986,562

PATENT SPECIFICATION

NO DRAWINGS

986,562

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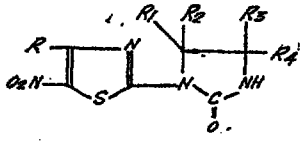
Index at acceptance:—C2 C(1F1B, 1F1D3, 1F4B, 1F4D3, 1F4F1, 1F4F4, 3A14A3A, 3A14A8C)
Int. Cl.:—C 07 d

COMPLETE SPECIFICATION

New 2-Oxo-Tetrahydro-Imidazole Compounds and Processes for preparing them

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, 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:—

The present invention provides as new compounds 2-oxo-tetrahydro-imidazoles of the formula



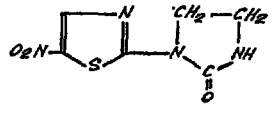
in which R and R_1 to R_4 each represents a hydrogen atom or lower aliphatic hydrocarbon group and R may also represent a phenyl group which may be substituted by a halogen atom or a trifluoromethyl, lower alkyl, lower alkoxy or nitro group as well as processes for preparing them.

Particularly suitable lower aliphatic hydrocarbon groups are lower alkyl groups, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl or pentyl groups, in addition to lower alkenyl groups, for example allyl or methallyl groups.

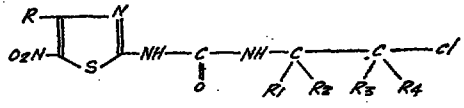
The term "lower" in qualifying aliphatic hydrocarbon groups, for example alkyl groups or the alkyl part of alkoxy groups, is used herein to mean those groups containing up to 5 carbon atoms.

The new compounds possess valuable antiparasitary properties, more especially towards bacteria, especially gram-negative germs, and towards protozoae and vermiculae, for example trichomonas, amebae, schistosomae and coccidiae. They are advantageously used as medicaments in human and veterinary medicine. In particular they are valuable for the treatment of diseases caused by the aforesaid micro-organisms. The new compounds are also valuable intermediates for the manufacture of other useful substances.

Particularly valuable because of its biological properties is 1 - [5 - nitrothiazolyl - (2)] - 2-oxo - tetrahydro - imidazole of the formula



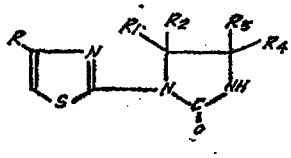
The new compounds are obtained when an N - [5 - nitrothiazolyl - (2)] - urea of the formula



in which R and R_1 to R_4 have the aforesaid meanings, is cyclized to form the imidazole with the simultaneous elimination of hydrochloric acid.

The cyclization is advantageously performed by heating, preferably in the presence of a basic condensing agent, for example an alkali metal acetate or an alkali metal carbonate, in a suitable polar solvent, preferably water or an acid amide, for example dimethyl formamide.

According to another process for the manufacture of the new compounds, a 2-oxo-tetrahydro-imidazole of the formula



in which R and R_1 to R_4 have the aforesaid meanings, is nitrated. The nitration is advantageously performed in a manner known in

the thiazole chemistry. If a phenyl group is present it may also be nitrated.

The starting materials to be used are known or can be made in a known manner. Advantageously, one uses those starting materials which lead to the particularly valuable final products mentioned above.

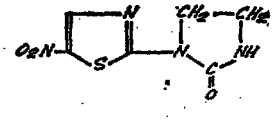
The new compounds may be used as medicaments, for example in the form of pharmaceutical preparations containing said compounds in admixture or conjunction with an organic or inorganic, solid or liquid pharmaceutical carrier suitable for enteral (for example oral) or parenteral administration. Suitable carriers are substances that do not react with the new compounds, for example water, gelatine, lactose, starches, magnesium stearate, talcum, vegetable oils, benzyl alcohols, gums, polyalkyleneglycols, cholesterol or other known medicinal carriers. The pharmaceutical preparations may be in the form of, for example, tablets, dragees or capsules, or in liquid form as solutions, suspensions or emulsions.

The compounds referred to above may also be used in conjunction with conventional additives or vehicles in veterinary medicine in the form of preparations or as animal fodder or additives to animal fodder in animal husbandry.

