

PATENT SPECIFICATION

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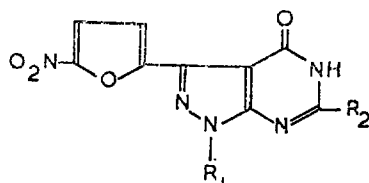
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(54) NITROFURYL-PYRAZOLOPYRIMIDINONES

(71) We, CIBA-GEIGY A.G., a body corporate organised according to the laws of Switzerland, of CH-4002, 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 substituted heterocyclic compounds, and in particular to nitrofuryl derivatives of pyrazolopyrimidinones and to processes for the production of these compounds.

According to the invention, there are provided compounds having the general formula I



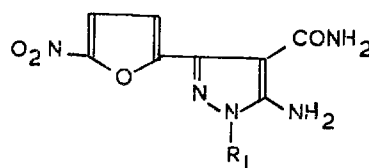
(I)

in which R₁ is an unsubstituted alkyl group containing from one to five carbon atoms, or a carbalkoxy group containing from one to five carbon atoms in the alkyl moiety, and R₂ is hydrogen, an alkyl group containing

from one to five carbon atoms which may be unsubstituted or in which one or more or all the hydrogens may be replaced by chlorine or bromine atoms, or is a cycloalkyl group containing from five to seven carbon atoms in the carbocyclic ring, an aralkyl group containing up to twelve carbon atoms or an alkenyl group containing from two to four carbon atoms.

Examples of alkyl groups which may form R₁ or R₂, or which may form the carbon skeleton for R₁ or R₂ are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tertiarybutyl and n-pentyl groups. If R₁ is an alkyl group then it preferably contains from one to three carbon atoms. If R₂ represents a cycloalkyl group the cycloalkyl group may be a cyclohexyl group; if R₂ is aralkyl, then it may be a benzyl group.

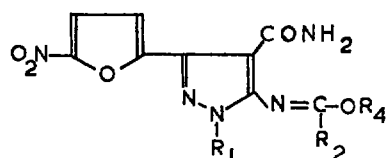
The invention also provides a process of producing the compounds of formula I which comprises treating a compound of the general formula II



(II)



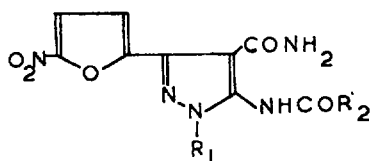
in which R_1 has the meaning as given under formula I, with a reagent $R_2.C(OR_4)_3$ where R_4 is an alkyl group containing from one to three carbon atoms, with or without a reaction promotor such as a carboxylic acid anhydride, to give an intermediate of formula III



(III)

wherein R_1 , R_2 and R_4 are as hereinbefore defined, which is cyclised without isolation.

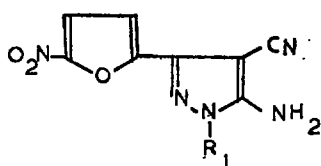
This reaction may be carried out directly between the compound II and the selected reagent, or may be carried out in the presence of an inert solvent, such as for example dimethylsulphoxide or dimethylformamide. The presence of an inert solvent is of course desirable if the compound II is a solid. In all cases, the reaction will preferably be carried out at a temperature of from 20°C. to the reflux temperature of the reaction mixture. Alternatively, a compound of the general formula II may be reacted with a carboxylic acid derivative $R_2.COX$ or $(R_2.CO)_2O$ where R_2 is as previously defined and X is hydroxyl, halogen (preferably chlorine or bromine), amino, or the grouping $-OR_3$ where R_3 is an alkyl or alkenyl group containing up to three carbon atoms, to give an intermediate of general formula IV



(IV)

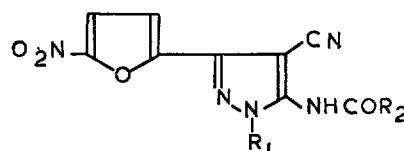
wherein R_1 and R_2 are as previously defined. The compounds of general formula IV are cyclised without isolation.

