

PATENT SPECIFICATION

NO DRAWINGS

1079,271



1079,271

Date of Application and filing Complete Specification: Oct. 8, 1964.

No. 41137/64.

Application made in France (No. 950193) on Oct. 10, 1963.

(Patent of Addition to No. 836854 dated May 6, 1958).

Complete Specification Published: Aug. 16, 1967.

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Index at acceptance: —C2 C2B30

Int. Cl.: —C 07 d 49/36

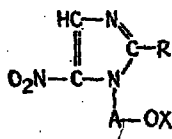
COMPLETE SPECIFICATION

Imidazole Derivatives

We, RHONE-POULENC S.A. a French Body Corporate of 22, Avenue Montaigne, 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 imidazole derivatives, to processes for their preparation and pharmaceutical preparations containing them. It is an improvement in or modification of the invention described and claimed in the Specification of our Patent No. 836854.

In the Specification of our Patent No. 836,854 there are described and claimed imidazoles conforming to the general formula:



I

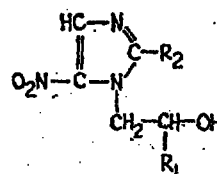
wherein R represents an alkyl group containing up to 5 carbon atoms, A represents a divalent saturated straight or branched chain aliphatic hydrocarbon group containing 2 to 4 carbon atoms, and X represents a hydrogen atom or an acyl group, and acid addition salts thereof. It is stated in the specification that the compounds possess chemotherapeutic properties and are useful in the treatment of infections due to pathogenic protozoa such as certain species of amoebae or trichomonas. All the imidazole compounds specifically described in the patent specification are of the type wherein symbol A represents an unsubstituted ethylene or trimethylene chain.

It has now been found after further research and experimentation that compounds of

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formula I in which A represents an ethylene group substituted by an alkyl group containing 1 to 6 carbon atoms, X represents hydrogen and R represents a hydrogen atom or an alkyl group as mentioned above, possess chemotherapeutic, in particular amoebicidal and trichomonacidal, properties to about the same degree of activity as the corresponding imidazoles of formula I in which the grouping —A—OX is 2-hydroxyethyl or 3-hydroxypropyl.

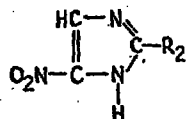
According to the present invention, therefore, there are provided the hitherto unknown imidazole derivatives of the formula:



II

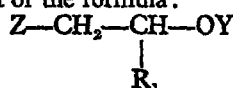
wherein R₁ represents an alkyl group containing 1 to 6 carbon atoms and R₂ represents a hydrogen atom or an alkyl group containing up to 5 carbon atoms, and acid addition salts thereof. As the compounds of formula II possess an asymmetric carbon atom, they can exist in three stereoisomeric forms, i.e. two optically active forms and a racemic form. The invention includes within its scope these three forms of each imidazole derivative. Preferred compounds are those in which R₂ represents an alkyl (preferably methyl or ethyl) group and R₁ represents methyl or ethyl, and in particular 1 - (2 - hydroxypropyl) - 2 - methyl - 5 - nitroimidazole and 1 - (2 - hydroxybutyl) - 2 - methyl - 5 - nitroimidazole, which are outstanding as trichomonocides.

According to a feature of the invention, the imidazole derivatives of formula II are prepared by the process which comprises reacting in the absence of a basic condensing agent a nitroimidazole of the formula:



III

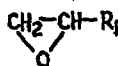
(where R_2 is as hereinbefore defined) with a compound of the formula:



IV

(wherein Z represents the acid residue of a reactive ester, such as a halogen atom or a sulphuric acid residue, e.g. the methoxy-sulphonyloxy group, or a sulphonic acid residue, e.g. the toluene - *p* - sulphonyloxy group, Y represents hydrogen or a radical which protects the hydroxyl group during the reaction and is readily replaceable by a hydrogen atom, for example a tetrahydropyranyl or benzyl group, and R_1 is as hereinbefore defined) and, where Y is other than a hydrogen atom, liberating the hydroxyl group by methods known *per se*, e.g. by acid hydrolysis when Y is tetrahydropyranyl or benzyl.

