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PATENT SPECIFICATION

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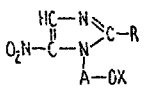
COMPLETE SPECIFICATION

New Imidazole Derivatives and processes for their preparation

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French body corporate, of 21 rue Jean-Goujon, Paris, 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 new imidazole derivatives and processes for their preparation.

According to the present invention there are provided new imidazoles conforming to the general formula:



(wherein R represents an alkyl group containing up to five carbon atoms (preferably methyl or ethyl), A represents a divalent saturated straight or branched chain aliphatic hydrocarbon group containing two to four carbon atoms and X represents a hydrogen atom or an acyl group, e.g. acetyl, dichloracetyl, stearoyl, cinnamoyl or salicyloyl) and acid addition salts thereof.

According to a feature of the present invention, compounds of the aforesaid general formula in which X is a hydrogen atom, are prepared by reacting in the absence of a basic condensing agent a 4(or 5) - nitroimidazole with a compound of the general formula Z—A—OY (wherein Z represents the acid residue of a reactive ester, such as a halogen atom or a sulphuric or sulphonic ester residue, Y represents a hydrogen atom or a radical which is readily replaceable by a hydrogen atom, for example a tetrahydropyranyl or benzyl group, and A is as hereinbefore defined) and, where Y is other than a hydrogen atom, liberating the hydroxyl group by known methods, e.g. by acid hydrolysis when Y is tetrahydropyranyl or benzyl.

According to a further feature of the present invention, compounds of the aforesaid general formula in which X is an acyl group, are prepared from the corresponding alcohols (X = H) by known methods of esterification, in particular, by the action of an acid chloride in the presence of pyridine.

By the words "known methods" as used in this specification and accompanying claims is meant methods heretofore employed or described in the chemical literature.

The imidazole derivatives of the aforesaid formula possess valuable chemotherapeutic properties; in particular, they have utility in the treatment of infections due to pathogenic protozoa such as certain species of amoebae (~~for example~~ *Endamoeba histolytica*) ~~or~~ trichomonas (for example *Trichomonas vaginalis*). They have a very low toxicity.

For therapeutic purposes, the new imidazoles are preferably employed as such or in the form of acid addition salts containing anions which are relatively innocuous to the animal organism in therapeutic doses of the salts (such as hydrochlorides and other hydrohalides, phosphates, nitrates, sulphates, maleates, fumerates, citrates, tartrates, methanesulphonates and ethanedisulphonates) so that the beneficial physiological properties inherent in the bases are not vitiated by side-effects ascribable to the anions.

The following Examples illustrate the invention; the melting points specified were determined on the Kofler bench.

EXAMPLE I

2 - Methyl - 4(or 5) - nitroimidazole (127 g.) is heated with ethylene chlorohydrin (795 g.) for 18 hours at 128—130° C. and the excess chlorohydrin (660 g.) is then distilled under reduced pressure (30 mm. Hg.). The residue is treated with water (300 cc.) and filtered, and the filtrate is made alkaline by the addition of sodium hydroxide solution (d = 1.33, 100 cc.). It is then extracted with chloroform (1,000 cc.) and, after evaporation of the chloroform *in vacuo*, there is obtained a pasty mass (77 g.) which is recrystallised from ethyl acetate (450 cc.) in the presence of

[*Price 3s. 6d.*]

Price 4s 6d

animal charcoal. There is thus obtained 1 - (2 - hydroxylethyl) - 2 - methyl - 5 - nitroimidazole (24 g.) as a creamy white crystalline powder melting at 158—160° C.

EXAMPLE II

2 - Methyl - 4(or 5) - nitroimidazole (12.7 g.) and 3 - benzyloxypropyl toluene - *p* - sulphonate (32 g.) (m.p. 33° C.) are heated for 2 hours at 135° C. When the reaction is complete, the reaction mixture is cooled to 25° C. and then agitated with hydrochloric acid (50 cc.). The 3 - benzyloxypropyl toluene - *p* - sulphonate which has not reacted is extracted with ether and the acid liquors are made alkaline with potassium carbonate. The suspension obtained is filtered to remove unreacted 2 - methyl - 4(or 5) - nitroimidazole starting material which is washed several times with water and then with chloroform. The chloroformic extracts are combined, dried over anhydrous potassium carbonate and then evaporated under reduced pressure. A crude oily product (22 g.) is obtained.

The crude product is dissolved in 15% hydrochloric acid (110 cc.) and debenzylation is effected by heating this solution for 5 hours under reflux. After cooling, the solution is extracted several times with chloroform and the acid liquors are then made alkaline with potassium carbonate. They are then extracted several times with chloroform and the chloroformic solutions are combined, dried over anhydrous potassium carbonate and then evaporated under reduced pressure. A crude oily product (22 g.) is obtained.

