

PATENT SPECIFICATION

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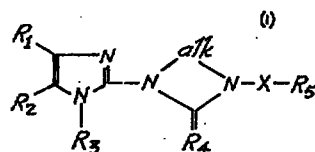
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(54) NEW IMIDAZOLES AND PROCESSES FOR THEIR PRODUCTION

(71) We, CIBA-GEIGY AG, 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 relates to imidazoles and processes for the production thereof. The invention provides new imidazoles of the formula I



wherein one of the groups R_1 and R_2 is a hydrogen or lower alkyl and the other a nitro group, R_3 is a lower alkyl group, R_4 is an oxo or thioxo group, X is a carbonyl, thiocarbonyl, sulphinyl or sulphonyl group and R_5 , when X is a carbonyl group is amino, a loweralkylamino or diloweralkylamino group, and also piperidino, morpholino or pyrrolidino, and when X is a thiocarbonyl, sulphinyl or sulphonyl group, R_5 is a lower alkyl, phenyl optionally substituted by one or more lower alkyl, lower alkoxy, halogen or trifluoromethyl; amino, a lower alkylamino or di-lower alkylamino group, and also piperidino or pyrrolidino, and alk is 1,2-ethylene, and their salts.

The term "lower" as used hereinbefore or hereinbelow in connection with the definition

of organic compounds, groups and radicals, signifies that such compounds, groups and radicals contain up to and including 7 carbon atoms preferably up to 4 carbon atoms.

Examples of lower alkyl groups are preferably methyl, ethyl n-propyl, isopropyl, n-butyl, isobutyl, sec. butyl, tert. butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, iso-hexyl or n-heptyl groups.

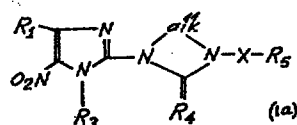
The phenyl group R_5 is optionally substituted by one or more than one substituent, and is mono- or di-substituted phenyl, particularly mono-substituted phenyl. Substituents are the above-defined loweralkyl groups, loweralkoxy groups, halogen atoms such as chlorine, bromine or fluorine or a trifluoromethyl group.

Lower alkoxy groups are e.g. the methoxy, ethoxy, n-propoxy, isopropoxy, n-butyloxy or n-pentyloxy groups. A loweralkylamino group R_5 is e.g. methylamino, ethylamino and diloweralkylamino is e.g. diethylamino, diethylamino or ethylmethylamino.

The new compounds show valuable pharmacological properties. They show, in particular, activity against bacteria, especially against gram negative bacteria, protozoa e.g. trichomonads and amoeba and helminths, e.g. schistosomes and above all amoeba, as shown in experimental animals, e.g. on the liver of hamsters infected with *Entamoeba histolytica*, at a dose between 10 and 100 mg/kg p.o. Thus, the new imidazoles are useful against amoeba, schistosomes, trichomonads and bacteria. Further, the new compounds are useful as starting materials or intermediates for

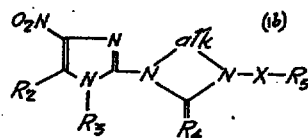
the preparation of other compounds, in particular, therapeutically active compounds.

The invention refers particularly to compounds of formula Ia



wherein R_1 represents hydrogen or a loweralkyl group, R_2 is a loweralkyl group, R_4 is an oxo group, X and alk have the earlier defined meanings, and R_5 when X is a carbonyl group is amino, a lower alkylamino or di - lower alkylamino group, and when X is a thiocarbonyl, sulphinyl or sulphonyl group, R_5 is a lower alkyl, phenyl optionally substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; amino, a lower alkylamino or di - loweralkylamino group, and their salts.

Furthermore the invention refers particularly to compounds of formula Ib,



wherein R_2 represents hydrogen or a lower alkyl group, R_4 is an oxo group, X and alk have the earlier defined meanings, and R_5 when X is a carbonyl group is amino, a lower alkylamino or di - lower alkylamino group, and when X is a thiocarbonyl, sulphinyl or sulphonyl group, R_5 is a lower alkyl, phenyl optionally substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; amino, a lower alkylamino or di - loweralkylamino group, and their salts.

Particularly the invention refers to compounds of formula Ia, wherein R_1 , R_3 , R_4 and alk have the meanings as defined under formula Ia, X is a carbonyl group and R_5 represents amino, a lower alkylamino or di - lower alkylamino group and to compounds of formula Ib, wherein R_2 , R_3 , R_4 and alk have the meanings as defined under formula Ib, X is a carbonyl group and R_5 is amino, a lower alkylamino or di - lower alkylamino group, and their salts.

Also of particular interest are compounds of formulae Ia and Ib, wherein R_1 or R_2 , R_3 , R_4 and alk have the meanings defined above, X is a thiocarbonyl and R_5 a loweralkyl, phenyl optionally substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; amino, a lower alkylamino or di - lower alkylamino group, and their salts.

Of particular interest are compounds of formulae Ia and Ib, wherein R_1 or R_2 , R_3 , R_4 and alk have the meanings defined above and X is a sulphinyl or sulphonyl group and R_5

is a lower alkyl, phenyl optionally substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; amino, a lower alkylamino or di - lower alkylamino group, and their salts.

Of similar interest are compounds of formulae Ia and Ib, wherein X is a thiocarbonyl, sulphinyl or sulphonyl group, R_1 and R_2 have the meaning given under formulae Ia or Ib, R_3 is a lower alkyl group as for example a methyl or ethyl group, and alk is 1,2 - ethylene, R_4 represents an oxo group, and R_5 is amino, a lower alkylamino or di - lower alkylamino group, and their salts.

Of particular interest are compounds of formulae Ia and Ib, wherein R_1 or R_2 is hydrogen, methyl or ethyl, R_3 is methyl or ethyl, X is a carbonyl group, R_5 is amino, methylamino, ethylamino, dimethylamino or diethylamino, and alk is 1,2 - ethylene, and their salts.

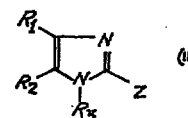
Furthermore compounds of formulae Ia and Ib are of interest, wherein R_1 or R_2 is hydrogen, methyl or ethyl, R_3 is methyl or ethyl, X is thiocarbonyl, R_5 is amino, methylamino, ethylamino, dimethylamino or diethylamino, and alk is 1,2 - ethylene, and their salts.

Also compounds of formulae Ia and Ib are of interest, wherein R_1 or R_2 is hydrogen, methyl or ethyl, R_3 is methyl or ethyl, X is a sulphonyl group, R_5 is amino, methylamino, ethylamino, dimethylamino or diethylamino, and alk is 1,2 - ethylene, and their salts.

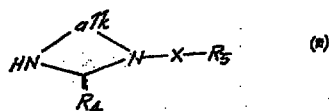
Among the nitroimidazole compounds which are to be mentioned especially are 1 - (methylsulphonyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitro - imidazolyl(2)] - tetrahydroimidazole, 1 - N,N - diethylcarbamoyl - 2 - oxo - 3 - [1 - methyl - 5 - nitro - imidazolyl(2)] - tetrahydroimidazole and 1 - N,N - dimethylcarbamoyl - 2 - oxo - 3 - [1 - methyl - 5 - nitro - imidazolyl - (2)] - tetrahydroimidazole, 1 - N - ethylthiocarbamoyl - 2 - oxo - 3 - [1 - methyl - 5 - nitro - imidazolyl - 2] - tetrahydroimidazole, 1 - N - methylthiocarbamoyl - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - 2] - tetrahydroimidazole whose use result in eradication of abscess on the liver of healthy hamsters infected with *Entamoeba histolytica*.

These compounds are thus useful as anti-amoebic preparations for which purposes doses of 10 to 100 mg/kg p.o. are indicated.