In a further process, compounds of general formula V



(V)

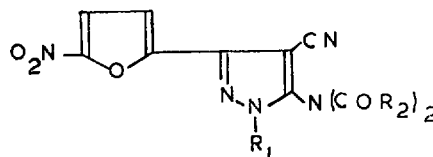
wherein R_1 is as herein before defined, may be reacted with formic acid or with a carboxylic acid derivative $R_2.COX$ or $(R_2.CO)_2O$, where R_1 , R_2 and X have their previous significance [except that X may not be hydroxyl] to give an intermediate of general formula VI



(VI)

the reaction being carried out in the presence of an acid or basic catalyst and the intermediate then cyclised with or without preliminary isolation. Compounds of general formula VI are novel per se, and have antimicrobial activity.

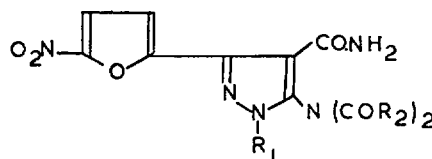
Compounds of formula I in which R_1 and R_2 are as previously defined may also be prepared, according to the invention, by a process which comprises treating a compound of the general formula V with an excess of an acid anhydride $(R_2.CO)_2O$, in the absence of catalyst, to form an intermediate of general formula VII



(VII)

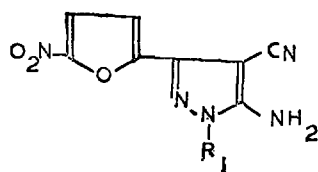
and subsequently protonating and hydrolysing this intermediate with or without preliminary isolation. Compounds of formula VII are novel, and have antimicrobial activity.

The present invention also provides a process of preparing the compounds of formula I which comprises cyclizing a compound of general formula VIII,



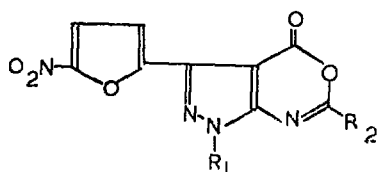
(VIII)

The present invention also provides a process of preparing the compounds of formula I which comprises treating a compound of the general formula V



(V)

with an acid anhydride $(R_2CO)_2O$ in the presence of an arylsulphonic acid catalyst to give an intermediate of general formula IX



(IX)

wherein R_1 and R_2 are as previously defined, and then reacting this intermediate with or without preliminary isolation, with ammonia or with a compound which will provide ammonia *in situ* under the conditions of the reaction.

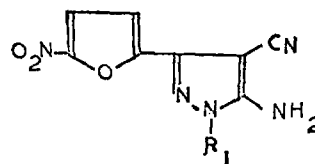
The first stage of the reaction may be carried out by contacting the selected compound of formula V with the selected acid anhydride directly, in the presence of the reaction catalyst, provided that R_1 and R_2 are of such nature that the reaction mixture is liquid. If desired, however, or if the reactants are solid, the reaction may be conducted in the presence of a solvent inert under the reaction conditions. One very satisfactory catalyst is *p*-toluene sulphonic acid, although other arylsulphonic acids may also be used.

Intermediates of formula IX are isolatable, and are novel compounds *per se*.

The second stage of the process involves the treatment of the intermediate of formula IX with ammonia or with a compound which will generate ammonia. If ammonia itself is to be used, then it may be used as an alcoholic solution, or may be used in the form of liquid ammonia; an example of a compound which will generate ammonia in the presence of water is hexamethylene tetramine. While there is no specific limitation on the temperature at which this stage is carried out, apart from obvious restrictions imposed by the reactants, it is preferred that the reaction be conducted at as low a temperature as possible consistent with a reasonable rate of reaction being obtained. For this reason, we prefer to use a solvent having a reasonably low boiling point, so that the reaction may be carried out under reflux and yet still at a moderate temperature.

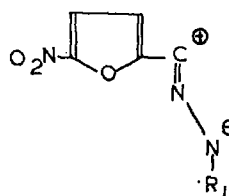
The starting compounds of formula II can be prepared by hydrolysing the corre-

sponding nitrofuryl-pyrazole derivative having the formulae V



(V)

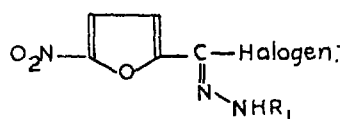
wherein R_1 has the previous significance. The compounds of formulae V are themselves prepared by reacting the corresponding nitrofuryl-nitrilimine which in one of its canonical forms may be represented by the formula X



(X)

with malononitrile, where R_1 has its previous significance.

The nitrofuryl-nitrilimine of formula X may conveniently be generated, as required, during the course of the reaction with malononitrile, by treating with a base the corresponding nitrofuryl - α - halo - hydrazone having the formula XI



(XI)

The process may, if desired, be effected in the presence of a conventional base or other hydrogen halide acceptor. The halogen present in the halohydrazone of formula XI is preferably chlorine or bromine.

