1,006,334

PATENT SPECIFICATION

NO DRAWINGS

1,006,334

Inventors: GRAHAM LAWSON LAW, DENNIS DAVID LIBMAN and EDGAR WILLIAM PARNELL

Date of filing Complete Specification: Oct. 28, 1963.

Application Date: Nov. 1, 1962. *No. 41455/62.*

Complete Specification Published: Sept. 29, 1965.

© *Crown Copyright 1965.*

Index at acceptance:—C2 C(1F3B, 1F3D3, 1F3E, 2B29, 2B30, 3A10E3A4, 3A10E5E, 3A10E5F1C, 3A10E5F2A, 3A13A3A4, 3A13A3B1, 3A13A3K)

Int. Cl.:—C 07 d

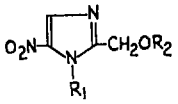
COMPLETE SPECIFICATION

Imidazole Derivatives

We, MAY & BAKER LIMITED, a British Company of Dagenham, in the County of Essex, 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 therapeutically useful imidazole derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

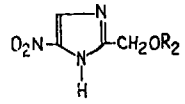
According to the present invention, there are provided the new imidazole derivatives of the formula:



I

wherein R_1 represents an alkyl group containing up to 6 carbon atoms (preferably methyl), and R_2 represents a hydrogen atom or an alkanoyl group containing up to 6 carbon atoms (preferably acetyl), and acid addition salts thereof. These imidazole compounds possess valuable therapeutic properties, particularly antiprotozoal activity, for example, against trichomoniasis and histomoniasis, and anti-bacterial activity. Preferred compounds are those in which R_2 represents a hydrogen atom, in particular, 2 - hydroxymethyl - 1-methyl - 5 - nitromidazone and its acid addition salts.

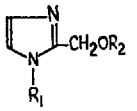
According to a feature of this invention, the imidazole derivatives of formula I are prepared by *N*-alkylating an imidazole of the formula:



II

(wherein R_2 is an hereinbefore defined) by reaction with an alkyl ester of the formula R_1X wherein X represents the acid residue of reactive ester, such as a halogen atom or a sulphuric or sulphonic ester residue, and R_1 is as hereinbefore defined. The reaction conditions employed will of course depend on the type of reactive ester used but in general the reaction may be carried out in the absence or presence of a solvent, such as an alcohol, ketone or benzene. For example, the imidazole derivatives of formula I in which R_1 represents a methyl group may be prepared by heating the corresponding compounds of formula II with dimethylsulphate.

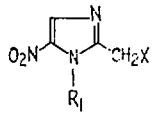
According to a further feature of the invention, the imidazole derivatives of formula I are prepared by nitrating a compound of the formula:



III

(wherein R_1 and R_2 are as hereinbefore defined) by known methods for the nitration of imidazoles, preferably by the use of a mixture of concentrated nitric and sulphuric acids. From this nitration there is obtained a mixture of two isomers in which the nitro substituent is in the 4- or 5-position of the imidazole ring. The desired imidazole product of formula I is separated from the mixture by, for example, fractional crystallisation.

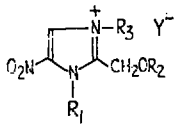
According to a still further feature of the invention, the imidazole derivatives of formula I are prepared from compounds of the formula:



IV

(wherein R_1 and X are as hereinbefore defined) by reaction with a compound of the formula $M.O.R_2$, wherein M represents an alkali metal atom, and R_2 is as hereinbefore defined.

According to another feature of the invention, the imidazole derivatives of formula I are prepared by the dequaternation of a quaternary salt of the formula:

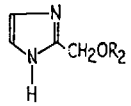


V

(wherein R_3 represents an alkyl group containing up to 6 carbon atoms, Y represents a halogen atom, and R_1 and R_2 are as hereinbefore defined), for example by heating in the presence or absence of an inert solvent.

Imidazole derivatives of formula I in which R_2 represents a hydrogen atom obtained by the aforementioned processes may, according to a still further feature of the invention, be acylated by known methods to form corresponding compounds in which R_2 is an alkanoyl group. The acylation may be effected by, for example, reaction of the 1 - alkyl - 2-hydroxymethyl - 5 - nitroimidazole with an acid anhydride, for example acetic anhydride.