The new imidazoles are prepared by methods which are in themselves known, (a) by the reaction of a compound of the formula II



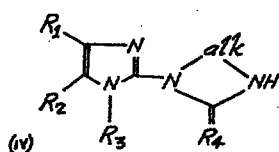
wherein R_1 , R_2 and R_3 have the meanings defined earlier and Z is methyl sulphonyl or methyl sulphinyl, with a compound of the formula III



wherein R_1 , R_2 , alk and X have the meanings defined above.

The reaction is carried out in the presence of a basic condensing agent or the compound of formula III is reacted in the form of its N - metal derivatives, such as N - alkali metal derivatives e.g. by the treatment of the compound of formula III with an amide, hydride, an hydroxide or alcoholate of an alkali metal such as lithium, sodium or potassium without isolation of the intermediate, if necessary. Selected basic condensing agents are e.g. alkali metal hydroxide or alkali earth hydroxide, such as sodium hydroxide, potassium hydroxide and calcium hydroxide or organic tertiary bases, such as trialkylamine, e.g. trimethylamine and triethylamine or pyridine. The reaction is carried out, if necessary, at a higher temperature and/or in the presence of an inert solvent, such as those with polar functional groups e.g. dimethylformamide, dimethylacetamide, dimethyl - sulphoxide, acetonitrile or a cyclic - aliphatic - ether such as dioxan or tetrahydrofuran.

Compounds of formula I may be prepared according to a second process which comprises reacting a compound of formula IV



wherein R_1 , R_2 , R_3 , R_4 and alk have the meanings given before with the isocyanate of the formula V.

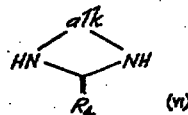


Compounds of the formula I which contain a nitro group as the radical R_2 and in which R_1 is hydrogen can be rearranged to give the corresponding 4 - nitroimidazoles, that is to say compounds of the formula I which contain a nitro group as the radical R_1 and in which R_2 is hydrogen. Such a rearrangement is effected by the action of, for instance, an excess of alkali metal iodide, especially potassium iodide, in the presence of an inert solvent, preferably a solvent with polar functional groups, such as dimethylformamide, dimethylacetamide, dimethylsulphoxide, acetonitrile or hexamethylphosphoric acid triamide.

The reactions of this invention are carried out in the usual manner, at room temperature or with cooling or heating, under atmospheric or superatmospheric pressure, if necessary, in

the presence of diluents, catalysts and condensing agents, and/or in the atmosphere of an inert gas, e.g. nitrogen.

Compounds of the formula III according to the first process are prepared by the action of a compound of the formula VI



where alk and R_1 have the meanings given before, i.e. an imidazolidin - 2 - one with a compound of the formula R_3-X-Z , wherein R_3 , X and Z have the earlier defined meanings.

Depending on the process conditions and the starting substances, the final substances are obtained in the free form or in the form of their acid addition salts which is also included in the invention. Thus, for example, basic, neutral or mixed salts and where relevant also hemihydrates, monohydrates, sesquihydrates or polyhydrates thereof can be obtained. The acid addition salts of the new compounds can be converted into the free compound in a manner which is in itself known, for example with basic agents, such as alkalis or ion exchangers. On the other hand, the resulting free bases can form salts with organic or inorganic acids. The acids used for the manufacture of acid addition salts are in particular those suitable for forming therapeutically usable salts. As examples of such acids there may be mentioned: hydrogen halide acids, sulphuric acids, phosphoric acids, nitric acid, perchloric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxylic acids or sulphonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid or pyruvic acid; phenylacetic acid, benzoic acid, or p - aminobenzoic acid, anthranilic acid, p - hydroxybenzoic acid, salicylic acid or p - aminosalicylic acid, embonic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid and ethylenesulphonic acid; halogenobenzene-sulphonic acid, toluenesulphonic acid, naphthalenesulphonic acid or sulphanilic acid; methionine, tryptophane, lysine or arginine.

These or other salts of the new compounds, such as, for example, the picrates, can also serve for the purification of the resulting free bases, by converting the free bases into salts, isolating these and again liberating the bases from the salts. Because of the close relationships between the new compounds in the free form and in the form of their salts, the free compounds are where appropriate also to be understood to include the corresponding salts, in the preceding and following text.

The invention also relates to those embodiments of the process in which a compound

obtainable as an intermediate product at any stage is used as the starting compound and the missing steps are carried out, or a starting substance is formed under the reaction conditions or used, where relevant, in the form of a salt and/or racemate or optical antipode.

Depending on the number of the asymmetrical C atoms and on the choice of the starting substances and procedures, the new compounds can be in the form of racemate mixtures, racemates or optical antipodes.

Racemate mixtures can be separated into the pure racemates on the basis of the physico-chemical differences of the constituents, in a known manner, for example by chromatography and/or fractional crystallisation.

Pure racemates can be resolved into the diastereomers according to known methods, for example by recrystallisation from an optically active solvent, with the aid of microorganisms or by reaction with an optically active acid which forms salts with the racemic compound and separation of the salts obtained in this manner, for example on the basis of their different solubilities, and from the diastereomers the antipodes can be liberated by the action of suitable agents. Particularly customary optically active acids are, for example, the D- and L-forms of tartaric acid, di-o-toluyt-tartaric acid, malic acid, mandelic acid, camphor-10-sulphonic or quinine acid. Resulting salts may be converted into other salts or into the free and optically active bases, and an optically active base may be converted into an acid addition salt by the methods referred to above.

According to their antimicrobial activity the compounds of formula I, and their salts may be used to protect a high molecular weight hydrophobic or other organic material susceptible to bacterial or other microbial deterioration by contacting the organic material with, impregnating in or otherwise treating with, the compounds in amounts up to about 5% by weight. The compounds also find application as growth-promoting additives to animal feedstuffs, to which they may be added in proportion of from 5 to 500 parts per million.

Accordingly, the invention also provides a therapeutic composition comprising an antimicrobially effective proportion of a compound of formula I, or pharmaceutically acceptable salts thereof and a pharmacologically acceptable solid carrier or liquid diluent.

The pharmaceutical compositions according to the invention contain at least one compound of the general formula I, or a pharmaceutically acceptable salt thereof as active substance together with a conventional pharmaceutical carrier. The type of carrier actually used depends to a great extent on the intended application; for external use, for example in disinfecting healthy skin, disinfecting wounds and

in treating dermatoses and affections of the mucous membranes caused by bacterial or fungi, ointments, powders and tinctures are used in particular. The ointment bases may be anhydrous, for instance they can consist of mixtures of wool fat and soft paraffin, or they can consist of aqueous emulsions in which the active substance is suspended. Suitable carriers for powders are, for instance, rice starch and other starches; the bulk weight of the carriers may be made lighter, if desired, for example by adding highly dispersed silicic acid, or may be made heavier by adding talcum. The tinctures may contain at least one active ingredient of the formula I, or a salt thereof in aqueous ethanol, in particular 45% to 75% ethanol, to which 10% to 20% of glycerol may be added, if desired. Solutions prepared from polyethylene glycol and other conventional solubility promoters, and also, optionally from emulsifying agents, may be used with particular advantage in disinfecting healthy skin. The content of active ingredient in pharmaceutical compositions for external application is preferably in the range of from 0.1% to 5%.

Gargles or concentrates for their preparation, and tablets for slow dissolution in the mouth, are suitable for the disinfection of the mouth and throat. The former are preferably prepared from alcoholic solutions containing 1% to 5% of active substance to which glycerol or flavourings may be added. Lozenges, that is solid dosage units, preferably have a relatively high content of sugar or similar substances and a relatively low content of active substance, for instance 0.2 to 20% by weight, as well as the usual conventional additives such as binding agents and flavourings.