The following Examples illustrate the invention.

EXAMPLE 1

25 grams of N-(2-chlorethyl)-N¹-[5-nitrothiazolyl-(2)]-urea are stirred into 1 litre of water and refluxed with continued stirring for 7 hours. The precipitate formed is filtered off and recrystallized from dimethylformamide + methanol, to yield 1-[5-nitrothiazolyl-(2)]-2-oxo-tetrahydro-imidazole of the formula



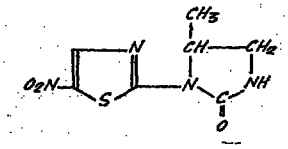
in yellow crystals melting at 259—260°C.

The urea used as starting material may be prepared as follows:

A solution of 25 grams of 2-amino-5-nitrothiazole and 50 grams of 2-chlorethyl isocyanate in 250 cc of tetrahydrofuran is heated in a closed vessel for 16 hours at 80 to 90°C. After cooling, 150 cc of tetrahydrofuran are evaporated, the precipitate formed is suctioned off and thoroughly washed with warm diisopropyl ether, to yield N-(2-chlorethyl)-N¹-[5-nitrothiazolyl-(2)]-urea in crystals melting at 140°C with decomposition.

EXAMPLE 2

25 g of N-(2-chloropropyl)-N¹-[5-nitrothiazolyl-(2)]-urea are boiled for 4 hours in a solution of 14 g of sodium acetate in 200 cc of water. The precipitate which forms is filtered off and recrystallized from dimethyl formamide + ethanol. There is thus obtained the 1-[5-nitrothiazolyl-(2)]-2-oxo-5-methyl-tetrahydroimidazole of the formula



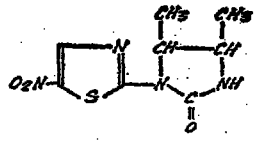
in the form of yellow crystals of melting point 237—238°C.

The urea used as starting material can be preared as follows:

To a suspension of 5 g of potassium carbonate in 50 cc of acetone are added 14.5 g of 2-amino-5-nitro-thiazole and 12 g of 2-chloro-propylisocyanate. The mixture is stirred at the boiling temperature for 3 hours and the precipitate that forms is filtered off and washed with water. The filter residue is recrystallized from ethanol + water. There is obtained N-(2-chloro-propyl)-N¹-[5-nitro-thiazolyl-(2)]-urea in the form of crystals which melt at 170—172°C.

EXAMPLE 3

22 g of N-[2-chloro-butyl-(3)]-N¹-[5-nitro-thiazolyl-(2)]-urea are heated at 100°C for 10 minutes with 13 g of sodium acetate in 40 cc of dimethyl formamide. There are then added 200 cc of water, and the precipitate which forms is filtered off. The filter residue is washed with 1N-sodium hydroxide solution and, for further purification, recrystallized from dimethyl formamide + ethanol. There is obtained the 1-[5-nitrothiazolyl-(2)]-2-oxo-4:5-dimethyltetrahydroimidazole of the formula



in the form of yellow crystals of melting point 242—243°C.

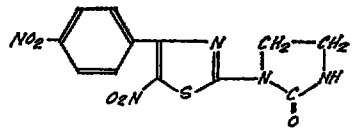
The urea used as starting material is prepared as follows:

14 g of 2-amino-5-nitrothiazole are heated to 100°C for four hours with 12 g of 2-chloro-butyl-(3)-isocyanate in 100 cc of absolute tetrahydrofuran. The solution is then evaporated to dryness under reduced pressure. The residue is recrystallized from ethanol to obtain N-[2-chloro-butyl-(3)]-N¹-[5-nitro-thiazolyl-(2)]-urea in the form of crystals melting at 195°C.

EXAMPLE 4

15 g of 1-[4-phenyl-thiazolyl-(2)]-2-oxo-tetrahydro-imidazole are introduced into 50 cc of concentrated sulphuric acid in such manner that the temperature does not rise

above 10°C. After that, 7 g of concentrated nitric acid are slowly added dropwise, and the mixture stirred at room temperature for 5 hours. The reaction mixture is poured onto precipitate forms which is filtered off and crystallized from dimethyl formamide. [4 - para - nitro - phenyl - 5 - nitro-1 - (2)] - 2 - oxo - tetrahydroimidazole formula



is obtained in the form of yellow crystals of melting point 286—288°C.

