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(54) **Pyrimido (4,5-c)pyridazines, compositions containing them and processes for their preparation.**

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Abstract

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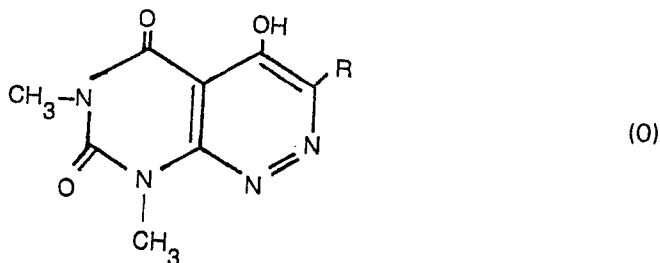
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Pyrimido(4,5-c)pyridazines, compositions containing them and processes for their preparation

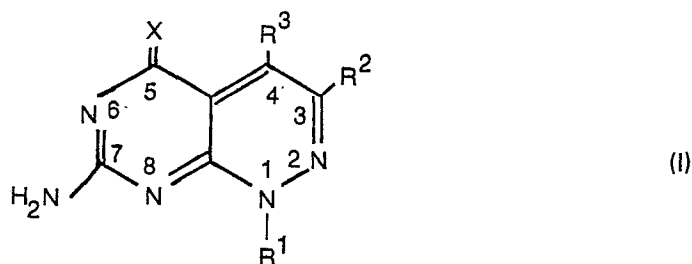
This invention relates to pyrimido(4,5-c)pyridazines, methods of their preparation, compositions and formulations containing them, and their use in the treatment of coccidiosis.

The first pyrimido(4,5-c)pyridazines were disclosed by Pfeleiderer and Ferch in 1958, *Ann. Chem.*, 615, 48 (1958) but no pharmacological activity was disclosed for these compounds which have the formula (O):



wherein R is a hydrogen atom or $-\text{CO}_2\text{C}_2\text{H}_5$ group. We have now discovered a group of pyrimido(4,5-c)pyridazines which are useful in the treatment of coccidiosis.

The present invention provides novel pyrimido(4,5-c)pyridazines of formula (I), or their tautomers, or salts thereof,



wherein R¹ is a benzyl group, or a lower alkyl group optionally substituted by a hydroxy group; R² is a hydrogen atom, a hydroxy group, a methyl group, a hydroxymethyl group, a benzyl group optionally substituted in the phenyl ring with a nitro group or one or two lower alkoxy groups, a phenacyl group optionally substituted in the phenyl ring with one or more hydroxy or lower alkoxy groups, a group $\text{CH}(\text{Y})\text{CO}_2\text{Z}$ in which Y is a hydrogen atom, a lower alkyl group, or a benzyl group, and Z is a hydrogen atom or a lower alkyl group; R³ is a hydroxy group, a methyl group, or a phenyl group optionally substituted with a hydroxy group; and X is an oxygen atom or a group NH; provided that

- (i) R³ is a methyl group only when R² is a methyl or hydroxy group;
- (ii) R³ is a phenyl group optionally substituted with a hydroxy group only when R² is a hydrogen atom;
- (iii) when R³ is a hydroxy group, R² is other than a hydrogen atom or a hydroxy group; and
- (iv) when R¹ is a methyl group and R³ is a hydroxy group X is NH.

The term "lower" as used herein in conjunction with an alkyl or alkoxy group is indicative of the fact that such groups have from 1 to 4 carbon atoms arranged in a straight or branched chain. The expression "phenacyl group" however is used to denote solely a $\text{C}_6\text{H}_5\text{COCH}_2-$ group.

It is to be understood that compounds where tautomerism is possible between, on the one hand, a hydroxy group and an oxo group, and on the other hand, an amino group and an imino group, at a particular position in either of the rings of the pyrimido(4,5-c)pyridazines of formula (I), the more stable forms are respectively, the oxo group and the amino group. However, the general formulae used in the present specification do not necessarily represent the more stable forms of such pyrimidopyridazines.

The above compounds of formula (I) have activity against coccidiosis either when used alone or in combination with a mixture of diaveridine and sulphaquinoxaline, such a mixture being known as an effective agent against coccidiosis. In particular, activity has been established against the organism *E. Tenella*, in *in vitro* and, in a number of instances, *in vivo* screens for compounds of formula (I) *per se* or with diaveridine and sulphaquinoxaline.

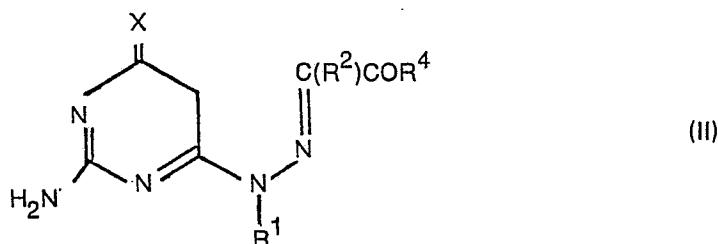
Those pyrimido(4,5-c)pyridazines which themselves have activity against *E. Tenella* are of formula (I), or their tautomers, or salts thereof, wherein R¹ is a lower alkyl group optionally substituted with a hydroxy group, or a benzyl group; R² is a hydrogen atom, a hydroxy group, a methyl group, a hydroxymethyl group, a benzyl group optionally substituted in the phenyl ring with a nitro or one or two

lower alkoxy groups, a phenacyl group optionally substituted in the phenyl ring with one or more lower alkoxy groups, or a group $\text{CH}(\text{Y})\text{CO}_2\text{Z}$ in which Y and Z are the same or different and each is a hydrogen atom or a lower alkyl group, and X is an oxygen atom or a group NH. Within this class there is a group of pyrimido(4,5-c)pyridazines which are particularly active and these have R^1 as a lower alkyl group, especially a methyl or n-butyl group; and R^2 as a hydrogen atom, a hydroxy group, a methyl group, a benzyl group optionally substituted in the phenyl ring with two methoxy groups, or a phenacyl group substituted in the phenyl ring with two methoxy groups. The most active compounds are 7 - amino - 1 - n - butyl - 5 - hydroxy - 3 - methyl - 4 - oxo - 1,4 - dihydropyrimido(4,5-c)pyridazine; 5,7 - diamino - 1,3 - dimethyl - 4 - oxo - 1,4 - dihydropyrimido(4,5-c)pyridazine; 7 - amino - 1,4 - dimethyl - 3,5 - dioxo - 1,2,3,5 - tetrahydropyrimido(4,5-c)pyridazine; 7 - amino - 5 - oxo - 1,3,4 - trimethyl - 1,5 - dihydropyrimido(4,5-c)pyridazine; 7 - amino - 1 - methyl - 5 - oxo - 4 - phenyl - 1,5 - dihydropyrimido(4,5-c)pyridazine; and 7 - amino - 4 - (4 - hydroxyphenyl) - 1 - methyl - 5 - oxo - 1,5 - dihydropyrimido(4,5-c)pyridazine.