Solid dosage units, in particular tablets, dragees (sugar coated tablets) and capsules, are convenient for use in intestinal disinfection. These units preferably contain from 10% to 90% of the compound of the general formula I, or a salt thereof to enable the administration of daily doses of from 0.1 to 2.5 grams to adults, or of suitably reduced doses to children to be made. Tablets and dragee cores are produced by combining the compounds of the general formula I, or a pharmaceutically acceptable salt thereof with solid, pulverulent carriers such as lactose, saccharose, sorbitol, maize starch, potato starch or amylopectin, cellulose derivatives or gelatines, preferably with the addition of lubricants such as magnesium or calcium stearate or polyethylene glycols of suitable molecular weight. Dragee cores may then be coated, for example with concentrated sugar solutions which can also contain gum arabic, talcum and/or titanium dioxide, or they may be coated with a lacquer dissolved in volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, for instance to differentiate be-

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or amylopectin,
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solvents or mix-
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differentiate be-
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tween varying dosages. Soft gelatine capsules
and other closed capsules consist, for ex-
ample, of a mixture of gelatines and glycerol
and may contain, for example, mixtures of
5 the compound of formula I, or a pharmaceutic-
ally acceptable salt thereof with polyethylene
glycol. Hard gelatine capsules contain, for ex-
ample, granulates of an active substance with
10 solid pulverulent carriers, for instance lactose,
saccharose, sorbitol, mannitol, starches (such as
potato starch, maize starch or amylopectin),
cellulose derivatives of gelatines, and mag-
nesium stearate or stearic acid.

In all forms of administration compounds
of the general formula I, a salt thereof can
be present as sole active ingredients or they
can also be combined with other known
pharmacologically active, and especially anti-
bacterial and/or antimycotically or other anti-
microbially active substances, for example to
20 broaden the range of application. They can
be combined for example, with 5,7 - dichloro-
2 - methyl - 8 - quinolinol or other derivatives
of 8 - quinolinol or other derivatives of 8 -
quinolinol, with sulfamerazine or sulfafurazole
or other derivatives of sulfanilamide, with
chloramphenicol or tetracycline or other anti-
biotics, with 3,4',5 - tribromosalicylanilide or
other halogenated salicylanilides, with halo-
30 genated carbanilides, with halogenated benz-
oxazoles or benzoxazolones, with polychloro-
hydroxy - diphenylmethanes, with halogen -
dihydroxy - diphenyl sulphides, with 4,4' - di-
chloro - 2 - hydroxy - diphenylether or 2,4,4' -
35 trichloro - 2 - hydroxydiphenylether or other
polyhalogenhydroxydiphenylethers, or with
bactericidal quaternary compounds or with cer-
tain dithiocarbamic acid derivatives such as
tetramethylthiuram disulphide or with other
40 nitrofurans. Also, carriers which themselves
have favourable pharmacological properties
may be used, for instance sulphur as a powder
base or zinc stearate as a component of oint-
ment bases.

A method of protecting an organic material
susceptible to bacterial or other microbial
attack comprises treating the material with a
compound of formula I or an acid addition salt
thereof. The organic material may be a natural
or synthetic polymeric material, a protein-
aceous or carbohydrate substance, or a neutral
or synthetic fibre or textile material formed
therefrom.

An animal feedstuff composition can com-
prise a compound of formula I, or a salt there-
of in an amount sufficient to promote the
growth of the animal fed with the composition.

Preparation of Tablets

100 g of 1 - (methylsulphonyl) - 2 - oxo -
3 - [1 - methyl - 5 - nitro - imidazolyl -
(2)] - tetrahydroimidazole are mixed with
60 60.0 g of maize starch and 35.0 g of lactose,
the mixture is moistened with a solution of
5.0 g of gelatin and 3.0 g of glycerol in 70.0

g of water and granulated through a sieve.
The granulate is mixed with a mixture of
15.0 g of talcum, 10.0 g of maize starch and
2.0 g of magnesium stearate. The resulting
mixture is pressed into 1,000 tablets, each
70 containing 100 mg of active substance. If
desired, the tablets can be grooved for better
adaption of the dosage.

Preparation of Dragées

Composition	for 1,000 dragées	
I 1 - (methylsulphonyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole	100.0 g	
Maize starch	27.0 g	80
Gelatine	8.0 g	
II Glycerol	2.0 g	
Distilled water q.s.		
ad 100 ml Maize starch	10.0 g	
III Talcum	7.0 g	85
Magnesium stearate	1.0 g	
	150.0 g	
IV White dragée coating		
Shellac	2.0 g	
Sugar	50.0 g	90
Talcum	38.0 g	
Gum arabic	7.4 g	
Colloidal silicon dioxide	2.2 g	
Titanium dioxide	0.4 g	

Composition I is granulated in the heat with
composition II through a sieve of 1.2 mm
mesh diameter. The dried granulate is mixed
with composition III and the resulting mixture
is pressed into 1,000 dragée cores. These are
then coated with composition IV and dried.
100 The dragées obtained weigh 255.0 mg and
contain 100 mg of active substance.

Preparation of syrup

Composition	for 1 liter	
1 - (methylsulphonyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitro - imidazolyl - (2)] - tetrahydroimidazole	100.0 g	105
Colloidal silicon dioxide	13.0 g	
p - Hydroxybenzoic acid methyl ester	1.4 g	110
p - Hydroxybenzoic acid propyl ester	0.6 g	
	115.0 g	
Citric acid	1.0 g	115
Sodium cyclamate	5.0 g	
Distilled water	610.0 g	
Glycerol	100.0 g	
Sodium carboxymethyl cellulose	4.0 g	120
Sugar	320.0 g	
	1155.0 g	

The active substance and the colloidal silicon dioxide are passed through a sieve of 1.2 mm mesh diameter (I).

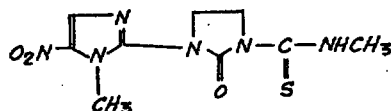
The *p* - hydroxybenzoic acid esters, the citric acid and the sodium cyclamate are dissolved in the given amount of boiling distilled water, the glycerol is then added to this solution (II). The sodium carboxymethyl cellulose and the sugar are thoroughly mixed (III).

Composition III is then added at 75°C to Solution II under stirring until complete dissolution of III. The viscous, slightly turbid liquid is cooled to room temperature, filtered, if necessary, and mixed with composition I. Water is added to the resulting mixture up to the prescribed weight of 1,155.0 g and the syrup obtained is homogenized.

Some examples now follow, all parts and percentages being by weight unless otherwise stated. The temperatures are given in centigrade.

Example 1

To a solution of 7.95 g 1 - (methylthiocarbamoyl) - 2 - oxo - 2,3,4,5 - tetrahydroimidazole in 100 ml of dimethyl formamide is added 2.4 g of a 50% slurry of sodium hydride in mineral oil. The mixture is heated and stirred at 50° for 30 min. 10.25 g of 1 - methyl - 2 - methanesulphonyl - 5 - nitroimidazole are now added and the mixture stirred at 100° for 4 hrs. The solution is concentrated in vacuo to a small volume and treated with water. The crystalline precipitate is filtered off, washed with water and ether. It is then recrystallized from alcohol to give 1 - (methylthiocarbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole of the formula



melting at 185—187°.

The starting material 1 - (methylthiocarbamoyl) - 2 - oxo - 2,3,4,5,5 - tetrahydroimidazole required for the above reaction is made as follows: a structure of 86 g ethyleneurea and 73 g methylisothiocyanate is heated at 100° with stirring for 4 hrs. The crystalline mass obtained on cooling is rubbed with ether and water, filtered and washed with alcohol-ether mixture. It is recrystallized from methanol; m.p. 168—171°.

