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12 SEP 1968

# PATENT SPECIFICATION

NO DRAWINGS

992,168

992,168

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*No. 49854/63.*

*Application made in Canada (No. 865,113) on Dec. 20, 1962.*

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**Index at acceptance:**—C2 C2B30

**Int. Cl.:**—C 07 d

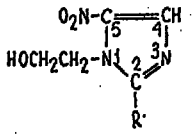
COMPLETE SPECIFICATION

## Process for the preparation of Imidazole Derivatives

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French body corporate, of 22, Avenue Montaigne, Paris 8°, France, 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:—

This invention relates to a process for the preparation of imidazole derivatives.

It is the object of the present invention to provide a new and improved process for the preparation of 1 - (2 - hydroxyethyl) - 5-nitroimidazoles of the general formula:



I

wherein R represents a hydrogen atom, or an alkyl group containing up to five carbon atoms, or an aryl (preferably phenyl), aralkyl (preferably benzyl), or alicyclic group. Compounds of this type, for example 1 - (2 - hydroxyethyl)-2 - methyl - 5 - nitroimidazole, have been shown to possess valuable chemotherapeutic properties. They have a very low toxicity and are especially useful for treatment of infections cause by pathogenic protozoa such as certain species of amoebae (for example *Endamoeba histolytica*) and trichomonas (for example *Trichomonas vaginalis*).

The compounds in which R represents an alkyl group containing up to five carbon atoms and their acid addition salts are claimed *per se* in our prior Patent No. 836,854.

These compounds have hitherto been prepared (see Specification No. 836,854) by reacting in the absence of a basic condensing agent a corresponding nitroimidazole compound (unsubstituted on a ring-nitrogen atom) with a compound of the formula $Z—CH_2CH_2OY$ (wherein Z represents the acid residue of a reactive ester, such as a halogen atom or a sulphuric or sulphonic ester residue, and Y represents a hydrogen atom or a radical which is readily replaceable by a hydrogen atom, for example a benzyl group) followed, when Y is other than a hydrogen atom, by liberation of the hydroxyl group, for example by acid hydrolysis when Y is a benzyl group. Examples of appropriate starting materials

$$Z—CH_2CH_2OY$$

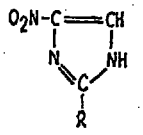
are ethylene chlorohydrin and benzyloxyethyl toluene-*p*-sulphonate. This hitherto known process necessitates heating the reactants together, sometimes for a considerable length of time, and generally results in relatively small yields of the desired nitroimidazole.

It has now unexpectedly been found after research and experimentation that the aforesaid 1 - (2 - hydroxyethyl) - 5 - nitroimidazoles can be prepared readily and generally in high yields, for example in excess of 60% of theory based upon the nitroimidazole consumed, from corresponding *N*-unsubstituted nitroimidazole compounds and without the necessity of applying external heat to the reaction mixture by replacing the reactive ester reactant

$$Z—CH_2CH_2OY$$

(Z and Y being as hereinbefore defined) by ethylene oxide and by carrying out the reaction in an organic acid solvent medium.

According to the present invention, therefore, there is provided a new and improved process for the preparation of 1-(2-hydroxyethyl) - 5 - nitroimidazoles of formula I which comprises reacting ethylene oxide with a nitroimidazole of the formula:



II

(wherein R is as hereinbefore defined) in solu-

[*Price 4s. 6d.*]

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methanol-ethyl acetate melted at 161°C. The yield was 99% based on unrecovered starting material.

EXAMPLE IV

Ethylene oxide (11 g.) was introduced slowly into a solution of 2 - methyl - 4(or 5) - nitroimidazole (6.35 g.) in a 1:1 mixture of formic and acetic acids (50 ml.). After standing at room temperature for 2½ hours, the reaction mixture was worked up as in Example I. There were recovered 0.52 g. of practically pure nitroimidazole starting material and 6.29 g. of 1 - (2 - hydroxyethyl) - 2 - methyl - 5 - nitroimidazole, m.p. 153—5°C., which after one recrystallisation from methanol-ethyl acetate melted at 161°C. The yield was 60.1% based on unrecovered starting material.