The compounds of the invention having the general formula I, have valuable antimicrobial properties, and in particular have antibacterial, antimycoplasmal, anthelmintic, antiprotozoal, coccidiostatic, trypanocidal and antimalarial activity of value in human or veterinary medicine. The compounds are particularly valuable in the treatment of infections of the intestinal and urinary tracts. The compounds may also 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, 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, 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 bacteria, 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 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 and for the oral treatment of urinary

tract infections. These units preferably contain from 10% to 90% of the active compound to enable the administration of daily doses of from 0.1 to 2.5 grams to adults, or of suitable reduced doses to children to be made. Tablets and dragee cores are produced by combining the active compounds 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 mixture of solvents. Dye-stuffs can be added to these coatings, for instance to differentiate between varying dosages. Soft gelatine capsules and other closed capsules consist, for example, of a mixture of gelatines and glycerol and may contain, for example, mixtures of the active compound with polyethylene glycol. Hard gelatine capsules contain, for example, granulates of an active substance with solid pulverulent carriers, for instance lactose, saccharose, sorbitol, mannitol, starches (such as potato starch, maize starch or amylopectin), cellulose derivatives of gelatines, and magnesium stearate or stearic acid.

In all forms for administration the active compounds can be present as sole active ingredients or they can also be combined with other known pharmacologically active and especially antibacterial and/or antimycotically or other antimicrobially active substances, for example to 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, with sulfamerazine or sulfafurazole or other derivatives of sulfanilamide, with chloramphenicol or tetracycline or other antibiotics, with 3,4',5-tribromosalicylanilide or other halogenated salicylanilides, with halogenated carbanilides, with halogenated benzoxazoles or benzoxazolones, with polychloro-hydroxydiphenylmethanes, with halogen - dihydroxy - diphenyl sulphides, with 4,4' - dichloro - 2 - hydroxy - diphenylether or 2',4,4' - trichloro - 2 - hydroxydiphenylether or other polyhalogenhydroxydiphenylethers, or with bactericidal quaternary compounds or with certain dithiocarbamic acid derivatives such as tetramethylthiuram disulphide. Also, carriers which themselves have favourable pharmacological properties may be used, for instance sulphur as a powder base or zine stearate as a component of ointment bases.

The invention also provides a method of protecting an organic material susceptible to bacterial or other microbial attack which

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comprises treating the material with a compound of formula I. The organic material may be, for instance, a natural or synthetic polymeric material, a proteinaceous or carbohydrate substance, or a natural or synthetic fibre or textile material formed therefrom.

5 The invention also provides an animal feed-stuff composition comprising a compound of formula I, in an amount sufficient to promote the growth of the animal fed with the composition.

10 Some examples will now be given, all parts and percentages being by weight unless otherwise stated. Example 17 illustrates the preparation of an intermediate.

EXAMPLE 1

15 A mixture of 10 grams of 5-amino-4-cyano-1-methyl-3-(5-nitro-2-furyl)-pyrazole and 100 millilitres of 90% formic acid was heated under reflux for 1 hour and cooled. The crystalline solid was collected, washed with water and recrystallised from dimethylformamide. The product was 1-methyl-3-(5-nitro-2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one, having melting point $>300^{\circ}\text{C}$.

EXAMPLE 2

20 The procedure described in Example 1 was carried out using 5-amino-4-carbamoyl-1-methyl-3-(5-nitro-2-furyl)-pyrazole as starting material instead of 5-amino-4-cyano-1-methyl-3-(5-nitro-2-furyl)-pyrazole, the reaction conditions being the same.

35 The product was 1-methyl-3-(5-nitro-2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one, having melting point $>300^{\circ}\text{C}$., identical with the product obtained in Example 1.

EXAMPLE 3

40 A mixture of 0.2 grams of 5-amino-4-carbamoyl-1-methyl-3-(5-nitro-2-furyl)-pyrazole and 5.0 millilitres of triethylorthoformate was heated under reflux for 3 hours and cooled. The crystalline solid was collected, washed with ethanol and dried. The product was 1-methyl-3-(5-nitro-2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one having melting point $>300^{\circ}\text{C}$.