Example 2

To a solution of 5 g of 1 - (methylcarbamoyl) - 2 - oxo - 2,3,4,5 - tetrahydroimidazole in 50 ml dimethyl formamide is added 1.7 g of 50% slurry of sodium hydride in mineral oil. The mixture is stirred

at 50° for 1 hr. A solution of 7.2 g of 1 - methyl - 2 - methanesulphonyl - 5 - nitroimidazole in 30 ml dimethyl formamide is now added and the mixture stirred at 100° for 3 hrs. The solvent is then removed *in vacuo* and water is added to the residue. The resultant red solution is then extracted with chloroform to give an oil, which upon rubbing with methanol affords a solid, recrystallized thrice from methanol to give 1 - (methylcarbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole melting at 176—177°.

The starting methylcarbamoylimidazole for the above experiment is made by heating a mixture of 8.6 g ethyleneurea and 5.7 g methylisocyanate in a sealed tube at 130° for 3 hrs. and crystallizing the solid so obtained first from water and then from chloroform - methanol; m.p. 198—200°.

Example 3

To a solution of 16.4 g 1 - (methylsulphonyl) - 2 - oxo - 2,3,4,5 - tetrahydroimidazole in 120 ml dimethyl formamide is added 4.8 g of 50% slurry of sodium hydride in mineral oil. The mixture is stirred at 50° for 30 min. A solution of 20.5 g 1 - methyl - 2 - methanesulphonyl - 5 - nitroimidazole in 70 ml dimethylformamide is now added and the mixture heated at 100° for 1 hr. The solvent is then removed *in vacuo* and the residue dissolved in water. Upon cooling, a crystalline precipitate is obtained, which is filtered off and recrystallized from acetone - methanol to afford 1 - (methylsulphonyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole melting at 202—204°.

The starting 1 - (methylsulphonyl) - 2 - oxo - 2,3,4,5 - tetrahydroimidazole for the above reaction is made as follows: A mixture of 86 g ethyleneurea and 115 g methanesulphonyl chloride is heated for 6 hrs. at 120° with stirring, while a stream of nitrogen is bubbled in to remove hydrogen chloride. After cooling, water is added and the mixture heated on a steam bath till a crystalline powder is formed. This is filtered off, washed with alcohol - ether and recrystallized from methanol; m.p. 192—195°C.

Example 4

To a suspension of 1.5 g 50% sodium hydride in 10 ml dry dimethyl formamide is added with stirring during 15 min. a solution of 5.3 g of 1 - (N - ethylthiocarbamoyl) - 2 - oxo - tetrahydroimidazole in 20 ml dry dimethyl formamide. The reaction mixture is stirred under nitrogen at 50° for 30 min. and a solution of 4.5 g of 1 - methyl - 2 - methylsulphonyl - 5 - nitroimidazole in 10 ml dry dimethyl formamide is added during 5 min., and then heated at 100° for 4 hrs. The solvent is evaporated off under *vacuo*; residue

7.2 g of 1 - 5 - (N,N - dimethylsulphamoyl) - 2 - oxo - tetrahydroimidazole is added under stirring during 15 min., a solution of 8.7 g of 1 - (N,N - dimethylsulphamoyl) - 2 - oxo - tetrahydroimidazole in 20 ml dry dimethyl formamide is added all at once. The reaction mixture is heated under stirring and nitrogen at 95° for 3 hrs. The solvent is removed by distillation *in vacuo* and the residue is recrystallized from a mixture of methylene chloride and ether to afford 1 - (N,N - dimethylsulphamoyl) - 2 - oxo - tetrahydroimidazole which melts at 133°.

Example 5

To a suspension of 2.2 g 50% sodium hydride in 10 ml dry dimethyl formamide is added under stirring during 15 min., a solution of 8.7 g of 1 - (N,N - dimethylsulphamoyl) - 2 - oxo - tetrahydroimidazole in 20 ml dry dimethyl formamide. The reaction mixture is stirred under nitrogen at 50° for 1 hr. and a solution of 9.25 g of 1 - methyl - 2 - methylsulphonyl - 5 - nitroimidazole in 20 ml of dry dimethyl formamide is added all at once. The reaction mixture is heated under stirring and nitrogen at 95° for 3 hrs. The solvent is removed by distillation *in vacuo* and the residue is recrystallized from a mixture of methylene chloride and ether to afford 1 - (N,N - dimethylsulphamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole which melts at 133°.

Example 7

To a suspension of 24.5 g of 50% sodium hydride in 100 ml dry dimethyl formamide is added under stirring during 15 min., a solution of 78.5 g of 1 - (N,N - dimethylcarbamoyl) - 2 - oxo - tetrahydroimidazole in 150 ml of dry dimethyl formamide. The reaction mixture is stirred under nitrogen at 50° for 1 hr. and a solution of 102.5 g of 1 - methyl - 2 - methyl - sulphonyl - 5 - nitroimidazole in 100 ml dry dimethyl formamide is added during 10 min. The reaction mixture is heated under stirring and nitrogen at 100° for 3 hours. It is worked up as described under example 4 and the residue is recrystallized from a mixture of methylene chloride and hexane to afford 1 - (N,N - dimethylcarbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole which melts at 190—191°.

The starting material required is prepared as follows: A mixture of 86 g of ethylene urea and 118 g of N,N - dimethylcarbamoyl chloride in 200 ml ethylene dichloride is heated under reflux for 3 hrs. under nitrogen. The solution is evaporated off to dryness and the residue dissolved in chloroform and chromatographed on a column of 1.5 kg of silica gel. The fractions that eluted with 5% methanol in chloroform are combined and recrystallized from a mixture of methylene chloride and hexane to afford 1 - (N,N - di-

triturated with 50 ml water and extracted with ethylene dichloride. The ethylene dichloride extract is dried over anhydrous sodium sulphate and evaporated off to dryness. The residue is chromatographed over silica gel. The fraction that is eluted with 2% methanol in chloroform affords 1 - (N - methylthiocarbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole which melts at 213° after recrystallization from a mixture of methylene chloride and hexane.

The starting material required for the above reaction is prepared as follows: A mixture of 8.6 of ethyleneurea and 8.7 g of ethyl isothiocyanate is heated at 100° for 4 hrs. On cooling, the crystalline product was recrystallized from a mixture of ethanol and ether to afford 1 - (N - ethyl - thiocarbamoyl) - 2 - oxo - tetrahydroimidazole which melts at 135—136°.

Example 5

To a suspension of 2.2 g 50% sodium hydride in 10 ml dry dimethyl formamide is added under stirring during 15 min., a solution of 8.7 g of 1 - (N,N - dimethylsulphamoyl) - 2 - oxo - tetrahydroimidazole in 20 ml dry dimethyl formamide. The reaction mixture is stirred under nitrogen at 50° for 1 hr. and a solution of 9.25 g of 1 - methyl - 2 - methylsulphonyl - 5 - nitroimidazole in 20 ml of dry dimethyl formamide is added all at once. The reaction mixture is heated under stirring and nitrogen at 95° for 3 hrs. The solvent is removed by distillation *in vacuo* and the residue is recrystallized from a mixture of methylene chloride and ether to afford 1 - (N,N - dimethyl - sulphamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole which melts at 217°.

The starting material required for the above reaction is prepared as follows: A mixture of 17.2 g of ethylene urea and 28.7 g of N,N - dimethyl sulphamoyl chloride is heated at 110° for 3 hours. The reaction mixture is cooled and triturated with 100 ml methanol. Some solid material separated which is discarded. The filtrate is evaporated off to dryness and the residue is dissolved in 5% methanol in chloroform and chromatographed on a column of 150 g of silica gel. The fraction which eluted with 2% methanol in chloroform is recrystallized from a mixture of methylene chloride and hexane to give 1 - (N,N - dimethylsulphamoyl) - 2 - oxo - tetrahydroimidazole which melts at 129°.