According to a further feature of the invention, the imidazole derivatives of formula I are prepared by a better process which comprises reacting a 1,2 - alkyleneoxide of the formula:



V

(wherein R_1 is as hereinbefore defined) with a nitroimidazole of formula III in solution in a liquid medium containing or consisting of at least one organic acid which is a solvent for the nitroimidazole starting material, and recovering the 1 - (2 - alkyl - 2 - hydroxyethyl) - imidazole product of formula II from the reaction mixture.

The reaction is preferably carried out at room temperature, viz. within the range of 20 to 30°C., but temperatures lower or higher than room temperature, for example 10 to 50°C., may be used. The preferred organic solvents are saturated aliphatic carboxylic acids containing up to 4 carbon atoms; in particular formic and acetic acids. Mixtures of organic acid solvents, such as formic acid with acetic acid, may be employed. The liquid reaction medium may consist solely of the organic acid or acids, or of the acid or acids diluted with water or

another acceptable diluent, for example methanol. The amount of organic acid or mixture of acids present in the reaction mixture should be such as to ensure complete solution of the nitroimidazole starting material at room temperature. The alkyleneoxide reactant is preferably used in excess; advantageously 3 to 6 moles of alkyleneoxide are employed per mole of nitroimidazole reactant.

The condensation product is isolated from the reaction mixture by methods known *per se*, for example by eliminating the excess alkyleneoxide and the acid solvent, followed by purification of the residue by crystallisation or by any other suitable procedure. Any unreacted nitroimidazole of formula III can be recovered easily.

The imidazole derivatives of formula II may be converted by methods known *per se* into acid addition salts. Thus, the acid addition salts may be obtained by the action of an acid on the imidazole derivative in an appropriate solvent such as an alcohol, an ether, a ketone, or water. The acid addition salt which is formed is precipitated, if necessary after concentration of its solution, and is separated by filtration or decantation.

By the term "methods known *per se*" as used in this specification and accompanying claims is meant methods heretofore used or described in the chemical literature.

For therapeutic purposes the bases of formula II are employed as such or in the form of non-toxic acid addition salts, i.e. 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, acetates, propionates, succinates, benzoates, fumarates, maleates, citrates, tartrates, methanesulphonates, ethanedisulphonates, methylene - bis - β - hydroxy - naphthoates and gentisates) 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.

EXAMPLE I

Propylene oxide (290 g.) is added over a period of 1½ hours to a solution of 2 - methyl - 5 - nitroimidazole (127 g.) in 85% formic acid (1 l.) cooled to 13°C. During the addition the temperature of the reaction mixture is kept constant at about 14°C. The mixture is left overnight at room temperature, and then formic acid (860 cc.) is distilled off under reduced pressure (20 mm. Hg). A product crystallises out from the residue. Water (100 cc.) is then added and the crystals filtered off, washed with water (200 cc.) and dried until their weight remains constant. 2 - Methyl - 5 - nitroimidazole (75.5 g.), m.p. 254—256°C., is thus recovered.

The washing liquors and the filtrate are combined, and 10N sodium hydroxide (220 cc.) is added slowly so that a pH of 9 is never exceeded. On completion of the addition, a product crystallises out. The mass is left overnight in a refrigerator, the crystals filtered off, washed with ice-water (50 cc.) and dried under reduced pressure (20 mm. Hg) to yield a compound, (41.2 g.) melting at 72—74°C. On recrystallisation from toluene (410 cc.) and, after filtering, washing and drying, there is obtained 1 - (2 - hydroxypropyl) - 2 - methyl - 5 - nitroimidazole (36 g.) melting at 76°C.

EXAMPLE II

1,2 - Epoxy - n - butane (19 g.) is added over a period of 20 minutes to a solution of 2 - methyl - 5 - nitroimidazole (6.7 g.) in 85% formic acid (50 cc.) while keeping the temperature between 5 and 10°C. The mixture is then left for 16 hours at room temperature, and afterwards concentrated to dryness under a pressure of about 30 mm. Hg. The residue is treated with ice-water (5 cc.), filtered, washed with water and the insoluble material dried. There is thus recovered 2 - methyl - 5 - nitroimidazole (4.95 g.).