EXAMPLE 4

50 The procedure described in Example 1 was carried out using 5-amino-4-cyano-1-isopropyl-3-(5-nitro-2-furyl)-pyrazole as starting material instead of 5-amino-4-cyano-1-methyl-3-(5-nitro-2-furyl)-pyrazole, the reaction conditions being the same.

55 The product was 1-isopropyl-3-(5-nitro-2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one.

EXAMPLE 5

The procedure described in Example 1 was carried out using 5-amino-4-cyano-3-(5-nitro-2-furyl)-1-n-pentyl-pyrazole as starting material instead of 5-amino-4-cyano-1-methyl-3-(5-nitro-2-furyl)-pyrazole, the reaction conditions being the same.

65 The product was 3-(5-nitro-2-furyl)-1-n-pentyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one.

EXAMPLE 6

A mixture of 10 grams of 5-amino-4-carbamoyl-1-methyl-3-(5-nitro-2-furyl)-pyrazole and 100 millilitres of acetic anhydride was heated under reflux for 6 hours and cooled. The crystalline solid was collected, washed with alcohol and recrystallised from dimethylformamide.

75 The product was 1,6-dimethyl-3-(5-nitro-2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one which has melting point $>300^{\circ}\text{C}$.

EXAMPLE 7

85 The procedure described in Example 6 was carried out using crotonic anhydride as starting material instead of acetic anhydride, the reaction conditions being the same.

The product was 1-methyl-6-(1-propenyl)-3-(5-nitro-2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one, which melting point $>300^{\circ}\text{C}$.

EXAMPLE 8

95 The procedure described in Example 6 was carried out using chloro-acetic anhydride as starting material instead of acetic anhydride, the reaction conditions being the same.

The product was 6-chloromethyl-1-methyl-3-(5-nitro-2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one, which has melting point $>300^{\circ}\text{C}$. with decomposition.

EXAMPLE 9

105 The procedure described in Example 6 was carried out using cyclohexane carboxylic anhydride as starting material instead of acetic anhydride, the reaction conditions being the same.

The product was 6-cyclohexyl-1-methyl-3-(5-nitro-2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one, which has melting point $>300^{\circ}\text{C}$.

EXAMPLE 10

115 The procedure described in Example 6 was carried out using phenylacetic anhydride as starting material instead of acetic anhydride, the reaction conditions being the same.

The product was 6-benzyl-1-methyl-3-(5-nitro-2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one, which has melting point $>300^{\circ}\text{C}$.

EXAMPLE 11

A mixture of 14.0 grams of 5-amino-4-cyano - 1 - methyl - 3 - (5 - nitro - 2 - furyl)-pyrazole, 7.8 grams of propionic anhydride and 2.0 grams of concentrated sulphuric acid (S.G. 1.84) was heated at a reaction temperature of 100—120°C. for 15 minutes and then cooled. The solid which crystallised was collected, washed with 100 millilitres of water and dried. Recrystallisation from dimethyl formamide gave 6-ethyl-1 - methyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H) - one, having melting point >300°C.

EXAMPLE 12

The procedure described in Example 11 was carried out using crotonic anhydride as starting material instead of propionic anhydride, the reaction conditions being the same.

The product was 1 - methyl - 3 - (5 - nitro - 2 - furyl) - 6 - (1 - propenyl - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H) - one, having melting point >300°C.

EXAMPLE 13

The procedure described in Example 11 was carried out using butyric anhydride as starting material instead of propionic anhydride, the reaction conditions being the same.

The product was 1 - methyl - 3 - (5 - nitro - 2 - furyl) - 6 - propyl - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H) - one, having melting point >300°C.

EXAMPLE 14

A mixture of 14.0 grams of 5-amino-4-cyano - 1 - methyl - 3 - (5 - nitro - 2 - furyl)-pyrazole, 9.5 grams isobutyric anhydride and 0.6 grams of concentrated sulphuric acid (S.G. 1.84) was heated at a reaction temperature of 100—120°C. for 15 minutes and then cooled. The solid which crystallised was collected, washed with ether and dried. Recrystallisation from aqueous dimethylformamide gave 4 - cyano - 5 - isobutyramido - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - pyrazole having melting point 225°C.

A mixture of 3.5 grams of 4-cyano-5-isobutyramido - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - pyrazole, 20 millilitres of dimethylformamide and 10 millilitres of concentrated sulphuric acid (S.G. 1.84) was heated under reflux for 1 hour and cooled. The mixture was then diluted with 50 millilitres of water and the solid which formed was collected, washed with water and dried. Recrystallisation from dimethylformamide gave 6 - isopropyl - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin-4(5H)-one, having melting point >300°C.

