for 2 hours. About 10 ml. of ethanol were then distilled off. The turbid reaction mixture was cooled to room temperature and filtered. The filtrate was acidified by addition of 5% hydrochloric acid, the mixture warmed to 70–80° C and cooled immediately to room temperature. It was made alkaline with dilute sodium hydroxide and exhaustively extracted with methylene chloride. The extract was washed with water, the solvent removed by distillation and the remaining 7-chloro-1-methyl-5-phenyl-1,4-3H-benzodiazepin-2(1H)-one (0.27 g, 82% theory) was recrystallized from ether. The pure product melted at 130° C.

EXAMPLE II

A suspension of 2-phthalimidoacetamido-5-chlorobenzophenone (3.02 g) in ethanol (75 ml) containing hydrazine hydrate (1.08 g) was stirred and heated under reflux for 90 minutes. After cooling to room temperature the reaction mixture was acidified with dilute hydrochloric acid, warmed on a water bath for 15 minutes, cooled to room temperature and filtered. The filtrate was made alkaline with dilute sodium hydroxide and exhaustively extracted with chloroform. Removal of the solvent left a high yield of 7-chloro-5-phenyl-1,4-3H-benzodiazepin-2(1H)-one, which was recrystallized from acetone. M.p. 200–201° C.

EXAMPLE III

A solution of 2-phthalimido-phenylacetamido-5-chlorobenzophenone (28 g) in ethanol (300 ml) containing hydrazine hydrate (9.2 g) was heated under reflux for two hours. After cooling the precipitated crystalline material was collected by filtration, suspended in 15% aqueous sodium hydroxide and stirred

for 30 minutes at room temperature whereby phthaloyl hydrazide went into solution. The undissolved 7-chloro-3,5-diphenyl-1,4-3H-benzodiazepin-2(1H)-one (13.4 g) was washed with water and purified by crystallization from "Cellosolve" (Trade Mark). M.p. 273° C.

EXAMPLE IV

A solution of 2-(N-methyl)-phthalimido-phenylacetamido-5-chlorobenzophenone (13.1 g) in ethanol (150 ml) containing hydrazine hydrate (4.15 g) was heated under reflux for 90 minutes. The reaction mixture was cooled, the crystalline precipitate collected by filtration, suspended in dilute aqueous sodium hydroxide and stirred for 30 minutes at room temperature. The undissolved product was collected by filtration and washed with water (yield: 6.5 g). The pure 7-chloro-1-methyl-3,5-diphenyl-1,4-3H-benzodiazepin-2(1H)-one had a m.p. of 223–4° C after crystallization from methanol benzene.

EXAMPLE V

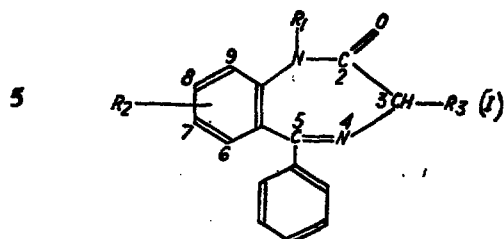
A solution of 2-(α -phthalimidopropionamido)-5-chlorobenzophenone (17.3 g) in ethanol (200 ml) containing hydrazine hydrate (6.85 g) was heated under reflux for 2 hours. The crystalline precipitate was removed by filtration and washed with ethanol. Dilution of the combined filtrate and washings with water caused precipitation of the reaction product (3.1 g), m.p. 216° C. Another 3.5 g of the same product were obtained when the first crystalline precipitate, containing mostly phthaloyl hydrazide, was suspended in dilute aqueous sodium hydroxide and stirred to remove the hydrazine. The combined crops of 7-chloro-3-methyl-5-phenyl-1,4-3H-benzodiazepin-2(1H)-one were purified by crystallization from ethanol, m.p. 224–5° C.