Example 6

A mixture of 34.4 g ethylene urea and 54.2 g N,N - diethylcarbamoyl chloride is heated

under nitrogen at 110° for 3 hrs. The reaction mixture is cooled and diluted with 200 ml acetone. It is filtered and the filtrate evaporated off to dryness. The oily product is chromatographed on a column of 450 g of silica gel. The fraction which eluted from 3% methanol in chloroform yields 1 - (N,N - diethylcarbamoyl) - 2 - oxo - tetrahydroimidazole as a colourless oil.

To a suspension of 5.8 g 50% sodium hydride in 20 ml dry dimethyl formamide is added under stirring during 15 min, a solution of 22 g of above mentioned 1 - (N,N - diethylcarbamoyl) - 2 - oxo - tetrahydroimidazole in 40 ml of dry dimethyl formamide. The reaction mixture is stirred under nitrogen at 50° for 1 hr and a solution of 24.6 g of 1 - methyl - 2 - methylsulphonyl - 5 - nitroimidazole in 40 ml of dry dimethyl formamide is added all at once.

The reaction mixture is worked up in the manner described under example 4 and the dark oily residue (36 g) is chromatographed over a column of 360 g of silica gel. The fraction that eluted with 2.5% methanol in chloroform yields a crystalline substance which is recrystallized from a mixture of methylene chloride and hexane to give 1 - (N,N - diethylcarbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazole - (2)] - tetrahydroimidazole which melts at 133°.

Example 7

To a suspension of 24.5 g of 50% sodium hydride in 100 ml dry dimethyl formamide is added under stirring during 15 min., a solution of 78.5 g of 1 - (N,N - dimethylcarbamoyl) - 2 - oxo - tetrahydroimidazole in 150 ml of dry dimethyl formamide. The reaction mixture is stirred under nitrogen at 50° for 1 hr. and a solution of 102.5 g of 1 - methyl - 2 - methyl - sulphonyl - 5 - nitroimidazole in 100 ml dry dimethyl formamide is added during 10 min. The reaction mixture is heated under stirring and nitrogen at 100° for 3 hours. It is worked up as described under example 4 and the residue is recrystallized from a mixture of methylene chloride and hexane to afford 1 - (N,N - dimethylcarbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole which melts at 190—191°.

The starting material required is prepared as follows: A mixture of 86 g of ethylene urea and 118 g of N,N - dimethylcarbamoyl chloride in 200 ml ethylene dichloride is heated under reflux for 3 hrs. under nitrogen. The solution is evaporated off to dryness and the residue dissolved in chloroform and chromatographed on a column of 1.5 kg of silica gel. The fractions that eluted with 5% methanol in chloroform are combined and recrystallized from a mixture of methylene chloride and hexane to afford 1 - (N,N - di-

methyl - carbamoyl) - 2 - oxo - tetrahydroimidazole which melts at 134—136°.

Example 8

5 To a suspension of 4.5 g of 50% sodium hydride in 10 ml dry dimethyl formamide is added under stirring during 15 min., a solution of 16 g of 1 - ethyl - sulphonyl - 2 - oxo - tetrahydroimidazole in 30 ml dry dimethyl formamide. The reaction is stirred under nitrogen at 50° for 45 min. and a solution of 18.5 g of 1 - methyl - 2 - methylsulphonyl - 5 - nitro - imidazole in 30 ml dry dimethyl formamide is added all at once and the reaction mixture heated at 100° for 3 hrs.

15 It is worked up in the manner described under example 4 and the residue is recrystallized from a mixture of methylene chloride and hexane to afford 1 - ethyl - sulphonyl - 2 - oxo - 3 - [1 - methyl - 5 - nitro - imidazolyl - (2)] - tetrahydroimidazole which melts at 176—177°.

20 The starting material required is prepared as follows: A mixture of 29.2 g of ethyleneurea and 43.7 g of ethane sulphonyl chloride is heated at 110° for 3 hrs under nitrogen. The reaction mixture is triturated with 30 ml methanol and filtered. The filtrate is evaporated off and the residue is dissolved in chloroform and chromatographed on a column of 750 g of silica gel. The fraction which eluted with 5% methanol in chloroform, is recrystallized from a mixture of methylene chloride and hexane to afford 1 - ethylsulphonyl - 2 - oxo - tetrahydroimidazole which melts at 114—116°.

Example 9

40 To a suspension of 1.2 g of 50% sodium hydride in 10 ml dry dimethyl formamide is added under stirring during 15 minutes, a solution of 5.8 g of 1 - (4 - fluorophenylsulphonyl) - 2 - oxo - tetrahydroimidazole in 28 ml dry dimethyl formamide. The reaction mixture is stirred under nitrogen at room temperature for 1 hr and then at 50° for an other hour. A solution of 5 g of 1 - methyl - 2 - methylsulphonyl - 5 - nitroimidazole in 10 ml dry dimethyl formamide is added all at once. The reaction mixture is heated under stirring and nitrogen at 100° for 3 hrs. and worked up in the manner described under example 4. The residue is chromatographed on a column of 150 g silica gel. The fractions which eluted with 2.5% methanol in chloroform gives a crystalline substance which is recrystallised from a mixture of methylene chloride and hexane to afford 1 - (4 - fluorophenylsulphonyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole which melts at 198—200°.

60 The starting material required is prepared as follows: A mixture of 17.2 g of ethyleneurea and 19.5 g of p - fluorobenzene sulphonyl chloride is heated at 110° for 3 1/2

hrs. The residue is recrystallized from a mixture of methanol and water to afford 1 - (4 - fluorophenylsulphonyl) - 2 - oxo - tetrahydroimidazole which melts at 183—185°.

Example 10

A solution of 0.4 g of 2 - oxo - 3 - [1 - methyl - 4 - nitroimidazolyl - (2)] - tetrahydroimidazole in 8 ml dry dimethyl formamide is added dropwise to a suspension of 0.1 g of 50% sodium hydride in 2 ml dry dimethyl formamide. The reaction mixture is stirred at room temperature for 15 minutes and a solution of 0.2 g of methyl isocyanate in 2 ml dry dimethyl formamide is added and the reaction mixture heated for 3 hrs. at 100° and worked up in the manner described under example 4. The residue is chromatographed on a column of 40 g silica gel. The fraction which eluted with 5% methanol in chloroform affords 1 - (methyl - carbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole which melts at 176—177°.

Example 11

To a stirred suspension of 1.3 g of 50% sodium hydride dispersion in mineral oil in 20 ml dry dimethyl formamide is added dropwise a solution of 1 - piperidinocarbonyl - 2 - oxo - tetrahydroimidazole in 15 ml dimethylformamide at ambient temperature. The temperature of the reaction is raised to 50° and stirred for 30 min. A solution of 5.12 g of 1 - methyl - 2 - methylsulfonyl - 5 - nitroimidazole in 20 ml dimethyl formamide is added dropwise in the course of 20 min, the temperature raised to 95° and maintained for 1 hr. The solvent is removed under reduced pressure, the residue washed with ether and treated with water containing crushed ice. The residue after removal of the aqueous layer is treated with isopropanol ether (5:1). The colourless granular precipitate is recrystallised from ethyl acetate - hexane to afford 1 - piperidinocarbonyl - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole melting at 152°.