EXAMPLE V

A solution of ethylene oxide (10.5 g.) in methanol (15 ml.) was added in portions to a solution of 2 - methyl - 4(or 5) - nitroimidazole (6.35 g.) in 98% formic acid (35 ml.). After standing for 1½ hours at room temperature, the reaction mixture was worked up as in Example I. There were recovered 2.13 g. of practically pure nitroimidazole starting material and 3.79 g. of 1 - (2 - hydroxyethyl) - 2 - methyl - 5-nitroimidazole, m.p. 152—153°C., which after one recrystallisation from methanol-ethyl acetate melted at 161°C. The yield was 65.5% based on the unrecovered starting material.

EXAMPLE VI

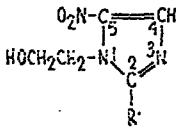
Ethylene oxide (30 g.) was bubbled over a period of 45 minutes into an agitated suspension of 4 (or 5)-nitroimidazole (11.3 g.) in 85% formic acid (100 ml.), the temperature being maintained between 10° and 20°C. Agitation was then continued for 3 hours, the temperature being kept between 25° and 30°C. The solvent was then removed *in vacuo*, first under a pressure of 20 mm. Hg and then under 1—2 mm. Hg. The partially crystalline oily residue was then treated with water (10 ml.) and the insoluble residue removed by filtration. There was thus recovered 6.8 g. (60%) of unreacted 4(or 5)-nitroimidazole. The filtrate obtained above was made alkaline to pH 9—10 by the addition of an aqueous solution of sodium hydroxide (d = 1.33), the temperature being kept below 20°C., and extracted 10 times with methylene chloride (total 500 ml.). The organic solution was dried over anhydrous potassium carbonate and evaporated to dryness yielding an oily residue (5.1 g.) consisting of crude 1 - (2 - hydroxyethyl) - 5 - nitroimidazole. The above residue was dissolved in acetone (40 ml.) and treated with a 2.5N ethereal solution of anhydrous hydrogen chloride. The hydrochloride crystallised and was separated by filtration, washed with a 1:1 mixture of acetone and diethyl ether and dried. There was thus obtained 1 - (2 - hydroxyethyl) - 5-nitroimidazole hydrochloride (3.7 g.) as a cream-coloured powder, m.p. 135—140°C.

The base was isolated by dissolving the hydrochloride in distilled water (5 ml.), adding an aqueous solution of sodium hydroxide (d = 1.33, 3 ml.), extracting several times with methylene chloride (total 150 ml.) and evaporating the organic solution to dryness. There was thus obtained 1 - (2 - hydroxyethyl) - 5-nitroimidazole (2.3 g.) as a light yellow crystalline powder, m.p. 93—95°C. The yield was 37% based on unrecovered starting material.

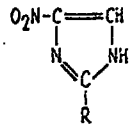
Recrystallisation from isopropanol gave a product, m.p. 99—100°C.

WHAT WE CLAIM IS:—

1. A process for the preparation of a 1-(2-hydroxyethyl)-5-nitroimidazole of the general formula:



(wherein R represents a hydrogen atom, or an alkyl group containing up to five carbon atoms, or an aryl, aralkyl or alicyclic group) or an acid addition salt thereof which comprises reacting ethylene oxide with a nitroimidazole of the general formula:



(wherein R is as hereinbefore defined) in solution in a liquid medium containing or consisting of at least one organic acid which is a solvent for the nitroimidazole, and recovering the 1 - (2 - hydroxyethyl) - 5 - nitroimidazole product from the reaction mixture in the form of the free base or as an acid addition salt.

2. A process according to claim 1 wherein the nitroimidazole starting material is in solution in an aliphatic carboxylic acid, or a mixture of aliphatic carboxylic acids.

3. A process according to claim 2 wherein the aliphatic carboxylic acid is formic acid.

4. A process according to claim 1 or 2 wherein the nitroimidazole starting material is in solution in a mixture of formic acid and acetic acids.

