

PATENT SPECIFICATION



NO DRAWINGS

1036.577

Date of Application and filing Complete Specification: July 9, 1964.

No. 28371/64.

Application made in United States of America (No. 294,142) on July 10, 1963.

Complete Specification Published: July 20, 1966.

© Crown Copyright 1966.

Index at acceptance:—C2 C(1E6K4, 1E6K6, 1Q4, 1Q6C, 1Q7A, 1Q8A, 1Q9B, 1Q11D, 1Q11J, 2B31)

Int. Cl.:—O 07 d 53/06

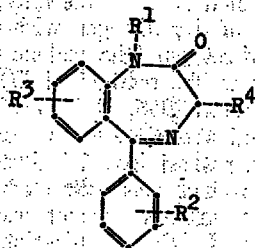
COMPLETE SPECIFICATION

The Manufacture of Benzdiaz[1,4]Epinones

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 valuable benzdiaz[1,4]epinones.

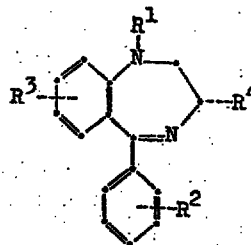
The valuable benzdiaz[1,4]epinone products of the process provided by the invention are compounds of the formula



wherein R¹ and R⁴ are lower-alkyl groups of which the former must be present when there is a single bond in the 4,5 - position, R² and R³ are each a halogen atom or a nitro, lower-alkyl or trifluoromethyl group and the broken lines (subject to the proviso in respect of R¹) denote optional bonds, and acid-addition salts thereof. They are useful as sedatives, tranquilizers, anticonvulsants and muscle relaxants. Those benzdiaz[1,4]epinone products in which R² (when present) is a halogen atom or a lower-alkyl or trifluoromethyl group and R³ has the significance given earlier are claimed *per se* in the specification of our Letters Patent No. 972,968. Those benzdiaz[1,4]epinone products in which a double bond is

present in the 4,5-position, R² is present and is a nitro group in the *ortho*-position and R³ (when present) is a nitro group in the 7-position are claimed *per se* in the specification of our Letters Patent No. 1,000,507.

According to the process, the products aforesaid are manufactured by oxidizing a benzdiaz[1,4]epine compound of the formula



(wherein R¹, R², R³, R⁴ and the broken lines have the significance given earlier) in a system having an oxidation potential greater than 0.74 volt and, where required, converting the resulting benzdiaz[1,4]epinone into an acid-addition salt.

The benzdiaz[1,4]epine starting materials of the second formula hereinbefore are claimed *per se* in the specification of our copending Application for Letters Patent No. 28946/62 (now serial no: 1,017,276) and may be prepared as described and claimed therein. One class of preferred starting materials comprises those benzdiaz[1,4]epines in which R² is either absent or is present in the *ortho*-position. When R² is present in said position it is preferably a fluorine or chlorine atom or the trifluoromethyl group. Another class of preferred starting materials comprises those benzdiaz[1,4]epines in which R³ is present in the 7-position and is a fluorine, chlorine or bromine atom or the nitro or trifluoromethyl group. Yet another class of preferred starting materials comprises those benzdiaz[1,4]epines

in which the lower-alkyl group in the 1-position (when present) is the methyl group. Especially preferred starting materials are 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz-[1,4]epine, 7 - chloro - 5 - phenyl - 1 - methyl - 2,3 - dihydro - 1H - benzdiaz[1,4]-epine and 7 - trifluoromethyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine.

In the process of the invention oxygen is introduced into the 2-position of a benzdiaz-[1,4]epine molecule by means of a strong oxidizing agent; that is, one which gives rise to a system having an oxidation potential greater than 0.74 volt. The oxidation is suitably effected using an agent containing in combination with oxygen a metal at a valency higher than its principal valency. It is preferred that the metal be vanadium, chromium, manganese or lead. By principal valency is meant that valency of the metal in which the metal has the largest number of stable compounds, that is, compounds containing the metal at the principal valency tend to be more stable than compounds containing the same metal at a different valency. Thus, the principal valency for vanadium and chromium is 3, whereas the principal valency for manganese and lead is 2. Suitable oxidizing agents for carrying out the process are lead peroxide, vanadium pentoxide, chromic acid and the permanganate ion. Preferred oxidizing agents are those formed from chromium or manganese in combination with oxygen at their higher valencies (for example, chromic acid or the permanganate ion). Chromic acid is especially preferred, and it will be understood that this term is used herein to include H_2CrO_4 (that is, an aqueous solution of chromium trioxide) as well as chromium trioxide dissolved in organic solvents (e.g. in acetic acid or pyridine).