It has previously been stated that in 1958 Pfeleiderer W. and Ferch H. (*Justus Liebig's Ann. Chem.*, 1958, 615, 48) reported the preparation of 4 - hydroxy - 6,8 - dimethylpyrimido(4,5-c)pyridazine - 5,7 - (6H, 8H) - dione by the cyclisation of glyoxylic acid ethyl ester-1,3-dimethyluracil-(4)-hydrazone. It has now been found that this cyclisation reaction can surprisingly be extended to a novel class of intermediates which have a number of different substituents.

There has further been described in the literature Castle, *et al.*, *J. Het. Chem.*, 1975, 12, 1221) a reaction between 6 - (α - methylhydrazino) - 3 - methyluracil and 2,3 - butanedione which leads to 1,3,4,6 - tetramethylpyrimido(4,5-c)pyridazine - 5,7 - (1H, 6H) - dione. Unexpectedly, pyrimido(4,5-c)pyridazines having different substituents and falling within the definition of formula (I) can be prepared by a modification of this reaction.

Thus the present invention further provides a method of preparing a compound of the formula (I), or a tautomer or salt thereof as hereinbefore defined, which comprises the cyclisation of a compound of the formula (II):



or a tautomer or salt thereof, wherein X, R^1 and R^2 are as hereinbefore defined and R^4 is a lower alkoxy group (to give compounds of the formula (I), where R^3 is OH) or a group R^3 as hereinbefore defined apart from a hydroxy group (to give compounds of formula (I) where R^3 is other than OH), and thereafter when X is an oxygen atom and R^2 is an acyloxymethyl group, optionally hydrolysing R^2 to a hydroxymethyl group.

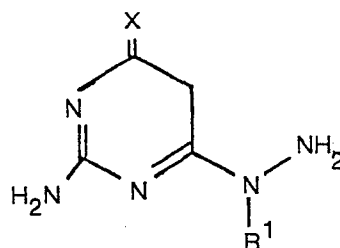
The nature of the substituents on the pyrimidine ring of the compounds of the formula (II) is such that when R^4 is a lower alkoxy group, unlike the Pfeleiderer and Ferch article, ring closure can apparently only be achieved when the nitrogen atom at the 6-position is substituted by R^1 as hereinbefore defined. Moreover this cyclisation reaction is particularly surprising since the report of Pfeleiderer and Ferch teaches that such reactions only work for those hydrazone intermediates which have a glyoxylic acid alkyl ester substitution, yet a corresponding substitution in the present intermediates results in little, if any, pyrimido(4,5-c)pyridazine.

The cyclisation reaction may be carried out in any suitable solvent but will desirably be carried out in a hydroxylic solvent at a non-extreme temperature, i.e. between 10°C and 110°C ; when R^4 is a lower alkoxy group the reaction is suitably carried out in glacial acetic acid, water or a C_{1-4} alkanol, at reflux temperature for up to several days and is preferably carried out in refluxing methanol, or in ethanol at the reflux temperature of methanol. When R^4 is group R^3 the reaction is preferably carried out in refluxing water.

The conditions for hydrolysing the lower acyloxymethyl group to a hydroxymethyl group are preferably alkaline, for example aqueous sodium hydroxide, and the reaction may conveniently be performed at room temperature for 15 to 60 minutes, for example 30 minutes.

The compounds of the formula (II) and tautomers thereof can be prepared, preferably *in situ*, by condensing a 2-amino-6-hydrazinopyrimidine of the formula (III):

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(III)

or a tautomer thereof with a compound of the formula: $R^2CO.CO.R^4$ wherein R^1 , R^2 , R^4 and X are as defined for formulae (I) and (II) above.

The reaction is suitably carried out under the same conditions as those used for the cyclisation reaction described above.

In the preparation of those compounds of the formula (I) wherein R^2 is a group $CH(Y)CO_2Z$ or a phenacyl group, some other bi-cyclic compound may be formed as a by-product. In such cases, it may be necessary to isolate the required compound by the usual procedures known in the art.

The compounds of the formulae (II) and (III) are novel.

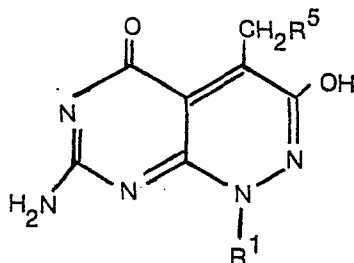
The compounds of formula (I) wherein R^1 is as hereinbefore defined, R^3 is a hydroxy group, X is an oxygen atom, and R^2 is a group $CH(Y)CO_2Z$ in which Y is as hereinbefore and Z is a lower alkyl group may be hydrolysed to give further compounds of formula (I) wherein R^1 is as hereinbefore defined, R^3 is a hydroxy group, X is an oxygen atom, and R^2 is a group $CH(Y)CO_2Z$ in which Y is as hereinbefore defined and Z is a hydrogen atom. The starting compounds of formula (I) may be prepared from the corresponding compounds of formula (II) as described previously.

The conditions for this reaction are preferably alkaline which may be achieved by using, for instance, aqueous sodium hydroxide, and the reaction may be conveniently performed at room temperature for 15 to 150 minutes, for example 90 minutes.

The compounds of formula (I) wherein R^1 , R^2 and R^3 are as hereinbefore defined and X is a group NH may be hydrolysed to give further compounds of formula (I) which are correspondingly substituted except that X is an oxygen atom and that, in the case where R^2 in the starting material is a group $CH(Y)CO_2Z$ in which Z is a lower alkyl group, Z is converted to a hydrogen atom. The starting compounds of formula (I) may be prepared from the corresponding compounds of formula (II) as described previously.