EXAMPLE 15

A mixture of 11.6 grams of 5-amino-4-cyano - 1 - ethoxycarbonyl - 3 - (5 - nitro - 2-furyl)-pyrazole, 4.1 grams of acetic anhydride and 2.0 grams of concentrated sulphuric acid (S.G. 1.84) was heated under reflux for 3 hours. The solid product which formed during reaction was collected by filtration, washed with ether and dried. Recrystallisation from dimethylformamide gave 1-ethoxycarbonyl - 6 - methyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H) - one, having decomposition point 296°C.

EXAMPLE 16

The procedure described in Example 11 was carried out using chloroacetic anhydride as starting material instead of propionic anhydride, the reaction conditions being otherwise essentially the same. The product was 6 - chloromethyl - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin-4(5H)-one, having melting point 300°C. with decomposition.

EXAMPLE 17

A mixture of 2.3 grams of 5-amino-4-cyano - 1 - methyl - 3 - (5 - nitro - 2 - furyl)-pyrazole, 15 millilitres of dimethylformamide, 15 millilitres of anhydrous pyridine and 0.8 grams of acetyl chloride was heated under reflux for 2 hours and cooled. The mixture was diluted with 50 millilitres of ice-water and the solid which precipitated was collected, washed with water and dried. Recrystallisation from aqueous dimethylformamide gave 5 - acetamido - 4 - cyano - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - pyrazole having melting point 250°C.

EXAMPLE 18

a) The procedure described in Example 17 was carried out using hexahydrobenzoyl chloride as starting material instead of acetyl chloride, the reaction conditions being the same.

The product was 4 - cyano - 5 - hexahydrobenzamido - 1 - methyl - 3 - (5 - nitro-2-furyl)-pyrazole, having melting point 234°C.

b) A mixture of 10.0 grams of 4-cyano-5-hexahydrobenzamido - 1 - methyl - 3 - (5 - nitro-2-furyl)-pyrazole, 60 millilitres of ethanol and 40 millilitres of concentrated sulphuric acid (S.G. 1.84) was heated under reflux for 1 hour and cooled. The mixture was then diluted with 50 millilitres of water and the solid product which formed was collected, washed with ether and dried. Recrystallisation from glacial acetic acid gave 6-cyclohexyl - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H)-one, having melting point >300°C.

EXAMPLE 19

A mixture of 11.6 grams of 5-amino-4-cyano - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - pyrazole, 7.7 grams of phenylacetic chloride, 50 millilitres of dimethylformamide and 30 millilitres of anhydrous pyridine was heated under reflux for 4 hours and cooled. The mixture was then diluted with 100 millilitres of ice-water and a crude solid was obtained. A mixture of this solid with 10 millilitres of dimethylformamide and 10 millilitres of concentrated sulphuric acid (S.G. 1.84) was heated under reflux for 30 minutes and cooled. Dilution of the mixture with 50 millilitres of ice-water yielded a product which on recrystallisation from dimethylformamide gave 6 - benzyl - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin-4(5H)-one, having melting point $>300^{\circ}\text{C}$.

EXAMPLE 20

A mixture of 0.5 grams of 5-amino-4-cyano - 3 - (5 - nitro - 2 - furyl) - 1 - n - propylpyrazole and 5 millilitres of acetic anhydride was heated under reflux for 3 hours and then cooled. The excess of acetic anhydride was removed by distillation under reduced pressure and the residue was triturated with ether, collected and dried. Recrystallisation from aqueous ethanol gave 4 - cyano - 5 - diacetylamino - 3 - (5 - nitro - 2 - furyl) - 1 - n - propylpyrazole, having melting point 156°C .

A mixture of 0.3 grams of 4-cyano-5-diacetylamino - 3 - (5 - nitro - 2 - furyl) - 1-n-propylpyrazole and 5 millilitres of ethanolic 40% w/w hydrogen chloride solution was heated under reflux for 30 minutes and cooled. The crystalline solid was collected, washed with water and dried to give 6 - methyl - 1 - n - propyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H)-one, having melting point 276°C .