Example 12

To a stirred suspension of 1.92 g of 50% sodium hydride dispersion in mineral oil in 25 ml dry dimethyl formamide is added dropwise a solution of 7.96 g of 1 - morpholinocarbonyl - 2 - oxo - tetrahydroimidazole in 15 ml dry dimethylformamide at ambient temperature. The above suspension is stirred at 50° for 30 min. A solution of 8.2 g of 1 - methyl - 2 - methylsulfonyl - 5 - nitroimidazole in 15 ml dimethyl formamide is added in the course of 5 min. The temperature of the reaction is raised to 95° and stirring continued for 2 hrs. The solvent is removed under reduced pressure, the residue is washed with ether and treated with crushed ice. The solid obtained is filtered to give 1 - morpholino-

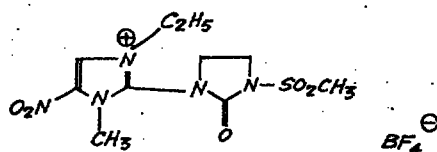
1.92 g of 50%
a mineral oil in 110
is added drop-
1 - morpholino-
hydroimidazole in
at ambient tem- 115
perature is stirred at
of 8.2 g of 1 -
- 5 - nitroimid-
- amide is added
temperature of the 120
stirring continued
removed under re-
is washed with
ed ice. The solid
1 - morpholino- 125

carbonyl - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole
melting at 180° after crystallization from ether.

1 - Morpholinocarbonyl - 2 - oxo - tetrahydroimidazole used as starting material is prepared as follows: To a stirred solution of 22.27 g of 1 - chloro - carbonyl - 2 - oxo - tetrahydroimidazole in 80 ml anhydrous benzene is added dropwise a solution of 26.1 g of morpholine in 20 ml benzene. The mixture is refluxed for 4 hrs. The product is filtered off, treated with a saturated solution of NaHCO_3 and filtered. Recrystallization from isopropanol affords 1 - morpholinocarbonyl - 2 - oxo - tetrahydroimidazole melting at 158° .

Example 13

A solution of 2.9 g 1 - (methylsulphonyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole and 1.9 g ethyloxonium fluoborate in 200 ml dry chloroform is set aside at room temperature for 72 hrs. A thick oil separates out, which crystallizes on treatment with alcohol. The solid is filtered off, boiled with acetone and filtered. The residue is crystallized from aqueous alcohol to give 1 - methyl - 2 - [3 - (methylsulphonyl) - 2 - oxo - tetrahydroimidazolyl - (1)] - 3 - ethyl - 5 - nitroimidazolium fluoborate of the formula



melting at 265—267°C.

Example 14

A solution of 3.0 g 1 - (methylsulphonyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole in 30 ml dimethylformamide containing 3.0 g potassium iodide is heated under reflux for 16 hours. The solvent is removed *in vacuo* and the residue treated with water and filtered. The filtrate is made acidic with 2N hydrochloric acid, cooled and filtered to remove unreacted starting material. The filtrate is cooled further and the crystals that separate are filtered off and recrystallized twice from acetone - methanol to give 1 - (methylsulphonyl) - 2 - oxo - 3 - [1 - methyl - 4 - nitroimidazolyl - (2)] - tetrahydroimidazole melting at 180—181°.

Example 15

A solution of 3.0 g 1 - (methylthiocarbonyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole in 25 ml dimethylformamide containing 3.0 g potassium iodide is heated under reflux for

16 hr. The solvent is removed *in vacuo* and water added to the residue. The mixture is filtered and the precipitate washed successively with hot ethanol and methanol and crystallized twice from acetone - methanol to give 1 - 60 (methylthiocarbamoyl) - 2 - oxo - 3 - [1 - methyl - 4 - nitroimidazolyl - (2)] - tetrahydroimidazole melting at 239—241°.

Example 16

A solution of 0.49 g 1 - (methylsulphonyl) - 2 - oxo - tetrahydroimidazole in 5 ml dimethylformamide is stirred with 0.15 g of a 50% suspension of sodium hydride in mineral oil at 50° for 1 hr. It is then treated with 0.57 g of 1 - methyl - 2 - (methylsulfinyl) - 5 - nitroimidazole and the solution heated and stirred at 100° for 3 hours. The solvent is evaporated off *in vacuo* and the water added to the residue. The crystalline precipitate is filtered off and recrystallized from acetone - methanol to give 1 - (methylsulphonyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole melting at 202—204° and is identical with the preparation described in Example 3.

The starting 1 - methyl - 2 - (methylsulfinyl) - 5 - nitroimidazole for the above reaction is made as follows:

A solution of 3.4 g 1 - methyl - 2 - (methylmercapto) - 5 - nitroimidazole and 5 ml 30% aqueous hydrogen peroxide in 20 ml β - methoxyethanol is heated at 100° with freshly prepared titanium dioxide for 6 hrs. It is then diluted with water and filtered. The filtrate is extracted with chloroform and the chloroform layer evaporated to give 2.5 g of an oil which solidifies slowly upon standing. The solid is crystallized once from ethanol and then from chloroform - ether to give 1 - methyl - 2 - (methylsulfinyl) - 5 - nitroimidazole.

Example 17

To a suspension of 6.1 g 50% sodium hydride in 20 ml dry dimethyl formamide is added under stirring during 15 min. a solution of 30 g 1 - (N,N - diethylsulphamoyl) - 2 - oxo - tetrahydroimidazole in 50 ml dry dimethyl formamide. The reaction mixture is stirred under nitrogen at 50° for 1 hour and a solution of 25.6 g of 1 - methyl - 2 - methylsulphonyl - 5 - nitro - imidazole in 40 ml of dry dimethyl formamide is added all at once. The reaction is heated under stirring and nitrogen at 95° for 3 hours. The solvent is removed by distillation *in vacuo* and the residue triturated with 100 ml water. The resulting suspension is extracted with ethylene dichloride, dried and evaporated to dryness. The residue is chromatographed on a column of silica gel and the fraction that elutes with 1% methanol in chloroform affords a crystalline mass. This is recrystallized from a mixture of methylene chloride and ether to

afford 1 - (N,N - diethyl sulphamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole which melts at 146—147°.

5 The starting material required for the above reaction is prepared as follows:

A mixture of 51.6 g of ethylene urea and 90 g of N,N - diethyl - sulphamoyl - chloride is heated to 110° for 3 hours. The reaction mixture is cooled and triturated with 300 ml of methanol, filtered and the filtrate evaporated off to dryness and the residue dissolved in 5% methanol in chloroform and chromatographed on a column of silica gel. That fraction which elutes with 5% methanol in chloroform is recrystallized from a mixture of methylene chloride and hexane to give 1 - (N,N - diethylsulphamoyl) - 2 - oxo - tetrahydroimidazole which melts at 80—82°.

20

Example 18

To a stirred suspension of 1.6 g of 50% sodium hydride dispersion in mineral oil in 30 ml dry dimethyl formamide is added during 15 min. a solution of 5.9 g of 1 - pyrrolidinocarbonyl - 2 - oxo - tetrahydroimidazole in 15 ml dry dimethyl formamide. The reaction is stirred under nitrogen at 50° for 1 hour and a solution of 6.6 g of 1 - methyl - 2 - methyl - sulphonyl - 5 - nitroimidazole in 20 ml dry dimethyl formamide is added all at once. The mixture is heated under stirring and nitrogen at 95° for 1 hour. The solvent is removed by distillation *in vacuo* and the residue is triturated with water and extracted with ethylene dichloride, dried and evaporated to dryness. The residue is chromatographed over silica gel and that fraction which elutes with 3% methanol in chloroform affords a crystalline mass. This is recrystallised from a mixture of methylene chloride and hexane to afford 1 - pyrrolidino - carbonyl - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole which melts at 155—156°.