The conditions for this reaction are preferably alkaline which may be achieved by using, for instance, aqueous sodium hydroxide, and the reaction may be conveniently performed under reflux for 10 to 40 hours, for example 24 hours. However, it should be noted that during the course of this reaction some decarboxylation may take place possibly giving rise to small amounts of by-product which may necessitate subsequent separation by known techniques. This hydrolysis reaction is not preferred for those compounds of formula (I) wherein R^2 is a group which may undergo hydrolytic cleavage, e.g. an optionally substituted phenacyl group, if it is desired to hydrolyse X without affecting the group R^2 .

Compounds of formula (I) wherein R is as hereinbefore defined, X is an oxygen atom, R^3 is a methyl group and R^2 is a hydroxy group can be prepared by the hydrolysis of a compound of formula (IV):

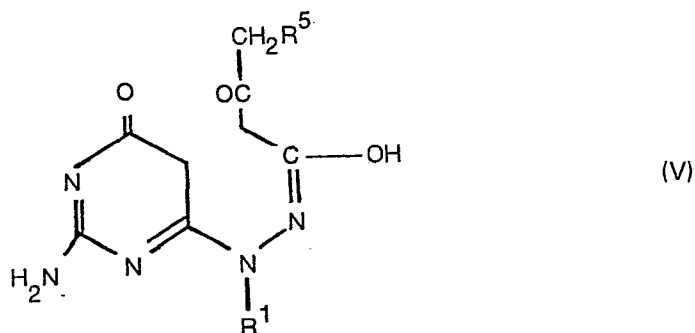


(IV)

wherein R^1 is as hereinbefore defined and R^5 is an aroyl group, preferably a benzoyl group, optionally substituted with one or more lower alkoxy groups, for example 3,4,5-trimethoxy substitution.

Compounds of formula (IV) are novel and represent a further aspect of the present invention.

In turn they may be prepared by the cyclisation of a compound of formula (V):



15 wherein R^1 and R^5 are as hereinbefore defined, the reaction preferably being performed under reflux in methyl cellosolve (Trade Mark).

Compounds of formula (V) are novel. Conveniently they are prepared, preferably *in situ* by the reaction of a compound of formula (III) wherein R^1 is as hereinbefore defined and X is an oxygen atom with a compound of the formula: $R^5CH_2.CO.CO.OR^6$ wherein R^5 is as hereinbefore defined and R^6 is a lower alkyl group, in methyl cellosolve, preferably under reflux.

All the starting materials specified above for the various syntheses may be prepared by standard methods taught in the art.

The present invention in a further aspect provides a composition for use in the treatment of coccidiosis which composition comprises non-toxic, effective anti-coccidial treatment amounts of each of diaveridine, sulphaquinoxaline and a compound of formula (I), or its tautomer, or a veterinary acceptable salt thereof, as hereinbefore defined, in particular such a compound wherein R^1 is a lower alkyl group optionally substituted with a hydroxy group, or a benzyl group; R^2 is a hydrogen atom, a hydroxy group, a phenacyl group optionally substituted in the phenyl ring with one or more hydroxy groups, or a group $CH(Y)CO_2Z$ in which Y is benzyl and Z is a lower alkyl group, and X is an oxygen atom.

The above tripartite compositions are prepared by admixture of the requisite non-toxic anti-coccidial treatment amounts of each of the active ingredients.

The compounds of formula (I), their tautomers, and veterinary acceptable salts, or compositions thereof, may be presented in association with a carrier in veterinary formulations particularly those suitable for oral administration. Such formulations may be presented in discrete units, such as tablets, each containing a predetermined amount of the compound, but may also be presented as a powder, as granules, as a solution or suspension in an aqueous or non-aqueous liquid. Most conveniently, however, they may be presented as a poultry feed, at 5 to 500 ppm in the diet, with a preferred dose range of 150 to 300 ppm.

Accordingly, the present invention provides a poultry feed in which there is a composition as hereinbefore defined of a non-toxic effective anti-coccidial treatment amount of a compound of formula (I), their tautomers, or veterinary acceptable salts thereof.

Examples of veterinary acceptable salts are those derived from mineral or organic acids, for example hydrochloric acid, hydrobromic acid, sulphuric acid, acetic acid, citric acid, tartaric acid, lactic acid, maleic acid or salicylic acid. Acid addition salts which are not veterinary acceptable may be rendered so by a conventional metathetical reaction. Further examples of veterinary acceptable salts are, in the case when R^2 in formula (I) is a group $CH(Y)CO_2Z$ in which Z is a hydrogen atom, are alkali metal, for example sodium, salts.

The compounds of the invention are useful in methods of treating poultry infected with coccidiosis, such methods comprising administering a composition or a non-toxic effective anti-coccidial treatment amount of a compound of formula (I) hereinbefore defined, preferably administering a veterinary formulation or poultry feed as hereinbefore defined to the infected poultry.

Further advantages of the present invention can be ascertained from the following examples which should not be construed as limiting the scope of the invention in any way.

All temperatures herein are given in degrees centigrade.

Example 1

6-(1-Methylhydrazino)isocytosine
(III) ($R^1=CH_3$; $X=O$)

A mixture of 6-chloroisocytosine (17.50 g) and methylhydrazine (27.70 g) in water (900 ml) was stirred and refluxed for 3 hours. The resulting solution was allowed to stand at room temperature for 6 hours, then at 0° overnight, in order that the product could crystallise out. The white crystals were collected by filtration, washed with water (800 ml) and subsequently with 95% ethanol (200 ml). Drying under vacuum at 70°C yielded 6-(1-methylhydrazino)isocytosine (11.01 g; 56% of theoretical yield; M.P. 274—280°C decomposition).

Elemental analysis: Calcd. for $C_5H_9N_5O \cdot 0.5H_2O$: C 36.58%, H 6.14%, N 42.66%.
 Found: C 36.42%, H 6.06%, N 42.61%.
 NMR (DMSO- d_6) δ 3.12 (s, 3H), 4.47 (br s, 2H), 5.00 (s, 1H), 6.16 (br s, 2H), 9.68 (br s, 1H).
 U.V. λ_{max} (CH₃OH) 225.5 nm (ϵ 24,000), 274 (17,300).