EXAMPLE 21

A mixture of 14.5 grams of 5-amino-4-cyano - 3 - (5 - nitro - 2 - furyl) - 1 - methylpyrazole, 50 millilitres of butyric anhydride and 3.0 grams of concentrated sulphuric acid was heated under reflux for 15 minutes and then cooled. The crystalline solid recrystallised from a mixture of ethanol and was collected, washed with ethanol and dimethylformamide to give 4 - carbamoyl - 5 - dibutyrylamino - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - pyrazole having melting point 225°C .

A mixture of 0.5 grams of 4-carbamoyl-5-dibutyrylamino - 1 - methyl - 3 - (5 - nitro - 2-furyl)-pyrazole and 5.0 millilitres of a solution of concentrated sulphuric acid in ethanol (ratio 3:1) was heated under reflux for 15 minutes and then cooled. To the mixture was then added 20 millilitres of ice-water and the precipitation solid was collected.

The solid was extracted with 50 millilitres of boiling water and the insoluble residue which remained was 1 - methyl - 3 - (5 - nitro - 2 - furyl) - 6 - propyl - 1H - pyrazolo[3,4 - d]pyrimidin-4(5H)-one, having melting point $>300^{\circ}\text{C}$.

EXAMPLE 22

A mixture of 20 grams of 5-amino-4-cyano - 1 - methyl - 3 - (5 - nitro - 2 - furyl)-pyrazole, 8 grams of *p*-toluenesulphonic acid and 600 millilitres of acetic anhydride was heated under reflux for 8 hours and cooled. The crystalline solid was collected, washed with ether and dried, giving 1,6-dimethyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]oxazin - 4 - one, having melting point 244°C .

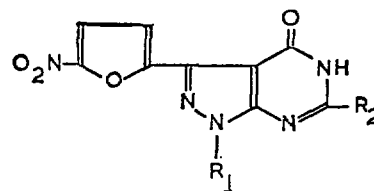
A mixture of 15 grams of 1,6-dimethyl-3-(5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]oxazin - 4 - one, 50 millilitres of ethanol and 50 millilitres of concentrated aqueous ammonia solution (S.G. 0.88) was heated under reflux for 15 minutes and cooled. The crystalline solid was collected, washed with water and dried. Recrystallisation from aqueous dimethylformamide gave 1,6 - dimethyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H) - one, having melting point $>300^{\circ}\text{C}$.

EXAMPLE 23

To a solution of 15 grams of hexamethylenetetramine in 50 millilitres of water was added 5 grams of 1,6-dimethyl-3-(5-nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]oxazin-4-one and the mixture was stirred for 24 hours at 30°C . The crystalline solid was collected, washed with water and dried. Recrystallisation from aqueous dimethylformamide gave 1,6 - dimethyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H)-one, having melting point $>300^{\circ}\text{C}$, with an infra-red spectrum identical to that of the product obtained in Example 22.

WHAT WE CLAIM IS:—

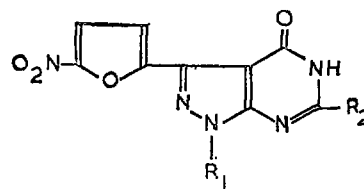
1. Compounds having the general formula I 110



(I)

in which R₁ is an unsubstituted alkyl group containing from one to five carbon atoms, or a carbalkoxy group containing from one to five carbon atoms in the alkyl moiety, and R₂ is hydrogen, an alkyl group containing 115

I



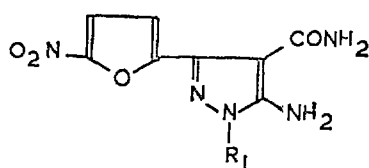
in which R₁ is an unsubstituted alkyl group containing from one to five carbon atoms, or a carbalkoxy group containing from one to five carbon atoms in the alkyl moiety, and R₂ is hydrogen, an alkyl group containing





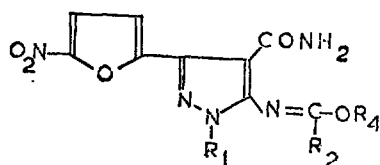
from one to five carbon atoms which may be unsubstituted or in which one or more or all of the hydrogens may be replaced by chlorine or bromine atoms, or is a cycloalkyl group containing from five to seven carbon atoms in the carbocyclic ring, an aralkyl containing up to twelve carbon atoms or an alkenyl group containing from two to four carbon atoms.