45 The starting material required for the above reaction is prepared as follows:

A mixture of 40 g ethylene urea and 72 g of 1 - pyrrolidinocarbonyl chloride (b.p. 100—104°/4.5 mm Hg.) is heated at 110° for 3 hours. The reaction mixture is cooled, 200 ml of chloroform added, the insoluble material filtered off and the filtrate evaporated to dryness. It is chromatographed on a column of silica gel. That fraction which elutes with 4% of methanol in chloroform is recrystallised from ethylacetate to give 1 - pyrrolidino - carbonyl - 2 - oxo - tetrahydroimidazole which melts at 153—154°.

60

Example 19

To a suspension of 3.5 g of 50% sodium hydride in 20 ml dimethyl formamide is added under stirring during 15 minutes, a solution of 15.6 g. of 1 - pyrrolidino - sulphonyl - 2 -

oxo - tetrahydroimidazole in 40 ml dry dimethyl formamide. The reaction mixture is stirred under nitrogen at 50° for 1 hour, and a solution of 14.4 g of 1 - methyl - 2 - methyl - sulphonyl - 5 - nitroimidazole in 30 ml dry dimethyl formamide is added all at once. The reaction mixture is heated under stirring and nitrogen at 95° for 3 hours. The solvent is removed by distillation *in vacuo* and the residue is triturated with 50 ml of water when a crystalline precipitate is formed. This is filtered and recrystallised from a mixture of methylene chloride and ether to afford 1 - pyrrolidino - sulphonyl - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole which melts at 226°.

The starting material required for the above reaction is prepared as follows:

A mixture of 30 g of ethyleneurea and 64.5 g of pyrrolidino - 1 - sulphonylchloride (b.p. 120°/11 mm Hg.) is heated at 110° for 3 hours. The reaction mixture is cooled, dissolved in 300 ml chloroform, filtered, the filtrate evaporated off and the residue is redissolved in 2.5% methanol in chloroform and chromatographed on a column of silica gel. That fraction which elutes with 2.5% methanol in chloroform affords 1 - pyrrolidino - sulphonyl - 2 - oxo - tetrahydroimidazole which is recrystallized from ethylacetate, m.p. 150°.

Example 20

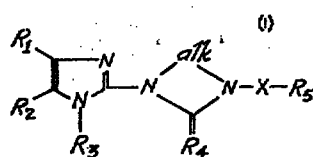
To a stirred suspension of 1.92 g of 50% sodium hydride dispersion in mineral oil in 20 ml dry dimethyl formamide is added dropwise a solution of 9.3 g of 1 - piperidino - sulfonyl - 2 - oxo - tetrahydroimidazole in 15 ml dimethyl formamide at ambient temperature. The temperature of the reaction is raised to 50° and stirred for 30 min. A solution of 8.2 g of 1 - methyl - 2 - methyl - sulfonyl - 5 - nitroimidazole in 25 ml of dimethyl formamide is added in one lot and the temperature of the reaction is maintained for 2 hrs. at 100°. The solvent is removed under reduced pressure and the residue treated with water containing crushed ice. The residue after removal of the aqueous layer is treated with isopropanol ether (5:1). The pale yellow precipitate so obtained is recrystallised from ethyl acetate to afford 1 - piperidino - sulfonyl - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole melting at 192°.

The starting material is prepared as follows:

To 17.4 of ethyleneurea is added with shaking 36 g of piperidinosulfonyl chloride (b.p. 130°/11 mm) and the mixture kept under nitrogen at 100° for 3 hrs. The mixture is cooled and the gummy material treated with methanol - isopropanol (1:1) to give a granular product of 1 - piperidinosulfonyl - 2 - oxo - tetrahydroimidazole which melts at 201° on recrystallization from methanol.

WHAT WE CLAIM IS:—

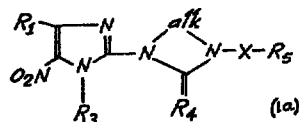
1. Compounds having the general formula I



wherein one of the groups R_1 and R_2 is a hydrogen or lower alkyl and the other a nitro group, R_3 is a lower alkyl group, R_4 is an oxo or thioxo group, X is a carbonyl, thiocarbonyl, sulphinyl or sulphonyl group and R_5 when X is a carbonyl group is amino, a lower alkylamino, di-lower alkylamino, piperidino, morpholino or pyrrolidino group, and when X is a thiocarbonyl, sulphinyl or sulphonyl group, R_5 is a lower alkyl, phenyl optionally substituted by one or more lower alkyl, lower alkoxy, halogen or trifluoromethyl; amino, a lower alkylamino, di-lower alkylamino, piperidino or pyrrolidino group, and alk is 1,2-ethylene, and their salts.

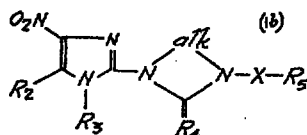
2. A compound having the formula I given in claim 1, in which formula R_1 , R_2 , R_3 , R_4 and alk have the meanings given in claim 1, X is a carbonyl, thiocarbonyl, sulphinyl or sulphonyl group and R_5 when X is a carbonyl group is amino, lower alkylamino or di-lower alkylamino group, and X is a thiocarbonyl, sulphinyl or sulphonyl group, R_5 is lower alkyl, phenyl optionally substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; amino, lower alkylamino or di-lower alkylamino group, and their salts.

3. Compounds having the general formula Ia



wherein R_1 represents hydrogen or a lower alkyl group, R_2 is a lower alkyl group, R_3 is an oxo group, X , R_4 and alk have the meanings defined in claim 2, and their salts.

4. Compounds having the general formula Ib



where R_2 represents hydrogen or a lower alkyl group, R_3 a lower alkyl group, R_4 is an oxo group, and X , R_5 and alk have the meanings defined in claim 2, and their salts.

5. Compounds of formula Ia, wherein R_1 , R_2 , R_3 , R_4 and alk have the meanings defined under formula Ia in claim 3, X is a carbonyl group and R_5 represents amino, a lower

alkylamino or di-lower alkylamino group, and their salts.

6. Compounds of formula Ib, wherein R_2 , R_3 , R_4 and alk have the meanings defined under formula Ib in claim 4, X is a carbonyl group and R_5 is amino, a lower alkylamino or di-lower alkylamino group, and their salts.

7. Compounds of formula Ia, wherein R_1 , R_2 , R_3 , R_4 and alk have the meanings defined under formula Ia in claim 3, X is a thiocarbonyl group and R_5 represents a lower alkyl, phenyl optionally substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; amino, a lower alkylamino or di-lower alkylamino group, and their salts.

8. Compounds of formula Ib, wherein R_2 , R_3 , R_4 and alk have the meanings defined under formula Ib in claim 4, X is a thiocarbonyl group and R_5 represents a lower alkyl, phenyl optionally substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; amino, a lower alkylamino or di-lower alkylamino group, and their salts.

9. Compounds of formula Ia, wherein R_1 , R_2 , R_3 , R_4 and alk have the meanings defined in claim 7 and X is a sulphinyl or sulphonyl group, and their salts.

10. Compounds of formula Ib, wherein R_2 , R_3 , R_4 , R_5 and alk have the meanings defined in claim 8 and X is a sulphinyl or sulphonyl group, and their salts.

11. Compounds of formula Ia, wherein R_1 is hydrogen or lower alkyl, R_2 represents lower alkyl, X is a thiocarbonyl group, R_3 is an oxo group, and R_4 is amino, lower alkylamino or di-lower alkylamino and alk is 1,2-ethylene, and their salts.

12. Compounds of formula Ib, wherein R_2 is hydrogen or lower alkyl, R_3 represents lower alkyl, X is a thiocarbonyl group, R_4 is an oxo group and R_5 is amino, lower alkylamino or di-lower alkylamino, and alk is 1,2-ethylene, and their salts.