5. A process according to claim 1, 2, 3 or 4 wherein the liquid solvent medium for the nitroimidazole starting material includes water.

6. A process according to any one of the preceding claims wherein the molar equivalent of acid solvent in the reaction mixture is greater than the molar equivalent of nitroimidazole starting material.

7. A process according to any one of the preceding claims wherein the molecular ratio of ethylene oxide to nitroimidazole reactant is greater than 1:1.

8. A process according to claim 7 wherein

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methanol-ethyl acetate melted at 161°C. The yield was 99% based on unrecovered starting material.

EXAMPLE IV

Ethylene oxide (11 g.) was introduced slowly into a solution of 2 - methyl - 4(or 5) - nitroimidazole (6.35 g.) in a 1:1 mixture of formic and acetic acids (50 ml.). After standing at room temperature for 2½ hours, the reaction mixture was worked up as in Example I. There were recovered 0.52 g. of practically pure nitroimidazole starting material and 6.29 g. of 1 - (2 - hydroxyethyl) - 2 - methyl - 5 - nitroimidazole, m.p. 153—5°C., which after one recrystallisation from methanol-ethyl acetate melted at 161°C. The yield was 60.1% based on unrecovered starting material.

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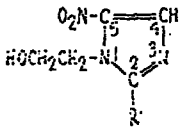
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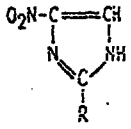
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(wherein R represents a hydrogen atom, or an alkyl group containing up to five carbon atoms, or an aryl, aralkyl or alicyclic group) or an acid addition salt thereof which comprises reacting ethylene oxide with a nitroimidazole of the general formula:



(wherein R is as hereinbefore defined) in solution in a liquid medium containing or consisting of at least one organic acid which is a solvent for the nitroimidazole, and recovering the 1 - (2 - hydroxyethyl) - 5 - nitroimidazole product from the reaction mixture in the form of the free base or as an acid addition salt.

2. A process according to claim 1 wherein the nitroimidazole starting material is in solution in an aliphatic carboxylic acid, or a mixture of aliphatic carboxylic acids.

3. A process according to claim 2 wherein the aliphatic carboxylic acid is formic acid.

4. A process according to claim 1 or 2 wherein the nitroimidazole starting material is in solution in a mixture of formic acid and acetic acids.

5. A process according to claim 1, 2, 3 or 4 wherein the liquid solvent medium for the nitroimidazole starting material includes water.

6. A process according to any one of the preceding claims wherein the molar equivalent of acid solvent in the reaction mixture is greater than the molar equivalent of nitroimidazole starting material.

7. A process according to any one of the preceding claims wherein the molecular ratio of ethylene oxide to nitroimidazole reactant is greater than 1:1.

8. A process according to claim 7 wherein

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the molecular ratio of ethylene oxide to nitroimidazole reactant is 3 to 5 : 1.

9. A process according to any one of claims 1 to 8 wherein the reaction between ethylene oxide and the nitroimidazole is carried out at a temperature between 10° and 40°C.

10. A process according to claim 9 wherein the reaction is carried out at a temperature between 20° and 30°C.

11. A process for the preparation of 1-(2-hydroxyethyl) - 5 - nitroimidazoles of the formula defined in claim 1 substantially as hereinbefore described with especial reference to any one of Examples I to V.

12. 1 - (2 - Hydroxyethyl) - 5 - nitroimidazoles of the formula defined in claim 1, and acid addition salts thereof, when prepared by a process claimed in any one of claims 1 to 11.

13. 1 - (2 - Hydroxyethyl) - 2 - methyl - 5-nitroimidazole, and acid addition salts thereof, when prepared by a process claimed in any one of claims 1 to 11.

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## ERRATUM

SPECIFICATION No. 992,168
Amendment No. 1

Page 3, line 104, *delete* "acid" *after* "formic"

THE PATENT OFFICE
*29th June 1965*