The oxidizing agents referred to earlier can either be added to a solution containing the benzdiaz[1,4]epine starting material or the benzdiaz[1,4]epine starting material can be added to a solution containing the oxidizing agent or the oxidizing agent can be formed *in situ*. The use of chromic acid formed *in situ* is especially preferred. This can be effected, for example, by the addition of chromium trioxide and an acid (for example, sulphuric acid) to the oxidation mixture.

In carrying out the process, the concentration of the reactants is not critical, but the oxidizing agent should preferably be present in a slight excess of the stoichiometric amount (that is, in excess of one stoichiometric equivalent but less than two stoichiometric equivalents). The time taken to effect the oxidation will vary with the specific reactants chosen (that is with the specific benzdiaz[1,4]epine being oxidized and with the specific oxidizing agent being used). The temperature at which the oxidation is carried out is suitably determined by the solubility of the

reactants in the oxidation medium and should suitably be one at which the reactants are miscible in the oxidation medium. As the oxidation medium, there can be used water, ketones, acids (both organic and inorganic), hydrocarbons or ethers, as well as mixtures thereof. Suitably, the oxidation medium should not itself be easily oxidizable. Examples of organic solvents which can serve as the oxidation medium are acetone and acetic acid. It has been found suitable when using acetone to conduct the oxidation at room temperature or a temperature up to the reflux temperature of acetone. However, when using acetic acid, it has been found most convenient to conduct the oxidation at room temperature or at a temperature below room temperature. Accordingly, the most convenient temperature (in terms of obtaining the best yield and carrying out the oxidation with greatest ease) will depend upon the medium chosen for any specific set of reactants.

The following Examples are illustrative of the manner in which the process may be carried into effect. In these Examples, the chromic acid reagent used was produced by diluting a solution of 26.72 g of chromium trioxide in 23 ml of concentrated sulphuric acid with water to a volume of 100 ml [see DJERASSI *et al.*, J.Org.Chem., 1956, 21, 1547].

EXAMPLE 1.

A solution of 1.0 g of 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine in 250 ml of purified acetone was treated under an atmosphere of dry nitrogen with 0.936 ml of chromic acid reagent [the acetone was purified according to the method of DJERASSI *et al.*, J.Org.Chem., 1956, 21, 1547]. The mixture was heated and allowed to reflux for 1 hour and then poured into 1.5 litres of cold water. The product was extracted into dichloro-methane and the extract was washed and concentrated. Recrystallization of the residue from methanol gave a first crop of prisms of unreacted starting material. A second crop of prisms was treated with ether and the ether-soluble portion was crystallized to yield 7 - nitro - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 224°—226°C.

EXAMPLE 2.

A solution of 1.0 g of 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine in 15 ml of glacial acetic acid was treated at room temperature with 0.936 ml of chromic acid reagent (prepared in the same manner as the chromate reagent used in Example 1) and stirred for 0.5 hour. The mixture was then poured into 800 ml of water, made basic with ammonium hydroxide and extracted with dichloro-methane. The organic layers were then combined, washed, dried and filtered over neutral alumina (WOELM Grade D). The alumina was eluted with dichloro -

methane and washed with methanol. The solvent was then removed and the residue recrystallized giving 7 - nitro - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 224°—226°C.

EXAMPLE 3.

According to the procedure described in Example 1 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine was reacted with chromium trioxide in dilute sulphuric acid and acetone. The reaction time was 3 hours and the product was 7 - chloro - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 216°—217°C.

EXAMPLE 4.

According to the procedure described in Example 2, 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine was reacted with chromium trioxide in sulphuric acid and glacial acetic acid. The reaction time was 18 hours. There was thus obtained 7 - nitro - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 224°—226°C.

EXAMPLE 5.

According to the procedure described in Example 2, 7 - trifluoromethyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine was reacted with chromium trioxide in sulphuric acid and glacial acetic acid. The reaction time was 0.5 hour. The product was 7 - trifluoromethyl - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 233°—235°C.

EXAMPLE 6

According to the procedure described in Example 1, 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine was reacted with chromium trioxide in dilute sulphuric acid and acetone. The reaction time was 3 hours. There was thus obtained 7 - chloro - 1 - methyl - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 130°—131°C.