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Example 2

6-(1-Ethylhydrazino)isocytosine
 (III) ($R^1=C_2H_5$; $X=O$)

A mixture of 6-chloroisocytosine (4.00 g) and ethylhydrazine (4.00 g) in water (80 ml) was
 10 refluxed for $1\frac{1}{2}$ hours after which time the resulting solution was filtered while hot to remove dust
 particles, flushed with nitrogen, and sealed. The solution was then allowed to cool slowly to room
 temperature so that the product could crystallise out. The straw-coloured crystals were collected by
 filtration, washed with water and subsequently methanol. Drying under vacuum at 70°C yielded 6-(1-
 ethylhydrazino)isocytosine (2.83 g; 59% of theoretical yield; M.P. 249—250°C decomposition).

15 Elemental analysis: Calcd. for $C_6H_{11}N_5O$: C 42.59%, H 6.55%, N 41.40%
 Found: C 42.33%, H 6.74%, N 41.18%.

NMR (DMSO- d_6) δ 1.03 (t, 3H), 3.59 (q, 2H) 4.33 (br. s, 2H), 4.99 (s, 1H), 6.15 (br s, 2H), 9.82 (br s,
 1H)

20 U.V. λ_{max} (CH₃OH) 226 nm (ϵ 25,000), 273 (18,200).

Example 3

6-[1-(2-Hydroxyethyl) hydrazino]isocytosine
 (III) ($R^1=CH_2CH_2OH$; $X=O$)

To a refluxing mixture of 6-chloroisocytosine (17.50 g) in water (300 ml) was added 2-
 25 hydroxyethylhydrazine (45.6 g). The resulting hazy solution became darker during further refluxing and
 after $1\frac{3}{4}$ hours it was filtered through Celite (Trade Mark). The filtrate was then allowed to stand
 overnight at room temperature in order that crystallisation of the product could take place on cooling.
 The white crystals were collected by filtration, washed with water (100 ml) and subsequently methanol
 (100 ml). Drying under vacuum at 70°C yielded 6-[1-(2-hydroxyethyl)hydrazino]isocytosine (12.02 g;
 30 54% of theoretical yield; M.P. 232—239°C decomposition).

Elemental analysis: Calcd. for $C_8H_{11}N_5O_2$: C 38.91%, H 5.99%, N 37.82%.

Found: C 38.95%, H 6.08%, N 37.81%.

NMR (DMSO- d_6) δ 3.61 (s, 4H), 4.45 (br s, 3H), 5.01 (s, 1H), 6.17 (br s, 2H), 9.75 (br s, 1H).

35 U.V. λ_{max} (CH₃OH) 224 nm (ϵ 23,500), 272 (16,700).

Example 4

6-(1-n-Butylhydrazino)isocytosine
 (III) ($R^1=n-C_4H_9$; $X=O$)

A mixture of 6-chloroisocytosine (17.50 g) and n-butylhydrazine (23.30 g) in water (900 ml) was
 40 stirred and refluxed for 4 hours. The resulting solution was allowed to stand at room temperature for 6
 hours in order that the product could crystallise out. The tan crystals were collected by filtration and
 washed with water (175 ml). Drying overnight in a vacuum desiccator protected from light yielded 6-
 (1-n-butylhydrazino)isocytosine (18.43 g; 77% of theoretical yield; M.P. 208—215°C decomposition).

Elemental analysis: Calcd. for $C_9H_{15}N_5O$: C 48.71%, H 7.67%, N 35.51%.

45 Found: C 48.76%, H 7.69% N 35.30%.

NMR (DMSO- d_6) δ 0.6—1.8 (m, 7H), 3.58 (t, 2H), 4.39 (br s, 2H), 5.05 (s, 1H), 6.22 (br. s, 2H), 9.85
 (br s, 1H).

U.V. λ_{max} (CH₃OH) 227 nm (ϵ 25,000), 274 (18,400).

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Example 5

6-(1-Benzylhydrazino)isocytosine
 (III) ($R^1=CH_2C_6H_5$; $X=O$)

A mixture of 6-chloroisocytosine (17.50 g), triethylamine (90.10 g), and benzylhydrazine
 dihydrochloride (46.90 g) in water (900 ml) was refluxed for 10 minutes after which time the resulting
 55 solution was filtered to remove impurities present in the hydrazine salt. After refluxing the filtrate for 9
 hours a white solid was collected by filtration from the hot reaction mixture, washed with water (250
 ml) and dried overnight at room temperature in a vacuum desiccator protected from the light to yield 6-
 (1-benzylhydrazino)isocytosine (18.65 g; 67% of theoretical yield, M.P. 270—290°C decomposition).

Elemental analysis: Calcd. for $C_{11}H_{13}N_5O$: C 57.13%, H 5.67%, N 30.29%.

60 Found: C 57.15%, H 5.75%, N 30.25%.

NMR (DMSO- d_6) δ 4.34 (br s, 2H), 4.81 (s, 2H), 5.07 (s, 1H), 6.20 (br s, 2H), 7.25 (s, 5H), 9.80 (br s,
 1H).

U.V. λ_{max} (CH₃OH) 226 nm (ϵ 27,000), 275 (20,000).

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Example 6

2,4-Diamino-6-(1-methylhydrazino)pyrimidine

(III) ($R^1=CH_3$; $X=NH$)

- To a refluxing solution of 6-chloro-2,4-diaminopyrimidine (4.0 g) in anhydrous methanol (40 ml) was added methylhydrazine (3.2 g). After 18 hours the refluxing mixture was allowed to cool to room temperature under a nitrogen atmosphere in order that the product could crystallise out. The white solid (3.0 g) was collected by filtration and dried under reduced pressure at 70°C. Recrystallisation of the product from methanol/methylhydrazine (50/1) gave straw-coloured crystals of 2,4-diamino-6-(1-methylhydrazino)pyrimidine (1.92 g; 56% of theoretical yield; M.P. 214—217°C decomposition).
- Elemental analysis: Calcd. for $C_5H_{10}N_6$: C 38.95%, H 6.54%, N 54.51%. Found: C 38.99%, H 6.62%, N 54.38%.
NMR ($DMSO-d_6$) δ 3.05 (s, 3H), 4.27 (br. s, 2H), 5.40 (s, 3H), 5.55 (br. s, 2H).
U.V. λ_{max} (CH_3OH 219 nm (ϵ 27,700) 277 (15,500).