The 1 - [4 - phenyl - thiazolyl - (2)]-2 - oxo - tetrahydroimidazole used as starting material can be prepared as follows:

10 g of 2-chloro-ethyl-isocyanate are added to 10 g of 2-amino-4-phenyl-thiazole in 50 cc of dimethyl formamide and the mixture heated at 80°C for 2 hours. The mixture is then cooled, treated with water, and the precipitate that forms recrystallized from ethanol. There is thus obtained N-[4-phenyl-thiazolyl-(2)]-N¹-(2-chlorethyl)-urea of melting point 173—174°C.

10 g of the urea are heated at 110°C for 30 minutes with 6 g of sodium acetate in 100 cc of dimethyl formamide. There are then added 300 cc of water. The precipitate which forms is recrystallized from aqueous dimethyl formamide to obtain 1-[4-phenyl-thiazolyl-(2)]-2-oxo-tetrahydro-imidazole in the form of white crystals melting at 250—252°C.

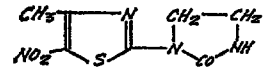
Example 5

The new compounds can be used in the form of pharmaceutical preparations, the daily dose for human beings amounting to 0.5—2g. They can be administered, for example, in the form of capsules containing the desired quantity of the active compound, advantageously 1 - [5 - nitrothiazolyl - (2)] - 2 - oxo - tetrahydro - imidazole.

An additive to animal fodder, for example for poultry, the new compounds particularly the 1 - [5 - nitrothiazolyl - (2)] - 2 - oxo-tetrahydro - imidazole, may be mixed with cerelose (content of active compound, for example, 0.1—1%, preferably 0.5%). This premix can then be added to the fodder in the usual manner, preferably in such an amount that the final concentration is about 0.01 of the active compound.

Example 6

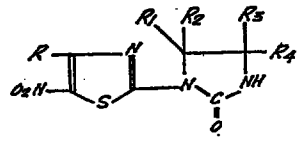
A mixture of 16.0 g of 2-amino-4-methyl-5-nitrothiazole, 11.0 g of β-chlorethylisocyanate, 5.0 g of potassium carbonate, and 150 cc of acetone is stirred while being boiled for 17 hours, N-(2-chlorethyl)-N¹-[4-methyl-5-nitro-thiazolyl-(2)]-urea being intermediately formed and partly cyclized. The batch is then cooled, treated with 200 cc of water, and the resulting precipitate, which is a mixture of N - (2 - chlorethyl) - N¹ - [4 - methyl - 5-nitro - thiazolyl - (2)] - urea and 1 - [4-methyl - 5 - nitro - thiazolyl - (2)] - 2 - oxo-tetrahydro - imidazole, is filtered off. The residue is introduced into 50 cc of dimethyl formamide and, after the addition of 10.0 g of sodium acetate, heated at 100°C for 30 minutes. Water is then added and the resulting precipitate recrystallized from dimethyl-formamide + ethanol. 1 - [4 - Methyl - 5-nitro - thiazolyl - (2)] - 2 - oxo - tetrahydro-imidazole of the formula



is obtained in the form of yellow crystals of melting point 241—243°C.

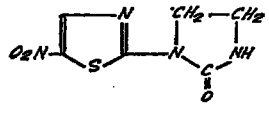
WHAT WE CLAIM IS:—

1. A 2-oxo-tetrahydro-imidazole of the formula

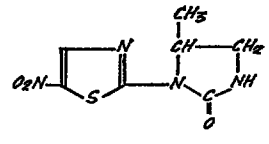


in which R and R_1 to R_4 each represents a hydrogen atom or lower aliphatic hydrocarbon group and R may also represent a phenyl group which may be substituted by a halogen atom or a trifluoromethyl, lower alkyl, lower alkoxy or nitro group.