EXAMPLE 7.

According to the procedure described in Example 1, 7 - chloro - 1 - methyl - 5 - phenyl - 1,3,4,5 - tetrahydro - 2H - benzdiaz[1,4]epine was reacted with chromium trioxide in dilute sulphuric acid and acetone. The reaction time was 10 minutes. The reaction was conducted at room temperature. There was thus obtained 7 - chloro - 1 - methyl - 5 - phenyl - 1,3,4,5 - tetrahydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 144°—145°C.

EXAMPLE 8.

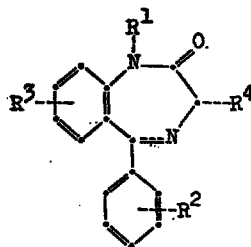
A solution of 2.1 g of 7 - nitro - 2,3 - dihydro - 1H - benzdiaz[1,4]epine in a mixture of 50 ml of pure acetone, 0.2 ml of pyridine and 0.2 ml of water was heated under reflux while 5.0 g of potassium permanganate were added portionwise. The resulting mixture was heated under reflux for 40 minutes, cooled and filtered over a diatomaceous earth filter aid. Solvents were removed under reduced pressure

and the residual oil was dissolved in chloroform and filtered over neutral activated alumina. Starting material was recovered from the chloroform eluant and this solvent was used until no more material was obtained from the alumina. By changing the solvent to methanol, 7 - nitro - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one was obtained; melting point=223°—225°C.

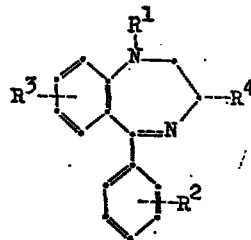
It will be appreciated that the term 'lower-alkyl' is used in the foregoing description and in the accompanying claims to mean straight-chain and branched-chain alkyl groups containing not more than seven carbon atoms (e.g. methyl, ethyl, propyl and isopropyl). The term 'halogen' includes fluorine, chlorine, bromine and iodine.

WHAT WE CLAIM IS:—

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



wherein R¹ and R⁴ are lower-alkyl groups of which the former must be present when there is a single bond in the 4,5-position, R² and R³ are each a halogen atom or a nitro, lower-alkyl or trifluoromethyl group and the broken lines (subject to the proviso in respect of R¹) denote optional bonds, and acid-addition salts thereof, which process comprises oxidizing a benzdiaz[1,4]epine compound of the formula



(wherein R¹, R², R³, R⁴ and the broken lines have the significance given earlier) in a system having an oxidation potential greater than 0.74 volt and, where required, converting the resulting benzdiaz[1,4]epinone into an acid-addition salt.

2) A process in accordance with claim 1, wherein the benzdiaz[1,4]epine starting material used is one in which R² (when present) is in the *ortho*-position.

3) A process in accordance with claim 2



* C L M S *

1,036,577

3

methane and washed with methanol. The solvent was then removed and the residue recrystallized giving 7 - nitro - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 224°—226°C.

EXAMPLE 3.

According to the procedure described in Example 1, 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine was reacted with chromium trioxide in dilute sulphuric acid and acetone. The reaction time was 3 hours and the product was 7 - chloro - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 216°—217°C.

EXAMPLE 4.

According to the procedure described in Example 2, 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine was reacted with chromium trioxide in sulphuric acid and glacial acetic acid. The reaction time was 18 hours. There was thus obtained 7 - nitro - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 224°—226°C.

EXAMPLE 5.

According to the procedure described in Example 2, 7 - trifluoromethyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine was reacted with chromium trioxide in sulphuric acid and glacial acetic acid. The reaction time was 0.5 hour. The product was 7 - trifluoromethyl - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 233°—235°C.

EXAMPLE 6

According to the procedure described in Example 1, 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine was reacted with chromium trioxide in dilute sulphuric acid and acetone. The reaction time was 3 hours. There was thus obtained 7 - chloro - 1 - methyl - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 130°—131°C.

EXAMPLE 7.

According to the procedure described in Example 1, 7 - chloro - 1 - methyl - 5 - phenyl - 1,3,4,5 - tetrahydro - 2H - benzdiaz[1,4]epine was reacted with chromium trioxide in dilute sulphuric acid and acetone. The reaction time was 10 minutes. The reaction was conducted at room temperature. There was thus obtained 7 - chloro - 1 - methyl - 5 - phenyl - 1,3,4,5 - tetrahydro - 2H - benzdiaz[1,4]epin - 2 - one melting at 144°—145°C.