The filtrate and the washing liquors are combined, made alkaline to a pH of 8 to 9 by addition of 10N sodium hydroxide (20 cc.) and left to stand for 16 hours at 0°C. The small amount of precipitate formed is removed by filtration and the filtrate extracted with diethyl ether (250 cc.). After drying the ethereal extracts over anhydrous potassium carbonate and concentration to dryness, a brown oil (16.3 g.) is obtained.

The oil is redissolved in 2.5N hydrochloric acid (25 cc.), the solution washed with diethyl ether, made alkaline to pH 8—9 with potassium carbonate (5.5 g.), the free base extracted with diethyl ether (150 cc.), and the ethereal solution dried over anhydrous potassium carbonate and concentrated to dryness to yield the purified light-brown oil base (10.4 g.).

The oily base is dissolved in anhydrous diethyl ether (10 cc.) and the hydrochloride precipitated in the form of a gum by the addition of a 3N solution (10 cc.) of hydrochloric acid in anhydrous diethyl ether. The hydrochloride is washed with diethyl ether, dissolved in water (10 cc.) and the picrate of the base precipitated in crystalline form by the addition of a 0.3N aqueous solution of lithium picrate (75 cc.). After filtering, washing with water, drying and recrystallisation from ethanol, the picrate of 1 - (2 - hydroxybutyl) - 2 - methyl - 5 - nitroimidazole (3.7 g.) is obtained as a yellow crystalline powder, m.p. 133—134°C.

The picrate is reconverted to the hydrochloride by treatment with 2N hydrochloric acid (25 cc.) and extracting the liberated

picric acid with nitrobenzene (250 cc.). After concentration to dryness of the aqueous phase, there is obtained 1 - (2 - hydroxybutyl) - 2 - methyl - 5 - nitroimidazole hydrochloride (1.6 g.) which, after recrystallisation from isopropanol, is in the form of a white crystalline powder melting at 157—158°C.

The present invention includes within its scope pharmaceutical preparations containing, as active ingredient, at least one of the imidazole derivatives of formula II, or non-toxic acid addition salt thereof, in association with a pharmaceutical carrier or coating. The invention includes especially such preparations made up for oral, parenteral or local administration.

Solid compositions for oral administration include tablets, pills, dispersible powders, and granules. In such solid compositions one or more of the active compounds is, or are, admixed with at least one inert diluent such as calcium carbonate, wheat or potato starch, alginic acid, sucrose or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate, and wetting, sweetening and flavouring agents. Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water and liquid paraffin. Besides inert diluents such compositions may also comprise adjuvants, such as wetting and suspending agents, and sweetening, flavouring and preserving agents. The compositions according to the invention, for oral administration, also include capsules of absorbable material such as gelatin containing one or more of the active substances with or without the addition of diluents or excipients.

Preparations according to the invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil, and injectable organic esters such as ethyl oleate. These compositions may also contain adjuvants such as preserving, wetting, emulsifying and dispersing agents. They may be sterilised by, for example, filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilising agents, by irradiation, or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

The preparations for local or topical administration may be in a variety of forms. Most frequently they are formulated as vaginal tablets or ovules which may also contain, in addition to the active ingredient or ingredients, inert diluents and lubricants identical with

those incorporated in preparations for oral administrations, or they may contain substances that facilitate the diffusion of the medicament *in situ*, such as sodium bicarbonate or magnesium carbonate.

The percentage of active ingredient in the preparations of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. The dosage depends on the desired therapeutic effect, on the route of administration and on the duration of the treatment. For oral administration to an adult suffering from trichomoniasis the dosage is generally 0.1 to 1 g. of active substance per day, while for vaginal administration it may vary from 0.25 to 1 g. per day.

The following Example illustrates pharmaceutical preparations according to the invention.