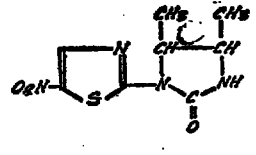
2. The 1-[5-nitrothiazolyl-(2)]-2-oxo-tetrahydro-imidazole of the formula



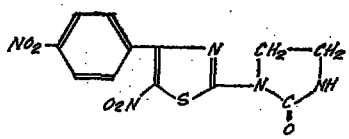
3. The 1-[5-nitrothiazolyl-(2)]-2-oxo-5-methyl-tetrahydro-imidazole of the formula



4. The 1-[5-nitro-thiazolyl-(2)]-2-oxo-4:5-dimethyl-tetrahydro-imidazole of the formula



above 10°C. After that, 7 g of concentrated nitric acid are slowly added dropwise, and the mixture stirred at room temperature for 5 hours. The reaction mixture is poured onto [illegible] precipitate forms which is filtered off and [illegible]ystallized from dimethyl formamide. [illegible] [4 - para - nitro - phenyl - 5 - nitro-[illegible] - (2)] - 2 - oxo - tetrahydroimidazole [illegible] formula



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The 1 - [4 - phenyl - thiazolyl - (2)] - 2 - oxo - tetrahydroimidazole used as starting material can be prepared as follows:

10 g of 2-chloro-ethyl-isocyanate are added to 10 g of 2-amino-4-phenyl-thiazole in 50 cc of dimethyl formamide and the mixture heated at 80°C for 2 hours. The mixture is then cooled, treated with water, and the precipitate that forms recrystallized from ethanol. There is thus obtained N-[4-phenyl-thiazolyl-(2)]-N¹-(2-chlorethyl)-urea of melting point 173—174°C.

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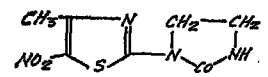
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An additive to animal fodder, for example for poultry, the new compounds particularly the 1 - [5 - nitrothiazolyl - (2)] - 2 - oxo-tetrahydro - imidazole, may be mixed with cerelose (content of active compound, for example, 0.1—1%, preferably 0.5%). This premix can then be added to the fodder in the usual manner, preferably in such an amount that the final concentration is about 0.01 of the active compound.

Example 6

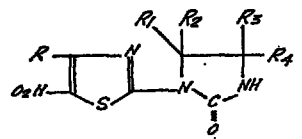
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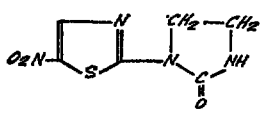
WHAT WE CLAIM IS:—

1. A 2-oxo-tetrahydro-imidazole of the formula

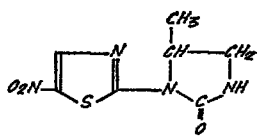


in which R and R_1 to R_4 each represents a hydrogen atom or lower aliphatic hydrocarbon group and R may also represent a phenyl group which may be substituted by a halogen atom or a trifluoromethyl, lower alkyl, lower alkoxy or nitro group.

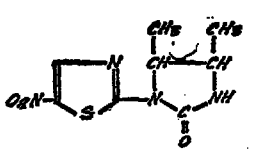
2. The 1-[5-nitrothiazolyl-(2)]-2-oxo-tetrahydro-imidazole of the formula



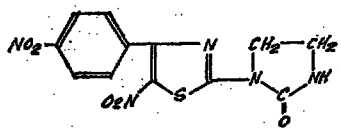
3. The 1-[5-nitrothiazolyl-(2)]-2-oxo-5-methyl-tetrahydro-imidazole of the formula



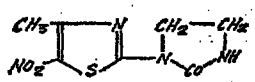
4. The 1-[5-nitro-thiazolyl-(2)]-2-oxo-4:5-dimethyl-tetrahydro-imidazole of the formula



5. The 1 - [4 - para - nitrophenyl - 5-nitrothiazolyl - (2)] - 2 - oxo - tetrahydro-imidazole of the formula



6. The 1 - [4 - methyl - 5 - nitro-thiazolyl - (2)] - 2 - oxo - tetrahydro - imid-azole of the formula



7. Pharmaceutical preparations which comprise a 2-oxo-tetrahydro-imidazole as claimed in claim 1 in admixture or conjunction with a pharmaceutically suitable carrier.

