

PATENT SPECIFICATION

NO DRAWINGS

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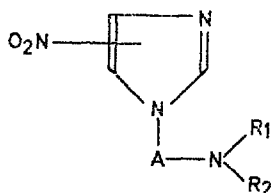
COMPLETE SPECIFICATION

New Imidazole-derivatives and their Preparation

We, CARLO ERBA S.P.A., an Italian body corporate of Via Imbonati 24, Milan, Italy, 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:—

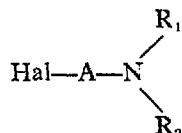
THIS INVENTION relates to certain new imidazole derivatives and to their production and use.

The new compounds have the general formula:



where A represents a straight or branched alkylene chain of 1 to 6 carbon atoms, R₁ and R₂, which may be the same or different, represent alkyl groups or together with the nitrogen atom to which they are attached from a heterocyclic ring, and the nitro group is in position 4 or 5.

These compounds can be prepared for example by reaction of metal salts, preferably sodium or silver salts, of 4(5)-nitro-imidazole with compounds of the formula:



where Hal is a halogen atom, A, R₁ and R₂ have the above meanings, in anhydrous solvents, for example xylene and toluene. The 4-nitro- and 5-nitro-isomers can be separated by fractional crystallisation.

[Price 4s. 6d.]

The invention includes also compositions comprising the new compounds in association with a pharmaceutically acceptable diluent or carrier.

Some compounds of those thus synthesized show a considerable "in vivo" and "in vitro" activity on many protozoa, particularly marked on "Trichomonas vaginalis". In addition to this, compounds of this class, such as for instance N-β-morpholinoethyl-(4(5)-nitroimidazoles, have a solubility in water much higher than that of similar products active on "Trichomonas vaginalis" such as N-β-hydroxyethyl-2-methyl-5-nitroimidazole. This makes resorption of the compounds considerably easier in "in vivo" administration, followed by quick removal so avoiding harmful accumulation phenomena. The following Examples illustrate but do not limit the invention:

EXAMPLE 1

6 g. of the sodium salt of 4(5)-nitroimidazole and 9 g. of β-chloroethylmorpholine are allowed to react in 200 ml. of dry toluene. The mixture is refluxed for 50 hours, then cooled and filtered from the solid residue. The solvent is evaporated under reduced pressure. The half-solid product thus obtained solidifies on addition of petroleum ether and diethyl ether.

Crystallization from water gives N-β-morpholinoethyl-5-nitroimidazole (m.p. 110—111° C.); from the mother liquors N-β-morpholinoethyl-4-nitroimidazole (m.p. 104—106° C.) is obtained.

EXAMPLE 2

4.2 g. of sodium salt of 4(5)-nitroimidazole and 4.02 g. of β-chloroethylpyrrolidine are refluxed in 120 ml of dry toluene for 24 hours, then the solid residue is filtered, and the solvent is evaporated under reduced pressure. The oil so obtained solidifies on addition of petroleum ether.

- Crystallization from hexane results in a mixture of N- β -pyrrolidinoethyl-5-nitroimidazole and N- β -pyrrolidinoethyl-4-nitroimidazole. The mixture is separated by fractional crystallization to give N- β -pyrrolidinoethyl-5-nitroimidazole (m.p. 75°—76° C.) and N- β -pyrrolidinoethyl-4-nitroimidazole (m.p. 80°—81° C.).

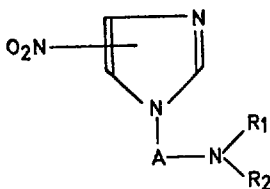
EXAMPLE 3

- 3.4 g. of 4(5)-nitroimidazole and 3.2 g. of β -diethylaminoethylchloride are refluxed for 24 hours in 120 ml. of dry toluene. After filtration and evaporation of the solvent, the residual oil is dissolved in ethanol and treated with bone charcoal. The residue thus obtained solidifies on addition of hexane.

- Crystallization from hexane results in a mixture of N- β -diethylaminoethyl-5-nitroimidazole and N- β -diethylaminoethyl-4-nitroimidazole. The mixture is separated by fractional crystallization to give N- β -diethylaminoethyl-5-nitroimidazole (a liquid which cannot be distilled) and N- β -diethylaminoethyl-4-nitroimidazole (m.p. 75°—76° C.).

25 WHAT WE CLAIM IS:—

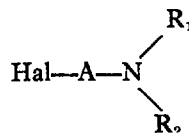
1. Imidazole-derivatives of the general formula:



where A represents a straight or branched

alkylene chain of 1 to 6 carbon atoms, R₁ and R₂, which may be the same or different, represent alkyl groups or together with the nitrogen atom to which they are attached form a heterocyclic ring, and the nitro group is in position 4 or 5.

2. N- β -morpholinoethyl-5-nitroimidazole.
3. N- β -morpholinoethyl-4-nitroimidazole.
4. N- β -pyrrolidinoethyl-5-nitroimidazole.
5. N- β -pyrrolidinoethyl-4-nitroimidazole.
6. N- β -diethylaminoethyl-5-nitroimidazole.
7. N- β -diethylaminoethyl-4-nitroimidazole.
8. Imidazole derivatives according to claim 1, substantially as hereinbefore described.
9. Process for the production of an imidazole derivative claimed in any one of claims 1—8, which comprises reacting a metal salt of 4(5)-nitroimidazole in solution in an anhydrous solvent with a compound of formula:



where Hal is a halogen atom, and A, R₁ and R₂ have the meanings given in claim 1, and subsequently separating the 4- and 5-nitroisomers formed by fractional crystallization.

10. Compositions comprising an imidazole derivative claimed in any one of claims 1—8 in association with a pharmaceutically acceptable diluent or carrier.

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- Crystallization from hexane results in a mixture of N- β -pyrrolidinoethyl-5-nitroimidazole and N- β -pyrrolidinoethyl-4-nitroimidazole. The mixture is separated by fractional crystallization to give N- β -pyrrolidinoethyl-5-nitroimidazole (m.p. 75°—76° C.) and N- β -pyrrolidinoethyl-4-nitroimidazole (m.p. 80°—81° C.).

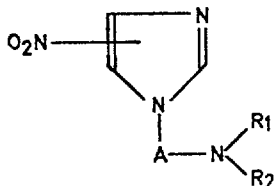
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- 10 3.4 g. of 4(5)-nitroimidazole and 3.2 g. of β -diethylaminoethylchloride are refluxed for 24 hours in 120 ml. of dry toluene. After filtration and evaporation of the solvent, the residual oil is dissolved in ethanol and treated
- 15 with bone charcoal. The residue thus obtained solidifies on addition of hexane.

- Crystallization from hexane results in a mixture of N- β -diethylaminoethyl-5-nitroimidazole and N- β -diethylaminoethyl-4-nitroimidazole. The mixture is separated by fractional crystallization to give N- β -diethylaminoethyl-5-nitroimidazole (a liquid which cannot be distilled) and N- β -diethylaminoethyl-4-nitroimidazole (m.p. 75°—76° C.).

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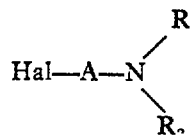
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