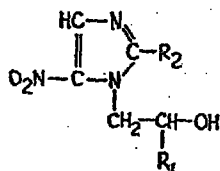
EXAMPLE III

Tablets having a unitary composition as indicated below are formulated by the usual methods of mixing the ingredients and tableting:

1 - (2 - hydroxypropyl) - 2 - methyl - 5 - nitroimidazole	0.250 g.
wheat starch	0.220 g.
colloidal silica	0.026 g.
magnesium stearate	0.004 g.

WHAT WE CLAIM IS:—

1. Imidazole derivatives of the general formula:



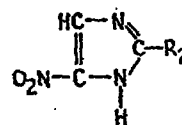
wherein R_2 represents a hydrogen atom or an alkyl group containing 1 to 5 carbon atoms, and R_1 represents an alkyl group containing 1 to 6 carbon atoms, and acid addition salts thereof.

2. Imidazole derivatives according to claim 1 wherein R_2 represents an alkyl group, and R_1 represents methyl or ethyl.

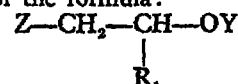
3. 1 - (2 - Hydroxypropyl) - 2 - methyl - 5 - nitroimidazole and acid addition salts thereof.

4. 1 - (2 - Hydroxybutyl) - 2 - methyl - 5 - nitroimidazole and acid addition salts thereof.

5. Process for the preparation of imidazole derivatives as claimed in claim 1 which comprises reacting in the absence of a basic condensing agent a nitroimidazole of the formula:



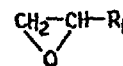
(wherein R_2 is as defined in claim 1) with a compound of the formula:



(wherein Z represents the acid residue of a reactive ester, Y represents a hydrogen atom or a radical which protects the hydroxyl group during the reaction, and is readily replaceable by a hydrogen atom, and R_1 is as defined in claim 1) and, where Y is other than a hydrogen atom, liberating the hydroxyl group by methods known *per se*.

6. Process according to claim 5 wherein Y represents a tetrahydropyranyl or benzyl group and the product obtained is subjected to acid hydrolysis to liberate the hydroxyl group.

7. A modification of the process claimed in claim 5 which comprises reacting a 1,2 - alkyleneoxide of the formula:



(wherein R_1 is as defined in claim 1) with a nitroimidazole of the formula specified in claim 5 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 - alkyl - 2 - hydroxyethyl)imidazole product from the reaction mixture.

8. Process according to claim 7 wherein the reaction is effected at a temperature within the range 10 to 50°C.

9. Process according to claim 8 wherein the temperature is 20° to 30°C.

10. Process according to claim 7, 8 or 9 wherein the nitroimidazole is in solution in a saturated aliphatic carboxylic acid, or a mixture of saturated aliphatic carboxylic acids, the acid or acids containing up to 4 carbon atoms.

11. Process according to claim 10 wherein the aliphatic carboxylic acid is formic acid.

12. Process according to claim 10 wherein the nitroimidazole is in solution in a mixture of formic and acetic acids.

13. Process according to any one of claims 7 to 12 wherein the liquid solvent medium for the nitroimidazole starting material includes water.



those incorporated in preparations for oral administrations, or they may contain substances that facilitate the diffusion of the medicament *in situ*, such as sodium bicarbonate or magnesium carbonate.

The percentage of active ingredient in the preparations of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. The dosage depends on the desired therapeutic effect, on the route of administration and on the duration of the treatment. For oral administration to an adult suffering from trichomoniasis the dosage is generally 0.1 to 1 g. of active substance per day, while for vaginal administration it may vary from 0.25 to 1 g. per day.

The following Example illustrates pharmaceutical preparations according to the invention.

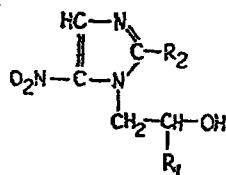
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colloidal silica	0.026 g.
magnesium stearate	0.004 g.

WHAT WE CLAIM IS:—

1. Imidazole derivatives of the general formula:



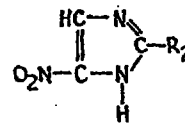
wherein R_2 represents a hydrogen atom or an alkyl group containing 1 to 5 carbon atoms, and R_1 represents an alkyl group containing 1 to 6 carbon atoms, and acid addition salts thereof.