EXAMPLE VI

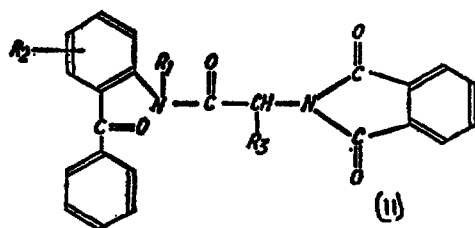
A solution of 2-(N-methyl- α -phthalimido- β -(p-hydroxyphenyl)-propionamido)-5-chlorobenzophenone (7 g) in ethanol (100 ml) containing hydrazine hydrate (2.1 g) was heated under reflux for 2 hours. After cooling the white precipitate was removed by filtration and washed with ethanol. The combined filtrate and washings were acidified with 5% hydrochloric acid, the solution heated to 60° C, cooled to room temperature, diluted with water and made basic with aqueous sodium hydroxide. The crystalline 7-chloro-1-methyl-3-(p-hydroxybenzyl)-5-phenyl-1,4-3H-benzodiazepin-2(1H)-one (4.7 g) was purified by crystallization from methanol, m.p. 217–18° C.

WHAT WE CLAIM IS:—

1. Process for the production of 5-phenyl-1,4-3H-benzodiazepin-2(1H)-ones represented by the following general formula I:



10 where R_1 represents a hydrogen atom, a methyl group or an ethyl group, R_2 represents a halogen atom and R_3 represents a hydrogen atom or a lower alkyl, phenyl or *p*-hydroxybenzyl group, which comprises reacting a 2-phthalimido-acylaminobenzophenone represented by the following general formula II:



15 where R_1 , R_2 and R_3 are as defined above, with more than one mol equivalent of hydrazine hydrate in the presence of an inert solvent.

2. Process as defined in claim 1, wherein the reaction is effected at reflux temperature.

20 3. Process as defined in claim 1 or 2, wherein the solvent is a lower aliphatic alcohol.

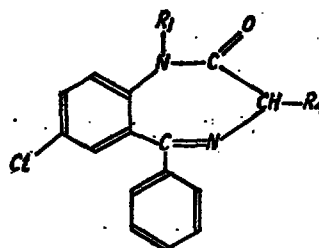
4. Process as defined in claim 3, wherein the alcohol is ethanol.

25 5. Process as defined in claim 1 substan-

tially as described in any one of the Examples.

6. A 5-phenyl-1,4-3H-benzodiazepin-2(1H)-one when obtained by the process of any preceding claim.

7. 5-phenyl-1,4-3H-benzodiazepin-2(1H)-ones of the formula:



where R_1 represents hydrogen or methyl and R_4 represents hydrogen, methyl, phenyl or *p*-hydroxybenzyl when obtained by the process of any of claims 1 to 5.

8. 7-chloro-5-phenyl-1,4-3H-benzodiazepin-2(1H)-one when obtained by the process of any one of claims 1 to 5.

9. 7-chloro-1-methyl-5-phenyl-1,4-3H-benzodiazepin-2(1H)-one when obtained by the process of any one of claims 1 to 5.

10. 7-chloro-3,5-diphenyl-1,4-3H-benzodiazepin-2(1H)-one when obtained by the process of any one of claims 1 to 5.

11. 7-chloro-1-methyl-3,5-diphenyl-1,4-3H-benzodiazepin-2(1H)-one when obtained by the process of any one of claims 1 to 5.

12. 7-chloro-3-methyl-5-phenyl-1,4-3H-benzodiazepin-2(1H)-one when obtained by the process of any one of claims 1 to 5.

13. 7-chloro-1-methyl-3-(*p*-hydroxybenzyl)-5-phenyl-1,4-3H-benzodiazepin-2(1H)-one when obtained by the process of any one of claims 1 to 5.

J. A. KEMP & CO.,
Chartered Patent Agents,
14, South Square,
Gray's Inn, London, W.C.1.