By the addition of ethereal hydrogen chloride to a solution of the base in acetone followed by recrystallisation from a mixture of ethanol and ether of the crystals obtained, there is finally obtained 1 - (3 - hydroxypropyl) - 2 - methyl - 5 - nitroimidazole hydrochloride (4 g.), m.p. 115° C.

EXAMPLE III

2 - Ethyl - 4(or 5) - nitroimidazole (23.8 g.) and benzyloxyethyl toluene - *p* - sulphonate (51.7 g.) (m.p. 43° C.) are heated for 3 hours at 135° C. After treatment of the reaction products as in Example I a crude oily product (26.2 g.) is obtained which is debenzylated by boiling in 15% hydrochloric acid (130 cc.). On treatment of the hydrochloric acid solution a crude crystalline base (8.2 g.) is obtained which is purified by recrystallisation from a mixture of ethyl acetate and heptane. There is finally isolated 1 - (2 - hydroxyethyl) - 2 - ethyl - 5 - nitroimidazole (7.25 g.), m.p. 87—88° C.

EXAMPLE IV

1 - (2 - Hydroxyethyl) - 2 - methyl - 5 - nitroimidazole (8.55 g.) is suspended in anhydrous chloroform (100 cc.). Anhydrous pyridine (4.15 g.) is added and, after cooling to 5° C., dichloroacetyl chloride (7.75 g.) is added dropwise over 20 minutes. When the addition is complete, the temperature is allowed to rise to 15° C. and the mixture is then boiled for 1 hour. The chloroform solution is then cooled and washed several times with water. After evaporation of the solvent the crude ester obtained is purified by successive recrystallisations from a mixture of benzene and heptane and then from di-*iso*propyl ether.

There is finally obtained 1 - (2 - dichloroacetoxyethyl) - 2 - methyl - 5 - nitroimidazole (7.2 g.), m.p. 86—87° C.

EXAMPLE V

Proceeding as in Example IV but commencing with 1 - (2 - hydroxyethyl) - 2 - methyl - 5 - nitroimidazole (8.55 g.), anhydrous pyridine (4.15 g.) dissolved in chloroform (100 cc.) and acetyl chloride (4.13 g.), a crude ester (8.25 g.) is obtained which is purified by recrystallisation from di - *iso*propyl ether. There is finally obtained 1 - (2 - acetoxyethyl) - 2 - methyl - 5 - nitroimidazole (6.4 g.), m.p. 74° C.

EXAMPLE VI

Proceeding as in Example IV but commencing with 1 - (2 - hydroxyethyl) - 2 - methyl - 5 - nitroimidazole (6.85 g.), anhydrous pyridine (3.32 g.) dissolved in anhydrous chloroform (80 cc.) and stearoyl chloride (12.7 g.), a crude ester (14.5 g.) is obtained which is purified by successive recrystallisations from petroleum ether. There is finally obtained 1 - (2 - stearoyloxyethyl) - 2 - methyl - 5 - nitroimidazole (6.1 g.), m.p. 51° C.

EXAMPLE VII

Proceeding as in Example IV but commencing with 1 - (2 - hydroxyethyl) - 2 - methyl - 5 - nitroimidazole (8.55 g.), anhydrous pyridine (4.15 g.) dissolved in anhydrous chloroform (100 cc.) and cinnamoyl chloride (8.75 g.), a crude ester (10.9 g.) is obtained, which is purified by successive recrystallisation from a mixture of ethyl acetate and heptane and from di - *iso*propyl ether. There is finally obtained 1 - (2 - cinnamoyloxyethyl) - 2 - methyl - 5 - nitroimidazole (6.7 g.), m.p. 100° C.

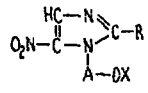
EXAMPLE VIII

1 - (2 - Hydroxyethyl) - 2 - methyl - 5 - nitroimidazole (8.55 g.) is suspended in anhydrous chloroform (100 cc.). Anhydrous pyridine (4.15 g.) is added and, after cooling to 5° C., salicyloyl chloride (8.4 g.) is added dropwise over 50 minutes, the temperature being kept below 5° C. After the addition the temperature is kept at 5° C. for 1 hour and the mixture is then agitated at room temperature for 19 hours. Water (60 cc.) is then added to the solution and a white precipitate is formed which is separated and some of the initial 1 - (2 - hydroxyethyl) - 2 - methyl - 5 - nitroimidazole is thus recovered. The filtrate is decanted and the chloroform solutions are washed several times with water and then with a 10% solution of sodium bicarbonate. After drying the chloroform solution over an-

hydrous sodium sulphate and evaporating the solvent, a crude oily base (9.7 g.) is obtained. After dissolving the latter in benzene and repeatedly extracting the solution with 15% hydrochloric acid, the acid fractions are combined and make alkaline with potassium carbonate. They are then extracted several times with chloroform and the combined chloroformic solutions are dried over anhydrous sodium sulphate. After evaporation of the solvent, the crude base obtained is purified by dissolving it in ethanol and adding ethereal hydrogen chloride. There is finally obtained 1 - (2 - salicyloyloxyethyl) - 2 - methyl - 5 - nitroimidazole hydrochloride, m.p. 154° C.