2. Imidazole derivatives according to claim 1 wherein R_2 represents an alkyl group, and R_1 represents methyl or ethyl.

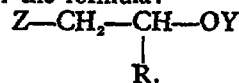
3. 1 - (2 - Hydroxypropyl) - 2 - methyl - 5 - nitroimidazole and acid addition salts thereof.

4. 1 - (2 - Hydroxybutyl) - 2 - methyl - 5 - nitroimidazole and acid addition salts thereof.

5. Process for the preparation of imidazole derivatives as claimed in claim 1 which comprises reacting in the absence of a basic condensing agent a nitroimidazole of the formula:



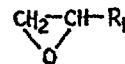
(wherein R_2 is as defined in claim 1) with a compound of the formula:



(wherein Z represents the acid residue of a reactive ester, Y represents a hydrogen atom or a radical which protects the hydroxyl group during the reaction, and is readily replaceable by a hydrogen atom, and R_1 is as defined in claim 1) and, where Y is other than a hydrogen atom, liberating the hydroxyl group by methods known *per se*.

6. Process according to claim 5 wherein Y represents a tetrahydropyranyl or benzyl group and the product obtained is subjected to acid hydrolysis to liberate the hydroxyl group.

7. A modification of the process claimed in claim 5 which comprises reacting a 1,2 - alkyleneoxide of the formula:



(wherein R_1 is as defined in claim 1) with a nitroimidazole of the formula specified in claim 5 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 - alkyl - 2 - hydroxyethyl)imidazole product from the reaction mixture.

8. Process according to claim 7 wherein the reaction is effected at a temperature within the range 10 to 50°C.

9. Process according to claim 8 wherein the temperature is 20° to 30°C.

10. Process according to claim 7, 8 or 9 wherein the nitroimidazole is in solution in a saturated aliphatic carboxylic acid, or a mixture of saturated aliphatic carboxylic acids, the acid or acids containing up to 4 carbon atoms.

11. Process according to claim 10 wherein the aliphatic carboxylic acid is formic acid.

12. Process according to claim 10 wherein the nitroimidazole is in solution in a mixture of formic and acetic acids.

13. Process according to any one of claims 7 to 12 wherein the liquid solvent medium for the nitroimidazole starting material includes water.

14. Process according to any one of claims 7 to 13 wherein the molecular ratio of 1,2 - alkyleneoxide to nitroimidazole reactant is 3 to 6:1.
- 5 15. Process for the preparation of imidazole derivatives of the formula specified in claim 1 and acid addition salts thereof substantially as hereinbefore described with especial reference to Example I or II.
- 10 16. Imidazole derivatives of the formula specified in claim 1 and acid addition salts thereof when prepared by a process claimed in any one of claims 5 to 15.
- 15 17. Pharmaceutical preparations which comprise, as active ingredient, at least one imidazole derivative as claimed in any one of claims 1 to 4 and 16, or non-toxic acid addition salt thereof, in association with a pharmaceutical carrier or coating.
18. Pharmaceutical preparations according to claim 17 which contain 1 - (2 - hydroxypropyl) - 2 - methyl - 5 - nitroimidazole or a non-toxic acid addition salt thereof. 20
19. Pharmaceutical preparations according to claim 17 which contain 1 - (2 - hydroxybutyl) - 2 - methyl - 5 - nitroimidazole or a non-toxic acid addition salt thereof. 25
20. Pharmaceutical preparations according to claim 17 substantially as hereinbefore described with especial reference to Example III. 30
- J. A. KEMP & CO.,
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14, South Square,
Gray's Inn, London, W.C.1.

Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1967
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

ERRATA

SPECIFICATION No. 1,079,271

Page 1, line 56, for "sterioisometric" read
"sterioisomeric"

Page 4, line 78, for "nitromidazole," read
"nitroimidazole,"

THE PATENT OFFICE
2nd October 1967



* C L M S *