- 5
10 2. A process of preparing the compounds of formula I as defined in claim 1 which comprises treating a compound of general formula II



(II)

- 15 in which R₁ has the meaning as defined in claim 1, with a reagent R₂C(OR₄)₃, where R₁ and R₂ are as defined in claim 1, and R₄ is an alkyl group containing from one to three carbon atoms, to give an intermediate of general formula III

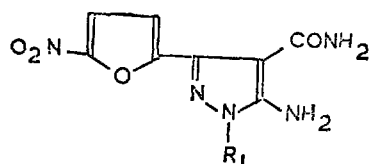


(III)

wherein R₁, R₂ and R₄ are as previously defined, which is cyclised without isolation.

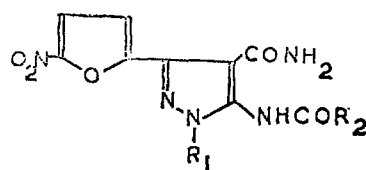
- 25 3. A process according to claim 2 in which the treatment is carried out in the presence of a carboxylic acid anhydride reaction promoter.

- 30 4. A process of preparing the compounds of formula I as defined in claim 1, which comprises treating a compound of general formula II



(II)

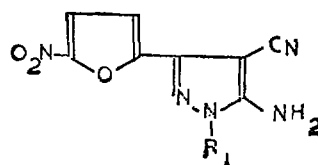
- 35 with a carboxylic acid derivative R₂COX or (R₂CO)₂O, where R₂ is as defined in claim 1 and X is hydroxyl, halogen, amino or —OR₃, where R₃ is an alkyl or alkenyl group containing up to three carbon atoms, to give an intermediate of general formula IV



(IV)

wherein R₁ and R₂ are as previously defined, which is cyclised without isolation.

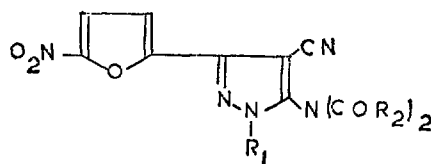
- 40 5. A process of preparing the compounds of formula I as defined in claim 1 which comprises treating a compound of the general formula V



(V)

wherein R₁ is as previously defined with an excess of an acid anhydride (R₂CO)₂O in the absence of catalyst, wherein R₂ is as defined in claim 1, to form an intermediate of the general formula VII

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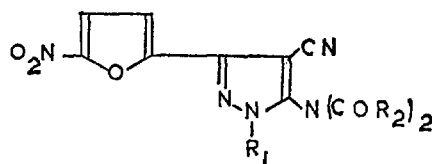


(VII)

wherein R₁ and R₂ are as defined in claim 1, and subsequently protonating and hydrolysing this intermediate with or without preliminary isolation.

55

6. A process of preparing the compounds of formula I as defined in claim 1 which comprises protonating and hydrolysing a compound of general formula VII

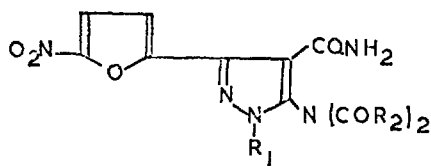


(VII)

wherein R₁ and R₂ are as defined in claim 1.

7. A process of preparing the compounds of formula I as defined in claim 1 which comprises cyclising a compound of general formula VIII

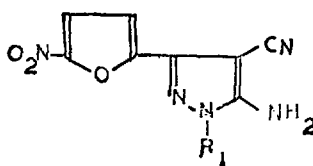
65



(VIII)

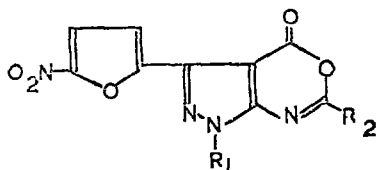
wherein R_1 and R_2 are as defined in claim 1.

- 5 8. A process of preparing the compounds of formula I as defined in claim 1 which comprises treating a compound of the general formula V



(V)

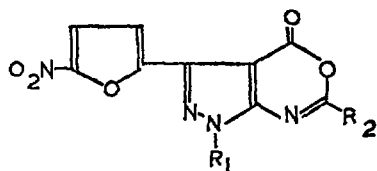
- 10 with an acid anhydride $(R_2CO)_2O$, wherein R_1 and R_2 are as defined in claim 1, in the presence of an arylsulphonic acid catalyst, to give an intermediate of general formula IX



(IX)

- 15 wherein R_1 and R_2 are as defined in claim 1, and then reacting this intermediate with or without preliminary isolation, with ammonia or with a compound which will provide ammonia *in situ* under the conditions of the reaction.