WHAT WE CLAIM IS:—

1. Imidazole derivatives of the general formula:



(wherein R represents an alkyl group containing up to five carbon atoms, A represents a divalent saturated straight or branched chain aliphatic hydrocarbon group containing two to four carbon atoms and X represents a hydrogent atom or an acyl group) and acid addition salts thereof.

2. Imidazoles according to claim 1 wherein R represents a methyl or ethyl group.

3. Imidazoles according to claim 1 or 2 wherein X represents an acetyl, dichloracetyl, stearoyl, cinnamoyl or salicyloyl group.

4. 1 - (2 - Hydroxyethyl) - 2 - methyl - 5 - nitroimidazole and its acid addition salts.

5. 1 - (3 - Hydroxypropyl) - 2 - methyl - 5 - nitroimidazole and its acid addition salts.

6. 1 - (2 - Hydroxyethyl) - 2 - ethyl - 5 - nitroimidazole and its acid addition salts.

7. 1 - (2 - Dichloroacetoxyethyl) - 2 - methyl - 5 - nitroimidazole and its acid addition salts.

8. 1 - (2 - Acetoxyethyl) - 2 - methyl - 5 - nitroimidazole and its acid addition salts.

9. 1 - (2 - Stearoyloxyethyl) - 2 - methyl - 5 - nitroimidazole and its acid addition salts.

10. 1 - (2 - Cinnamoyloxyethyl) - 2 - methyl - 5 - nitroimidazole and its acid addition salts.

11. 1 - (2 - Salicyloyloxyethyl) - 2 - methyl - 5 - nitroimidazole and its acid addition salts.

12. Process for the preparation of the imidazoles claimed in claim 1 in which X is a hydrogen atom which comprises reacting in the absence of a basic condensing agent a 4(or 5) - nitroimidazole with a compound of the general formula Z—A—OY (wherein Z represents the acid residue of a reactive ester, Y represents a hydrogen atom or a radical which is readily replaceable by a hydrogen atom, and A is as defined in claim 1) and, where Y is other than a hydrogen atom, liberating the hydroxyl group by known methods.

13. Process according to claim 12 wherein Y represents a tetrahydropyranyl or benzyl group and the product obtained is subjected to acid hydrolysis to liberate the hydroxyl group.

14. Process for the preparation of the imidazoles claimed in claim 1 in which X is an acyl group which comprises esterifying by known methods an alcohol as prepared by the process of claim 12 or 13.

15. Process according to claim 14 wherein esterification is effected by the action of an acid chloride on said alcohol in the presence of pyridine.

16. Process for the preparation of imidazoles as claimed in claim 1 substantially as described in any one of the foregoing Examples.

17. Imidazoles as defined in claim 1 when prepared by a process claimed in any one of claims 12 to 16.

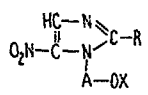
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WHAT WE CLAIM IS:—

1. Imidazole derivatives of the general formula:



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7. 1 - (2 - Dichloroacetoxyethyl) - 2 - methyl - 5 - nitroimidazole and its acid addition salts.

8. 1 - (2 - Acetoxyethyl) - 2 - methyl - 5 - nitroimidazole and its acid addition salts.

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11. 1 - (2 - Salicyloyloxyethyl) - 2 - methyl - 5 - nitroimidazole and its acid addition salts.

12. Process for the preparation of the imidazoles claimed in claim 1 in which X is a hydrogen atom which comprises reacting in the absence of a basic condensing agent a 4(or 5) - nitroimidazole with a compound of the general formula Z—A—OY (wherein Z represents the acid residue of a reactive ester, Y represents a hydrogen atom or a radical which is readily replaceable by a hydrogen atom, and A is as defined in claim 1) and, where Y is other than a hydrogen atom, liberating the hydroxyl group by known methods.

13. Process according to claim 12 wherein Y represents a tetrahydropyranyl or benzyl group and the product obtained is subjected to acid hydrolysis to liberate the hydroxyl group.

14. Process for the preparation of the imidazoles claimed in claim 1 in which X is an acyl group which comprises esterifying by known methods an alcohol as prepared by the process of claim 12 or 13.

15. Process according to claim 14 wherein esterification is effected by the action of an acid chloride on said alcohol in the presence of pyridine.

16. Process for the preparation of imidazoles as claimed in claim 1 substantially as described in any one of the foregoing Examples.

17. Imidazoles as defined in claim 1 when prepared by a process claimed in any one of claims 12 to 16.

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