The intermediates of formulae II, III, IV and V may be prepared by methods known *per se*. Thus, the imidazoles of formula II may be prepared by the nitration of compounds of the formula:

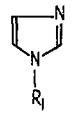


VI

(wherein R_2 is as hereinbefore defined) using a mixture of concentrated nitric and sulphuric acids.

The imidazoles of formula III may be conveniently prepared by the alkylation of a compound of formula VI with a reactive ester of the formula R_1X (R_1 and X being as hereinbefore defined) using the general reaction conditions set out above for the preparation of the imidazoles of formula I by alkylation of the compounds of formula II.

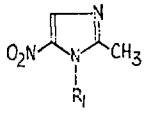
Alternatively, the compounds of formula III in which R_2 represents a hydrogen atom may be conveniently prepared by the reaction of an imidazole derivative of the formula:



VII

(wherein R_1 is as hereinbefore defined) with formaldehyde under pressure. The corresponding compounds of formula III in which R_2 represents an alkanoyl group may be prepared from those of formula III in which R_2 is a hydrogen atom by known methods of acylation.

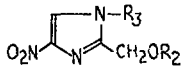
The intermediates of formula IV may be prepared from imidazoles of the formula:



VIII

wherein R_1 is as hereinbefore defined. For example, the intermediates of formula IV in which X represents a halogen atom may be prepared by the direct halogenation of a compound of formula VIII.

Intermediates of formula V may be prepared by the reaction of an imidazole of the formula:



IX

(wherein R_2 and R_3 are as hereinbefore defined) with an alkyl halide of the formula R_1Y, wherein R_1 and Y are as hereinbefore defined. The 4 - nitro compounds of formula IX may themselves be prepared by similar methods to those described above for the preparation of the isomeric compounds of formula I.

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

When the imidazole derivatives of general formula I are used for therapeutic purposes in the form of acid addition salts, it should be understood that only those such salts should in practice be employed as contain anions that are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial physiological properties inherent in the parent compounds are not viti-

ated by side-effects ascribable to those anions; in other words, only non-toxic salts are contemplated. Suitable acid adition salts are those rived from strong acids and include hydrohalides (for example, hydrochlorides), phosphates, sulphates, methanesulphonates, isethionates and ethane disulphonates. These may be made from the bases of general formula I by methods heretofore used in the art for making acid addition salts. For example, the acid addition salts may be made by mixing the base with an equivalent quantity of a non-toxic acid in a solvent and isolating the resultant salt by filtration after, if necessary, evaporation of part or all of the solvent. They may be purified by crystallisation or by any other method commonly used in the art.

The following Examples illustrate the preparation of imidazole derivatives according to the invention.

EXAMPLE I

2 - Hydroxymethyl - 4(or 5) - nitroimidazole (1.43 g.) and dimethylsulphate (0.95 ml.) were heated on a steam bath for 5 minutes to produce a clear melt. The reaction mixture was cooled, triturated with ethyl acetate, filtered and the resulting solid dissolved in water (10 ml.). The resulting aqueous solution was basified with sodium hydroxide, saturated with sodium chloride and extracted with ethyl acetate (3 × 10 ml.). The dried ethyl acetate extracts were combined and evaporated to give a solid, m.p. 92—97° C. This solid was crystallised from benzene to give 2 - hydroxymethyl - 1 - methyl - 5-nitroimidazole, as elongated prisms of m.p. 116—117° C.

The 2 - hydroxymethyl - 4(or 5) - nitroimidazole used as starting material was prepared as follows:—

2 - Hydroxymethylimidazole (19.6 g.) was dissolved with cooling in concentrated sulphuric acid (40 ml.). Nitric acid (40 ml.) was added in small portions during about 30 minutes, the mixture being heated after the first addition to initiate a vigorous reaction. After heating for a further 5 minutes when the addition was complete, the resulting solution was cooled, poured on to ice and the pH of the solution adjusted to 6.5 with sodium carbonate. The sodium sulphate which separated was filtered off and the filtrate evaporated to dryness. The residue was extracted with warm glacial acetic acid, filtered and the filtrate evaporated to dryness. The gummy residue was dissolved in water, the solution clarified with charcoal and concentrated to give the crude product. This was crystallised from ethyl acetate to give pure 2 - hydroxymethyl-4(or 5) - nitroimidazole, m.p. 155—156° C.