EXAMPLE 8.

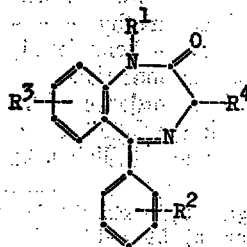
A solution of 2.1 g of 7 - nitro - 2,3 - dihydro - 1H - benzdiaz[1,4]epine in a mixture of 50 ml of pure acetone, 0.2 ml of pyridine and 0.2 ml of water was heated under reflux while 5.0 g of potassium permanganate were added portionwise. The resulting mixture was heated under reflux for 40 minutes, cooled and filtered over a diatomaceous earth filter aid. Solvents were removed under reduced pressure

and the residual oil was dissolved in chloroform and filtered over neutral activated alumina. Starting material was recovered from the chloroform eluant and this solvent was used until no more material was obtained from the alumina. By changing the solvent to methanol, 7 - nitro - 5 - phenyl - 1,3 - dihydro - 2H - benzdiaz[1,4]epin - 2 - one was obtained; melting point=223°—225°C.

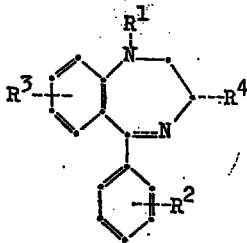
It will be appreciated that the term 'lower-alkyl' is used in the foregoing description and in the accompanying claims to mean straight-chain and branched-chain alkyl groups containing not more than seven carbon atoms (e.g. methyl, ethyl, propyl and isopropyl). The term 'halogen' includes fluorine, chlorine, bromine and iodine.

WHAT WE CLAIM IS:—

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



wherein R¹ and R⁴ are lower-alkyl groups of which the former must be present when there is a single bond in the 4,5-position, R² and R³ are each a halogen atom or a nitro, lower-alkyl or trifluoromethyl group and the broken lines (subject to the proviso in respect of R¹) denote optional bonds, and acid-addition salts thereof, which process comprises oxidizing a benzdiaz[1,4]epine compound of the formula



(wherein R¹, R², R³, R⁴ and the broken lines have the significance given earlier) in a system having an oxidation potential greater than 0.74 volt and, where required, converting the resulting benzdiaz[1,4]epinone into an acid-addition salt.

2) A process in accordance with claim 1, wherein the benzdiaz[1,4]epine starting material used is one in which R² (when present) is in the *ortho*-position.

3) A process in accordance with claim 2

- wherein R^2 is present and is a fluorine or chlorine atom or the trifluoromethyl group.
- 4) A process in accordance with claim 1, wherein the benzdiaz[1,4]epine starting material used is one in which R^3 is present in the 7-position and is a fluorine, chlorine or bromine atom or the nitro or trifluoromethyl group.
- 5) A process in accordance with claim 1, wherein the benzdiaz[1,4]epine starting material used is one in which the lower-alkyl group in the 1-position (when present) is the methyl group.
- 6) A process in accordance with claim 1, wherein 7-nitro-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epine is used as the starting material.
- 7) A process in accordance with claim 1, wherein 7-chloro-5-phenyl-1-methyl-2,3-dihydro-1H-benzdiaz[1,4]epine is used as the starting material.
- 8) A process in accordance with claim 1, wherein 7-trifluoromethyl-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epine is used as the starting material.
- 9) A process in accordance with any one of the preceding claims, wherein the oxidation is carried out using an oxidizing agent which contains in combination with oxygen a metal at a valency higher than its principal valency.
- 10) A process in accordance with claim 9, wherein the metal is vanadium, chromium, manganese or lead.
- 11) A process in accordance with claim 10, wherein chromic acid as hereinbefore defined is the oxidizing agent used.
- 12) A process in accordance with claim 11, wherein the said chromic acid is formed *in situ*.
- 13) A process in accordance with claim 12, wherein the said chromic acid is formed from chromium trioxide and sulphuric acid.
- 14) A process for the manufacture of the compounds of the first formula given in claim 1, and acid addition salts thereof, substantially as described with reference to the Examples.
- 15) Compounds of the first formula given in claim 1, and acid addition salts thereof, when manufactured by the process claimed in any one of claims 1 to 14 inclusive.

W. D. WHITAKER,
Patent Agent,
for F. Hoffmann-La Roche & Co.,
Aktiengesellschaft.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1966. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.



* C L M S *