- 20 9. A process of preparing the compounds of formula I as defined in claim 1 which comprises reacting a compound of general formula IX

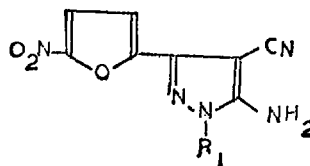


(IX)

- 25 with ammonia or with a compound which will provide ammonia *in situ* under the conditions of the reaction, R_1 and R_2 being as defined in claim 1.

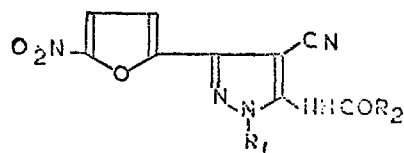
10. A process of preparing the compounds of formula I as defined in claim 1 which

comprises treating a compound of general formula V



(V)

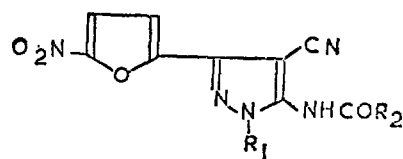
with formic acid, or with a carboxylic acid derivative R_2COX or $(R_2CO)_2O$ wherein R_1 and R_2 are as defined in claim 1 and X is as defined in claim 4 [except that X may not be hydroxyl], in the presence of an acid or basic catalyst, to give an intermediate of general formula VI



(VI)

wherein R_1 and R_2 are as previously defined, which is cyclised with or without preliminary isolation.

11. A process of preparing the compounds of formula I as defined in claim 1, which comprises cyclising a compound of formula VI



(VI)

wherein R_1 and R_2 are as defined in claim 1.

12. 1 - Methyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H) - one.

13. 1 - Isopropyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H) - one.

14. 3 - (5 - Nitro - 2 - furyl) - 1 - n - pentyl - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H) - one.

15. 1,6 - Dimethyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H) - one.

16. 1 - Methyl - 3 - (5 - nitro - 2 - furyl) - 6 - (1 - propenyl) - 1H - pyrazolo [3,4 - d] - pyrimidin-4(5H)-one.

17. 6 - Chloromethyl - 1 - methyl - 3 -

- (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin-4(5H)-one.
18. 6 - Cyclohexyl - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin-4(5H)-one. 40
19. 6 - Benzyl - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin-4(5H)-one.
20. 6 - Ethyl - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin-4(5H)-one. 45
21. 1 - Methyl - 3 - (5 - nitro - 2 - furyl) - 6 - propyl - 1H - pyrazolo[3,4 - d]pyrimidin-4(5H)-one.
22. 6 - Isopropyl - 1 - methyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin-4(5H)-one. 50
23. 1 - Ethoxycarbonyl - 6 - methyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin - 4(5H) - one. 55
24. 6 - Methyl - 1 - n - propyl - 3 - (5 - nitro - 2 - furyl) - 1H - pyrazolo[3,4 - d]pyrimidin-4(5H)-one.
25. A process according to claim 2 substantially as described in Example 3 herein. 60
26. A process according to claim 4 substantially as described in any one of Examples 2, 6, 7, 8, 9 and 10.
27. A process according to claim 5 substantially as described in Example 20 herein. 65
28. A process according to claim 6 substantially as described in Example 20 herein.
29. A process according to claim 7 substantially as described in Example 21 herein.
30. A process according to claim 8 substantially as described in Example 22 or Example 23 herein.
31. A process according to claim 9 substantially as described in Example 22 or Example 23.
32. A process according to claim 10 substantially as described in any one of Examples 1, 4, 5, 11 to 16, 18 and 19.
33. A process according to claim 11 substantially as described in Example 18 herein.
34. A therapeutic composition comprising a compound of formula I as defined in claim 1 and a pharmacologically acceptable solid carrier or liquid diluent.
35. A method of protecting an organic material susceptible to bacterial or other-microbial attack which comprises treating the material with a compound of formula I, as defined in claim 1.
36. A method according to claim 35 in which the organic material is a natural or synthetic polymeric material, a proteinaceous or carbohydrate substance, or a natural or synthetic fibre or textile material formed therefrom.
37. Organic material protected by a method according to claim 35 or 36.
38. An animal feedstuff composition comprising a compound of formula I as defined in claim 1.

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