EXAMPLE II

2 - Hydroxymethyl - 1 - methyl - 5-nitroimidazole (obtained as described in Example I) (200 mg.), acetic anhydride (1.0 ml.) and concentrated sulphuric acid (about 0.01 ml.) were heated on the steam bath for 30 minutes and the excess anhydride was removed by evaporation under reduced pressure. The residue was treated with cold aqueous potassium carbonate solution and the solid which separated extracted with ethyl acetate. Evaporation of the ethyl acetate solution gave 2 - acetoxymethyl - 1 - methyl - 5-nitromidazole (250 mg.), m.p. 78—82° C., which crystallised from a 50:50 mixture of benzene and light petroleum (b.p. 60—80° C.) as elongated prisms (200 mg.), m.p. 81—82° C.

The present invention includes within its scope pharmaceutical compositions which comprise, as active ingredient, at least one imidazole derivative of formula I, or non-toxic acid addition salt thereof, in association with a pharmaceutical carrier. The invention includes especially compositions made up for oral or parenteral administration. In clinical practice the compounds of the present invention will normally be administered orally so that compositions suitable for oral administration are preferred.

Solid compositions for oral administration include compressed tablets, pills, dispersible powders, and granules. In such solid compositions one or more of the active compounds of the invention is or are admixed with at least one inert diluent such as calcium carbonate, potato starch, alginic acid, 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. 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 and flavouring 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 compounds of the invention with or without the addition of diluents or excipients.

For topical application the active compound may be incorporated in a suitable vehicle such as a cream, ointment, lotion or suspension, or in a pessary or ovule.

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 oil such as olive oil, and injectable organic esters such as ethyl oleate. These compositions may also contain adjuvants such as 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 percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously several unit dosage forms may be administered at about the same time.

The following Example illustrates pharmaceutical compositions according to the invention.

EXAMPLE III

Tablets were prepared in the usual manner containing the following ingredients:—

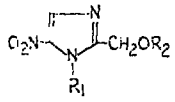
2 - hydroxymethyl - 1 - methyl - 5-nitroimidazole	78.4%
starch	14.2%
dextrin	5.5%
sodium carboxymethylcellulose	0.88%
stearic acid	0.6%
magnesium stearate	0.42%

the percentages being by weight.

Similarly there may be prepared pharmaceutical compositions in the form of tablets in which the imidazole compound specified in the preceding Examples is replaced by a like quantity of any other imidazole derivative within the scope of formula I.

WHAT WE CLAIM IS:—

1. Imidazole derivatives of the formula:



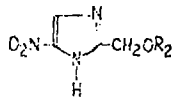
wherein R_1 represents an alkyl group containing up to 6 carbon atoms, and R_2 represents a hydrogen atom or an alkanoyl group containing up to 6 carbon atoms, and acid addition salts thereof.

2. Imidazole derivatives according to claim 1 wherein R_2 represents a hydrogen atom.

3. 2 - Hydroxymethyl - 1 - methyl - 5-nitroimidazole and acid addition salts thereof.

4. 2 - Acetoxymethyl - 1 -methyl - 5-nitroimidazole and acid addition salts thereof.

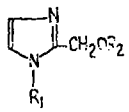
5. Process for the preparation of imidazole derivatives according to claim 1 which comprises N-alkylating an imidazole of the formula:



by reaction with an alkyl ester of the formula R_1X, wherein X represents the acid residue of reactive ester, and R_1 and R_2 are as defined in claim 1.

6. Process according to claim 5 wherein the imidazole starting material is *N*-methylated by heating with dimethylsulphate.

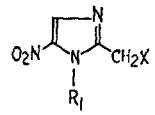
7. Process for the preparation of imidazole derivatives according to claim 1 which comprises nitrating a compound of the formula:



(wherein R_1 and R_2 are as defined in claim 1) by known methods for the nitration of imidazoles, and separating from the reaction mixture the 5-nitroimidazole product.

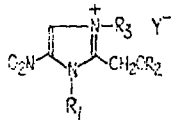
8. Process according to claim 7 wherein the nitration is effected with a mixture of concentrated nitric and sulphuric acids.

9. Process for the preparation of imidazole derivatives according to claim 1 which comprises reacting a compound of the formula:



(wherein X represents the acid residue of a reactive ester, and R_1 is as defined in claim 1) with a compound of the formula $M.O.R_2$, wherein M represents an alkali metal atom and R_2 is as defined in claim 1.

10. Process for the preparation of imidazole derivatives according to claim 1 which comprises the dequaternation of a quaternary salt of the formula:



wherein R_3 represents an alkyl group containing up to 6 carbon atoms, Y represents a halogen atom, and R_1 and R_2 are as defined in claim 1.