15

Example 7

(i) 2-(N-(2,4-Diamino-6-pyrimidinyl)-N-methylhydrazino)propionaldehyde Oxime

- To 240 ml of glacial acetic acid that had been degassed of oxygen with nitrogen was added 8.00 g (0.0519 mol) of 2,4-amino-6-(1-methylhydrazino)pyrimidine and 5.42 g (0.0623 mol) of pyruvaldoxime. A positive nitrogen pressure was applied, and the initial mixture was stirred and heated in a 60° oil bath. After 2 hours 47 minutes the resulting solution was allowed to cool to room temperature and was filtered to remove a small amount of solid.
- The filtrate was concentrated under vacuum at 45° to a yellow solid to which was added 400 ml of ethyl acetate. The solid was pulverized, collected, washed with 2x80 ml of ethyl acetate, and dried overnight under vacuum at 70°, yield 9.00 g of yellow solid shown by NMR to be desired product contaminated with acetic acid and little else. A 1.00 g sample of solid was recrystallised from ethyl acetate, yield 0.632 g (48%); MP 216° dec; NMR ($DMSO-d_6$) δ 2.10 (s, 3H), 3.25 (s, 3H), 5.31 (s, 1H), 5.72 and 5.92 (overlapping br s's, 4H), 7.87 (s, 1H), 11.65 (br s, 1H). A small amount of ethyl acetate was indicated; U.V. λ_{max} (CH_3OH) 257 nm sh (ϵ 11,300), 268 sh (10,500), 330.5 (5,800). Mass spectrum of a different batch (160°): M^+ , m/e 223, 16%; m/e 179, 100%. An exact mass scan indicated the following accurate masses: 223.1183 ($C_8H_{13}N_7O$), 179.1047 ($C_7H_{11}N_6$).
- Anal. Calcd. for $C_8H_{13}N_7O$: 43.30; H 5.95%; N 42.91. Found: C 43.59%; H 6.01%; N 42.93%.

- (ii) 7-Amino-1,5-dihydro-5-imino-1,3-dimethylpyrimido(4,5-c)pyridazine Trifluoroacetate
- To 10 ml of stirred, refluxing trifluoroacetic acid was added 0.146 g (0.000654 mol) of 2-(N-(2,4-diamino-6-pyrimidinyl)-N-methylhydrazono)propionaldehyde oxime. After 2 hours 17 minutes the solution was allowed to cool to room temperature.
- The solution was concentrated under vacuum at 40° to an orange residue to which was added a little methanol in order to esterify at least some residual trifluoroacetic acid. The methanol was removed under vacuum at 40°, and the residue was dissolved in 25 ml of ethyl acetate. Triethylamine was added to the solution until no more solid precipitated. Yellow solid was collected, washed with 2x2 ml of ethyl acetate, and dried under vacuum at 70° yield 0.099 g (49%); MP 232 dec; NMR ($DMSO-d_6$) δ 2.56 (s, 3H), 4.14 (s, 3H), 8.22 brs and 8.33 brs (2H), 8.63 (s, 1H), 8.85 (br s, 2H). A small amount of ethyl acetate was indicated; UV of a different batch λ_{max} (CH_3OH) 2.63.5 nm (ϵ 16,500), 267 sh (16,000), 350 sh (3,700), 401.5 (5,300).
- Anal. Calcd. for $C_8H_{10}N_6 \cdot C_2HF_3O_2 \cdot 0.03C_4H_8O_2 \cdot 0.20H_2O$: C 39.15%; H 3.78%; N 27.07%; F 18.36. Found: C 39.10%; H 3.74%; N 27.02%; F 18.29.

- (iii) 5,7-Diamino-1,3-dimethylpyrimido(4,5-c)pyridazin-4(1H)-one
- To a solution of 0.049 g (0.00016 mol) of 7-amino-1,5-dihydro-5-imino-1,3-dimethylpyrimido(4,5-c)pyridazine trifluoroacetate in 3 ml of water was added 0.022 g (0.00026 mol) of sodium bicarbonate, and the yellow solution was allowed to stand at room temperature while loosely covered and exposed to oxygen.
- After 22 days precipitated yellowish-brown solid was collected, washed with water, and dried under vacuum at 70°, yield 0.018 g ($\leq 54\%$). NMR, tlc, uv, and mass spectral data indicated this solid to be the same as that written up in Example 8 with the exception that some minor impurities were present.

Example 8

5,7-Diamino-1,3-dimethylpyrimido[4,5-c]pyridazin-4(1H)-one

(I) ($R^1=CH_3$; $R^2=CH_3$; $R^3=OH$; $X=NH$)

- To a refluxing solution of 2,4 - diamino - 6 - (1 - methylhydrazino)pyrimidine (500 mg) in anhydrous methanol (15 ml) was added methyl pyruvate (496 mg) over a five minute period. Reflux was continued for 5 hours after which time the solid which had separated was collected by suction filtration of the hot mixture, washed with methanol, and dried under vacuum at 70°C to yield tan

crystals of 5,7 - diamino - 1,3 - dimethylpyrimido[4,5 - c]pyridazin - 4(1H) - one (508 mg; 76% of theoretical yield; M.P. >275°C)

Elemental analysis: Calcd. for $C_8H_{10}N_6O$: C 46.59%, H 4.89%, N 40.76%.

Found: C 46.66%, H 4.98%, N 40.69%.

5 NMR (DMSO- d_6) δ 2.14 (s, 3H), 3.74 (s, 3H), 6.84 (br s, 2H)*, 7.72 (br. d, 1H, J=4Hz)*, 8.96 (br d, 1H, J=4Hz)*.

U.V. λ_{max} (CH₃OH) 222 nm (ϵ 12,800), 247 (31,100), 306 (11,600).

*=exchangeable with D₂O.