8. Pharmaceutical preparations which comprise 1 - [5 - nitrothiazolyl - (2)] - 2 - oxo-5 - methyl - tetrahydro - imidazole, in admixture or conjunction with a pharmaceutically suitable carrier.

9. Pharmaceutical preparations which comprise 1 - [5 - nitrothiazolyl - (2)] - 2 - oxo-4:5 - dimethyl - tetrahydroimidazole, in admixture or conjunction with a pharmaceutically suitable carrier.

10. Pharmaceutical preparations which comprise 1 - [5 - nitrothiazolyl - (2)] - 2 - oxo-tetrahydro - imidazole, in admixture or conjunction with a pharmaceutically suitable carrier.

11. Pharmaceutical preparations which comprise 1 - [4 - para - nitrophenyl - 5 - nitro-thiazolyl - (2)] - 2 - oxo - tetrahydroimidazole, in admixture or conjunction with a pharmaceutically suitable carrier.

12. Pharmaceutical preparations which comprise 1 - [4 - methyl - 5 - nitrothiazolyl-(2)] - 2 - oxo - tetrahydro - imidazole, in admixture or conjunction with a pharmaceutically suitable carrier.

13. Veterinary preparations which comprise a 2-oxo-tetrahydro-imidazole as claimed in claim 1 in admixture or conjuncton with a carrier suitable for veterinary purposes.

14. Veterinary preparations which comprise 1 - [5 - nitro - thiazolyl - (2)] - 2 - oxo - 5-methyl - tetrahydro - imidazole, in admixture or conjunction with a carrier suitable for veterinary purposes.

15. Veterinary preparations which comprise 1 - [5 - nitro - thiazolyl - (2)] - 2 - oxo - 4:5-dimethyl - tetrahydro - imidazole, in admixture or conjunction with a carrier suitable for veterinary purposes.

16. Veterinary preparations which comprise 1 - [5 - nitrothiazolyl - (2)] - 2 - oxo - tetrahydro - imidazole, in admixture or conjunction with a carrier suitable for veterinary purposes.

17. Veterinary preparations which comprise 1 - [4 - para - nitrophenyl - 5 - nitro-thiazolyl - (2)] - 2 - oxo - tetrahydro - imid-azole, in admixture or conjunction with a carrier suitable for veterinary purposes.

18. Veterinary preparations which comprise 1 - [4 - methyl - 5 - nitrothiazolyl - (2)] - 2-oxo - tetrahydro - imidazole, in admixture or conjunction with a carrier suitable for veterinary purposes.

19. Animal fodder or additives to animal fodder which contain a 2-oxo-tetrahydro-imidazole as claimed in claim 1.

20. Animal fodder or additives to animal fodder which contain 1 - [5 - nitro - thiazolyl-(2)] - 2 - oxo - 5 - methyl - tetrahydro-imidazole.

21. Animal fodder or additives to animal fodder which contain 1-[5-nitrothiazolyl-(2)]-2-oxo-4:5-dimethyl-tetrahydro-imidazole.

22. Animal fodder or additives to animal fodder which contain 1-[5-nitrothiazolyl-(2)]-2-oxo-tetrahydroimidazole.

23. Animal fodder or additives to animal fodder which contain 1 - [4 - para - nitro-phenyl - 5 - nitrothiazolyl - (2)] - 2 - oxo-tetrahydro - imidazole.

24. Animal fodder or additives to animal fodder which contain 1-[4-methyl-5-nitro-thiazolyl-(2)]-2-oxo-tetrahydro-imidazole.

25. Process for the manufacture of compounds as claimed in claim 1 conducted substantially as described hereinbefore.

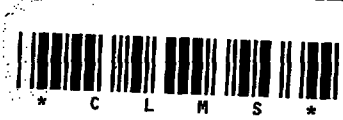
26. Process for the manufacture or compounds as claimed in claim 1 conducted substantially as described in Example 1.

27. Process for the manufacture of compounds as claimed in claim 1 conducted substantially as described in any one of Examples 2—4.

28. Process for the manufacture of compounds as claimed in claim 1 conducted substantially as described in Example 6.

ABEL & IMRAY,
Chartered Patent Agents,
Quality House, Quality Court,
Chancery Lane, London, W.C.2.

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