11. Process according to claim 10 wherein the quaternary salt is dequaternated by heating.

12. Process according to any one of claims

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 percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously several unit dosage forms may be administered at about the same time.

The following Example illustrates pharmaceutical compositions according to the invention.

EXAMPLE III

Tablets were prepared in the usual manner containing the following ingredients:—

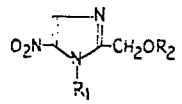
2 - hydroxymethyl - 1 - methyl - 5-nitroimidazole	78.4%
starch	14.2%
dextrin	5.5%
sodium carboxymethylcellulose	0.88%
stearic acid	0.6%
magnesium stearate	0.42%

the percentages being by weight.

Similarly there may be prepared pharmaceutical compositions in the form of tablets in which the imidazole compound specified in the preceding Examples is replaced by a like quantity of any other imidazole derivative within the scope of formula I.

WHAT WE CLAIM IS:—

1. Imidazole derivatives of the formula:



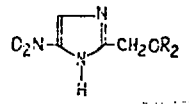
wherein R_1 represents an alkyl group containing up to 6 carbon atoms, and R_2 represents a hydrogen atom or an alkanoyl group containing up to 6 carbon atoms, and acid addition salts thereof.

2. Imidazole derivatives according to claim 1 wherein R_2 represents a hydrogen atom.

3. 2 - Hydroxymethyl - 1 - methyl - 5-nitroimidazole and acid addition salts thereof.

4. 2 - Acetoxymethyl - 1 -methyl - 5-nitroimidazole and acid addition salts thereof.

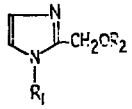
5. Process for the preparation of imidazole derivatives according to claim 1 which comprises N-alkylating an imidazole of the formula:



by reaction with an alkyl ester of the formula R_1X, wherein X represents the acid residue of reactive ester, and R_1 and R_2 are as defined in claim 1.

6. Process according to claim 5 wherein the imidazole starting material is *N*-methylated by heating with dimethylsulphate.

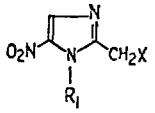
7. Process for the preparation of imidazole derivatives according to claim 1 which comprises nitrating a compound of the formula:



(wherein R_1 and R_2 are as defined in claim 1) by known methods for the nitration of imidazoles, and separating from the reaction mixture the 5-nitroimidazole product.

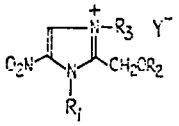
8. Process according to claim 7 wherein the nitration is effected with a mixture of concentrated nitric and sulphuric acids.

9. Process for the preparation of imidazole derivatives according to claim 1 which comprises reacting a compound of the formula:



(wherein X represents the acid residue of a reactive ester, and R_1 is as defined in claim 1) with a compound of the formula $M.O.R_2$, wherein M represents an alkali metal atom and R_2 is as defined in claim 1.

10. Process for the preparation of imidazole derivatives according to claim 1 which comprises the dequaternation of a quaternary salt of the formula:



wherein R_3 represents an alkyl group containing up to 6 carbon atoms, Y represents a halogen atom, and R_1 and R_2 are as defined in claim 1.

11. Process according to claim 10 wherein the quaternary salt is dequaternated by heating.

12. Process according to any one of claims

5 to 11 followed by the step of acylating by known methods a 1 - alkyl - 2 - hydroxymethyl - 5 - nitroimidazole product obtained to a corresponding 1 - alkyl - 2 - alkanoyloxyethyl - 5 - nitroimidazole.

13. Process according to claim 12 wherein the acylation of the 1 - alkyl - 2 - hydroxymethyl - 5 - nitroimidazole is effected by reaction with an acid anhydride.

14. Process for the preparation of imidazole derivatives as claimed in claim 1 substantially as hereinbefore described with especial reference to Example I or II.

15. Imidazole derivatives of the formula defined in claim 1 when prepared by the process claimed in any one of claims 5 to 14.

16. Pharmaceutical compositions which comprise, as active ingredient, at least one imidazole derivative as claimed in any one of claims 1 to 4 and 15, or non-toxic acid addition salt thereof, in association with a pharmaceutical carrier.

17. Pharmaceutical compositions according to claim 16 substantially as hereinbefore described with especial reference to Example III.

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

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1965. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