10

Example 9

7-Amino-3-acetoxymethyl-1-methylpyrimido[4,5-c]pyridazine-4,5 (1H, 6H) dione

To a stirred, refluxing solution of 6 - (1 - methylhydrazino)isocytosine hemihydrate (0.16 g) in methanol (5 ml) was added methyl 3-acetoxy-2-oxo-propanoate (0.19 g). After refluxing for a further 22 hours, the solid formed during the course of the reaction was collected by filtration of the hot reaction mixture and washed with methanol to yield 7 - amino - 3 - acetoxymethyl - 1 - methylpyrimido[4,5 - c]pyridazine - 4,5(1H, 6H) dione (0.107 g; 40% of theoretical yield; M.P. >280°C).

15

Elemental analysis: Calcd. for $C_{10}H_{11}N_5O_4$: C 45.28%, H 4.18%, N 26.41%.

Found: C 45.11%, H 4.24%, N 26.37%.

NMR (TFA) δ 2.32 (s, 3H), 4.27 (s, 3H); 5.51 (s, 2H), 7.25 (br s, 2H).

20

U.V. λ_{max} (CH₃OH) 258 nm (ϵ 37,100) 299.5 (7,400).

Example 10

7-Amino-1-methyl-4-phenylpyrimido[4,5-c]pyridazin-5-(1H)-one

(I) ($R^1=CH_3$; $R^2=H$; $R^3=C_6H_5$; $X=O$)

25

To a mixture of 6-(1-methylhydrazino)isocytosine hemihydrate (0.82 g) and methanol (100 ml) stirred at reflux was added 97% phenylglyoxal monohydrate (1.14 g). The immediate formation of a yellow solution was followed by a rapid precipitation. Reflux was continued for 4½ hours before the hot mixture was filtered (suction). The collected solid was washed with methanol and dried under vacuum (70°) to yield, 98 mg of yellow solid¹. After 2 hours, the yellow needles that had separated from the filtrate were collected, washed with methanol and dried under vacuum (70°), yield 0.63 g of the pure product: m.p. 262.5—264°d; nmr (CF₃COOH) δ 4.49 (s, 3H), 7.18 (br s, 2H), 7.60 (s, 5H), 8.72 (s, 1H); uv λ_{max} (IN HCL) 238 nm (ϵ 18,500), 262 (21,300), 270 sh (19,900), 358 (10,400).

30

Anal. Calcd. for $C_{13}H_{11}N_5O$: C 61.65%, H 4.38%, N 27.65%; Found: C 61.67%, H 4.43%, N 27.76%.

35

¹The nmr spectrum suggested that this solid was a 1.2:1.0 mixture of desired product and non-cyclic hydrazone.

Example 11

7-Amino-4-(3-hydroxyphenyl)-1-methylpyrimido[4,5-c]pyridazin-5(1H)-one

40

(I) ($R^1=CH_3$; $R^2=H$; $R^3=C_6H_4OH$; $X=O$)

To a stirred solution of *m*-hydroxyphenylglyoxal monohydrate¹ (0.90 g) in methanol (100 ml) at room temperature was added 6-(1-methylhydrazino)isocytosine hemihydrate (0.70 g). The mixture was heated to reflux within a 10-minute period to give a yellow solution. Reflux was continued for 3 hours before the yellow solid that precipitated was collected, washed with methanol and dried under vacuum (70°) to yield 1.04 g of crude product shown by nmr to be a 5.5:1 mixture of desired product and its 3-(3-hydroxyphenyl)isomer. Recrystallization² of 1.0 g of this mixture from methanol gave 0.41 g. of pure 4-substituted isomer: m.p. >300°C; nmr (CH₃COOH) δ 4.49 (s, 3H), 7.18—7.30 m, 7.41 br s and 7.67 m (6H), 8.69 (s, 1H); uv (IN HCL) λ_{max} 237 nm (ϵ 18,600), 261 (20,800), 357 (8,300).

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Anal. Calcd. for $C_{13}H_{11}N_5O_2$: C 57.99%, H 4.12%, N 26.01%; Found: C 57.82%, H 4.14%, N 26.02%.

50

¹G. Fodor and O. Kovacs, *J. Am. Chem. Soc.* 71, 1045 (1949).

²A second crop of yellow needles obtained from the recrystallisation was characterised as a 5:2 mixture of 4- to 3-substituted isomers.

55

Anal. Calcd. for $C_{13}H_{11}N_5O_2$: C 57.99%, H 4.12%, N 26.01%; Found: C 57.75%, H 4.15%, N 25.92%.

Example 12

α -[N-(2-Amino-4-oxo-3,4-dihydro-6-pyrimidyl)-N-methylhydrazono]-4-hydroxyacetophenone hydrate

(II) $R^1=CH_3$, $R^2=H$, $R^4=C_6H_4OH$, $X=O$

60

To a stirred mixture of 6-(1-methylhydrazino)isocytosine hemihydrate (0.82 g) and glacial acetic acid (25 ml) protected by a drying tube) was added 4-hydroxyphenylglyoxal hydrate (1.26 g) at once. The mixture was stirred at room temperature for 1½ hours before being quickly heated to boiling. Reflux was continued for only 5 minutes, just long enough to effect a complete, dark orange solution. This solution deposited a yellow solid during a 2 hour period at room temperature. The collected solid was washed first with a small quantity of glacial acetic acid and then with ether and dried under vacuum

65

(70°C), yield, 0.69 g. of the crude product. Recrystallisation of 130 mg from methanol provided 61 mg of the product as a hydrate: m.p. >300; nmr (DMSO-d₆) δ 3.49 (s, 3H), 5.44 (s, 1H), 6.65 (br s, 2H), 6.87 (d, 2H, J=9 Hz), 7.56 (s, 1H), 7.94 (d, 2H, J=9 Hz), 10.36 (br s, 2H), and 3.31 (H₂O); uv λ_{max} (CH₃OH) 228 nm (ϵ 20,000), 255 sh (15,500), 285 (23,900), 310 sh (17,400), 345 (14,100). Mass spectrum (field desorption): m/e 288, 30%; M, m/e 287, 25%; m/e 270, 88%; m/e 166, 100%.