13. Compounds of formula Ia, wherein R_1 is hydrogen or lower alkyl, R_2 represents lower alkyl, X is a sulphinyl or sulphonyl group, R_3 is an oxo group, and R_4 is amino, lower alkylamino or di-lower alkylamino, and alk is 1,2-ethylene, and their salts.

14. Compounds of formula Ib, wherein R_2 is hydrogen or lower alkyl, R_3 represents lower alkyl, X is a sulphinyl or sulphonyl group, R_4 is an oxo group, and R_5 is amino, lower alkylamino or di-lower alkylamino, and alk is 1,2-ethylene, and their salts.

15. Compounds of formulae Ia and Ib, wherein R_1 and R_2 is hydrogen, methyl or ethyl, R_3 is methyl or ethyl, X is a carbonyl group and R_5 is amino, methylamino, ethylamino, dimethylamino or diethylamino and alk is 1,2-ethylene, and their salts.

16. Compounds of formulae Ia and Ib, wherein R_1 or R_2 is hydrogen, methyl or ethyl, R_3 is methyl or ethyl, X is a thiocarbonyl and



R_5 is amino, methylamino, ethylamino, dimethylamino or diethylamino and alk is 1,2-ethylene, and their salts.

17. Compounds of formulae Ia and Ib, wherein R_1 and R_2 is hydrogen, methyl or ethyl, R_3 is methyl or ethyl, X is a sulphonyl group and R_5 is amino, methylamino, ethylamino, dimethylamino or diethylamino and alk is 1,2-ethylene, and their salts.

18. 1 - (Methylthiocarbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

19. 1 - (Methylcarbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

20. 1 - (Methylsulphonyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

21. 1 - (N - Ethylthiocarbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

22. 1 - (N,N - Dimethyl - sulphamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

23. 1 - (N,N - Diethylcarbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

24. 1 - (N,N - Dimethylcarbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

25. 1 - Ethylsulphonyl - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

26. 1 - (4 - Fluorophenylsulphonyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

27. 1 - (N - Methylcarbamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

28. 1 - Piperidino - carbonyl - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

29. 1 - Morpholino - carbonyl - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

30. 1 - Methyl - 2 - [3 - (methylsulphonyl) - 2 - oxo - tetrahydroimidazolyl - (1)] - 3 - ethyl - 5 - nitroimidazolium - fluoborate.

31. 1 - (Methylsulphonyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

32. 1 - (N,N - Diethylsulphamoyl) - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

33. 1 - Pyrrolidino - carbonyl - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

34. 1 - Pyrrolidino - sulphonyl - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

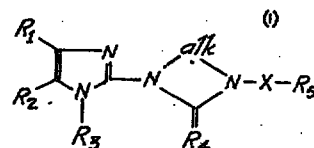
35. 1 - Piperidino - sulphonyl - 2 - oxo - 3 - [1 - methyl - 5 - nitroimidazolyl - (2)] - tetrahydroimidazole.

36 The compounds mentioned in one of

claims 18 to 29 and 31 to 35 in the form of their salts.

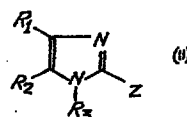
37. The compounds mentioned in one of claims 18 to 29 and 31 to 35 in the form of their pharmaceutically acceptable salts.

38. Process for the production of compounds having the general formula I

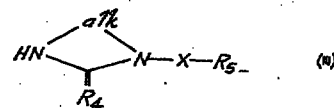


wherein all the symbols have the meanings given in claim 1, and their salts which comprises

a) reacting a compound of formula II

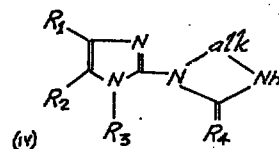


wherein R_1 , R_2 and R_3 have the meanings defined above and Z is methyl sulphonyl or methyl sulphonyl with a compound of formula III



wherein R_4 , R_5 alk and X have the meanings defined above or

b) reacting a compound of formula IV



wherein R_1 , R_2 , R_3 , R_4 and alk have the above defined meanings, with the isocyanate of formula V



and if desired, a resulting compound of the formula I, in which formula R_2 is a nitro group and R_1 represents hydrogen, is rearranged by treatment with an alkali metal iodide to a compound of the formula I, in which R_2 represents hydrogen and R_1 is a nitro group, and/or, if desired, resulting racemate mixtures are separated into the optical antipodes, and/or resulting salts are converted into the free compounds or other salts, or resulting free compounds are converted into their salts.



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5 in the form of
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(i)
V-X-R₅

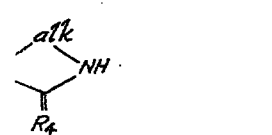
ve the meanings
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the meanings de-
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-R₅- (ii)

have the meanings

formula IV



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the isocyanate of

(V)

compound of the
ula R₂ is a nitro
hydrogen, is re-
in an alkali metal
the formula I, in
gen and R₁ is a
desired, resulting
separated into the
resulting salts are
compounds or other
compounds are con-

39. Process for the manufacture of compounds having the general formula I shown in claim 1, in which formula all the symbols have the meanings given in claim 2, and their salts, which comprises

5 a) reacting a compound of the formula II shown in claim 38, in which formula all the symbols have the meanings given in claim 38, with a compound of the formula III, in which formula R₁, alk and X have the meanings given in claim 38 and R₃ has the meaning given in claim 2 or

10 b) reacting a compound of formula IV shown in claim 38, in which formula R₁, R₂, R₃, R₄ and alk have the meanings given in claim 1, with the isocyanate of formula V shown in claim 38, and, if desired, a resulting compound of the formula I, in which formula R₂ is a nitro group and R₁ represents hydrogen, is rearranged by treatment with an alkali metal iodide to a compound in which R₂ represents hydrogen, and R₁ is a nitro group, and/or, if desired, resulting racemate mixtures are separated into the optical antipodes, and/or

25 resulting salts are converted into the free compounds or other salts, or resulting free compounds are converted into their salts.

40. A therapeutic composition comprising a compound of formula I as defined in claim 1 and a pharmaceutically acceptable solid carrier or diluent therefore.

41. A therapeutic composition comprising a compound of formula I as defined in claim 2 and a pharmaceutically acceptable solid carrier or diluent therefore.

42. An antibacterial active composition useful as gram negative bacteriocidal agent comprising a compound having the general formula I as defined in claim 1 or a pharmaceutically acceptable acid addition salt of such a compound and a pharmaceutically acceptable diluent or carrier therefore.

43. An antibacterial active composition use-

ful as gram negative bacteriocidal agent comprising a compound having the general formula I as defined in claim 2 or a pharmaceutically acceptable acid addition salt of such a compound and a pharmaceutically acceptable diluent or carrier therefore.

44. An antiprotozoic active composition useful as an antiprotozoic active agent against trichomonads and amoeba comprising a compound having the general formula I as defined in claim 1 or a pharmaceutically acceptable acid addition salt of such a compound and a pharmaceutically acceptable diluent or carrier therefore.

45. An antiprotozoic active composition useful as an antiprotozoic active agent against trichomonads and amoeba comprising a compound having the general formula I as defined in claim 2 or a pharmaceutically acceptable acid addition salt of such a compound and a pharmaceutically acceptable diluent or carrier therefore.

46. An anthelmintic active composition useful as an anthelmintic active agent against schistosoma comprising a compound having the general formula I as defined in claim 1 or a pharmaceutically acceptable acid addition salt of such a compound and a pharmaceutically acceptable diluent or carrier therefore.

47. An anthelmintic active composition useful as an anthelmintic active agent against schistosoma comprising a compound having the general formula I as defined in claim 2 or a pharmaceutically acceptable acid addition salt of such a compound and a pharmaceutically acceptable diluent or carrier therefore.

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