Anal. Calcd. for C₁₃H₁₃N₅O₃·H₂O: C 51.20%, H 4.95%, N 22.94%; Found: C 50.99%, H 4.98%, N 22.83%.

Example 13

10 7-Amino-4-(4-hydroxyphenyl)-1-methylpyrimido(4,5-c)pyridazin-5(1H)one

(I) (R¹=CH₃; R²=H; R³=C₆H₄OH; X=O)

A mixture of crude α -[N-(2-Amino-4-oxo-3,4-dihydro-6-pyrimidyl)-N-methylhydrazono]-4-hydroxyacetophenone hydrate (200 mg) and glacial acetic acid¹ (10 ml) (drying tube) was heated at reflux for 4 hours. A dark solution gradually formed during the first 2 hours; no uv change was detected after 3 hours. The resulting dark solution, on standing for 3 days at room temperature, deposited orange crystals which were collected by filtration, washed with glacial acetic acid and dried under vacuum (70°C), yield 124 mg of the pyrimidopyridazinone, 1.75 acetic acid: m.p. >300°; nmr (CF₃COOH) δ 4.47 (s, 3H), 7.17 (br s, 2H), 7.18 (d, 2H, J=9 Hz), 7.63 (d, 2H, J=9 Hz), 8.71 (s, 1H) and 2.28 (s, acetic acid, 1.75 mol); uv λ_{max} (1N HCl) 241 nm (ϵ 20,800), 264 (19,600), 384 (10,700). Mass spectrum (70 ev, 280°) M, m/e 269, 31%; m/e 268, 100%.

Anal. Calcd. for C₁₃H₁₁N₅O₂·1.75 C₂H₄O₂: C 52.94; H, 4.85%, N 18.71%; Found: C 52.80%, H 4.86%, N 18.63%.

¹Attempts to cyclise this hydrazone in either methanol or methanol/acetic acid at reflux failed.

Example 14

25 7-Amino-1-methyl-4-(3,4,5-trimethoxyphenacyl)pyrimido[4,5-c]pyridazine-3,5-(1H, 2H)-dione

(IV) (R¹=CH₃; R⁵=CO.C₆H₂ (OCH₃)₃)

To a stirred, refluxing solution of 6-(1-methylhydrazino)isocytosine hemihydrate (4.00 g) in methyl cellosolve (400 ml) was added 8.64 g (0.0292 mol) of methyl 3,4,5-trimethoxybenzoyl-pyruvate*. After 1 hour 50 minutes reddish-orange solid was collected from the hot mixture, washed with three portions of methanol totalling 150 ml, and dried under vacuum at 75°, yield 4.29 g (44% theoretical): m.p. >300°; nmr (CF₃COOH) δ 4.08 and 4.13 (overlapping s's, 9H), 4.33 (s, 3H), 5.39 (s, 2H), 6.96 (br s, 2H), 7.54 (s, 2H); uv λ_{max} (CH₃OCH₂CH₂OH) 248.5 nm (ϵ 18,700), 268 sh (18,300), 271.5 (18,500), 317.5 (8,900), 388.5 weak sh (4,400), 413 sh (6,800), 464 sh (33,300), 486 (42,500). Mass spectrum (field desorption) M m/e 401.

Anal. Calcd. for C₁₈H₁₉N₅O₈: C 53.86%, H 4.77%, N 17.45%; Found: C 53.75%, H 4.80%, N 17.58%.

*Made from 3,4,5-trimethoxyacetophenone and methyl oxalate in the presence of methanolic sodium methoxide.

Example 15

7-Amino-1,4-dimethylpyrimido[4,5-c]pyridazine,3,5-(1H, 2H)-dione

(I) (R¹=CH₃; R²=OH; R³=CH₃; X=O)

7-Amino-1-methyl-4-(3,4,5-trimethoxyphenacyl)pyrimido[4,5-c]pyridazine-3,5 (1H, 2H)-dione (1.0 g) was dissolved in N NaOH (40 ml). After 17½ hours the green solution was brought to neutrality with concd. HCl. Yellowish-green solid was collected, washed with two portions of water totalling 40 ml, and dried under vacuum at 75°, yield 0.500 g.

The product was stored for three days under 60 ml of ether, pulverised, collected, and dried under vacuum at 75°C, yield 0.488 g (85% theoretical): m.p. >300°; nmr (CF₃COOH) δ 3.03 (s, 3H), 4.27 (s, 3H), 6.85 (br s, 2H); uv λ_{max} (N NaOH) 258.5 nm (ϵ 32,800), 282.5 sh (7,500), 402 (5,200). Mass spectrum (310°): M, m/e 207, 100%; m/e 206, 7%. The following accurate masses were determined: 207.0772 (C₈H₉N₅O₂), 206.0701 (C₈H₈N₅O₂).

Anal. Calcd. for C₈H₉N₅O₂·0.75H₂O: C 43.53%, H 4.80%, N 31.73%; Found: C 43.61%, H 4.72%, N 31.59%.

Example 16

By addition of the appropriate α -ketoester to a refluxing mixture or solution prepared from a very pure, appropriately substituted alkylhydrazinoisocytosine of formula (III) and filtered solvent in the proportion of 1 g. in 100 ml., collection by filtration of the precipitated compound of formula (I) from the hot reaction mixture, washing with a small portion of fresh reaction solvent and drying under vacuum at 70°, the following compounds of formula (I) were prepared (see Table 1):

TABLE 1

COMPOUND OF FORMULA (I)

R ¹	R ²	R ³	X	Molar Ratio (V:IV)	Reflux Solvent & Reflux time	Yield (%)	ELEMENTAL ANALYSIS F = Found Ca = Calculated
C ₂ H ₅	CH ₃	OH	O	1.25:1	H ₂ O 1 hr.	74	Ca:-C48.86% H5.01% N31.66% F:-C48.79% H5.04% N31.47%
C ₂ H ₄ OH	CH ₃	OH	O	2:1	H ₂ O 1½ hrs.	61	Ca:-C45.57% H4.67% N29.53% F:-C45.66% H4.72% N29.38%
n-C ₄ H ₉	CH ₃	OH	O	2:1	H ₂ O 4 hrs.	80	Ca:-C53.00% H6.07% N28.10% F:-C53.07% H6.12% N28.00%
CH ₂ C ₆ H ₅	CH ₃	OH	O	2.5:1	H ₂ O 23 hrs.	87	*Ca:-C57.52% H4.83% N23.96% F:-C57.30% H4.85% N23.74%

*For the hemihydrate

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Example 17

7-Amino-1,3,4-trimethylpyrimido(4,5-c)pyridazin-5(1H)-one

To a stirred, refluxing mixture of 6-(1-methylhydrazino)isocytosine hemihydrate (1.62 g) in methanol (150 ml) was added at once diacetyl (1.8 ml). After 19 hours, a brown solid was collected, washed with methanol (5 ml) and dried under vacuum at 70°C; yield, 2.02 g of crude pyrimidopyridazinone, suggested by nmr to be over 90% pure. Obtained as needles by recrystallisation from glacial acetic acid in a nitrogen atmosphere and dried under vacuum at 25°, the product was characterised as the pyrimidopyridazinone. 2.47 CH₃COOH: mp >300°; nmr (CF₃COOD) δ 2.78 (s, 3H), 3.09 (s, 3H), 4.42 (s, 3H) and 2.28 (s, acetic acid, 2.5 mol); uv λ_{max} (CH₃OH) 245 nm (ε 21,000), 261 (17,400) 266 sh (16,100), 332 sh (3,700) 370 (4,800). Mass spectrum (330°): M. m/e 205, 100%; m/e 177, 18%; m/e 163, 44%.

Anal. Calcd. for C₉H₁₁N₅O. 2.47 CH₃COOH: C 47.36%; H 5.95%; N 19.81%; Found: C 47.26%; H, 5.98%; N 19.85%.

Example 18

5,7-Diamino-1-methyl-3-(3,4,5-trimethoxybenzoyl)methylpyrimido(4,5-c)pyridazin-4(1H)-one

To a stirred, refluxing solution of 2,4-diamino-6-(1-methylhydrazino)pyrimidine (1.54 g) in absolute ethanol (150 ml; drying tube) was added methyl 2,4-dioxo-4-(3,4,5-trimethoxyphenyl)-n-butyrate (4.45 g). After 4 hours, the resulting mixture was filtered to remove an uncharacterised solid (0.17 g). The filtrate was refluxed for an additional 22 hours before more unidentified solid (0.09 g) was removed by filtration. The filtrate was heated at reflux for another 3 hours to give a precipitate which was collected by filtration, washed with ethanol and dried under vacuum at 70°, yield 0.31 g (7.7% of theoretical) of pure pyrimidopyridazinone, a white solid: mp >300°; nmr (CF₃COOH) δ 4.05 s, 4.10 s (12 H), 4.69 (s, 2H), 7.50 (s, 2H), 8.45 (br s, 2H); uv λ_{max} (CH₃OH) 218.5 nm (ε 35,700), 248 (31,700), 256 (27,600), 304 (20,600). Mass spectrum (180°): M, m/e 400, 23%; m/e 205, 1.5%; m/e 195, 100%.

Anal. Calcd. for C₁₈H₂₀N₆O₅: C 53.99%; H 5.03%; N 20.99%. Found: C 53.98%; H 5.06%; N 20.97%.

Example 19

A. A compound of formula (I) was tested for anti-coccidial activity *in vivo* in combination with diaveridine (DV) and sulphaquinoxaline (SQ), each at 20 ppm, according to the following procedure.

Groups of five, seven day old chicks were each infected orally with 100,000 sporulated oocysts of the Weybridge strain of *E. tenella*. The drug was administered as a mixture in LD5 chick mash deficient in vitamin K, beginning one day prior to infection and continuing for 8 days. On the sixth day after infection, caecal lesions of surviving chicks were scored on a scale of 0, 1, 2 or 3 and any dead chicks with lesions were scored as 4. The activity of the drug is expressed as follows for each group:

+++ = mean lesion score of 0.0 to 0.9

++ = mean lesion score of 1.0 to 1.9

+ = mean lesion score of 2.0 to 3.4

The following results were obtained:—

Compound of formula (I)				Activity (conc. in p.p.m.)
R ¹	R ²	R ³	X	
C ₂ H ₅	CH ₃	OH	O	+ (180) (60) (20)

Example 20

The anticoccidial activity of compounds of formula (I) in combination with a mixture of diaveridine and sulphaquinoxaline *in vitro* against *E. tenella* was tested using standard techniques.

The following results were obtained wherein activity is expressed as follows:—

5 = No parasite development

4 = 1—25% parasite development

3 = 26—50% parasite development

2 = 51—75% parasite development
 1 = 76—95% parasite development
 0 = 95—100% parasite development

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TABLE 2

COMPOUND OF FORMULA I

10

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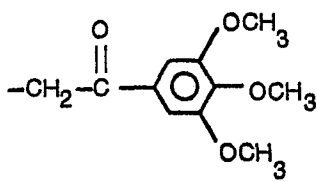
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R ¹	R ²	R ³	X	Activity (concentration $\mu\text{g/ml.}$)
C ₂ H ₄ OH	CH ₃	OH	O	1(100) 1(25) 0(6.25)
CH ₂ C ₆ H ₅	CH ₃	OH	O	2(25) 0(6.25)
n-C ₄ H ₉	CH ₃	OH	O	4(25) 2(6.25)
CH ₃	CH ₃	OH	NH	3(100) 3(25) 1(6.25)
CH ₃		OH	NH	3(100) 1(25)
CH ₃	CH ₃	CH ₃	O	3(25) 0(6.25)
CH ₃	H	C ₆ H ₅	O	4(25) 2(6.25)
CH ₃	H	C ₆ H ₄ OH(4)	O	4(25) 2(6.25)

Example 21

Following the procedure of Example 20, compounds of formula (I) were tested for anti-coccidial activity alone *in vitro*. The following results were obtained:—

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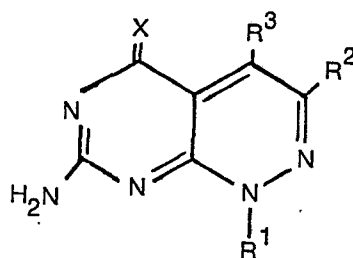
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COMPOUNDS OF FORMULA I

R ¹	R ²	R ³	X	Activity (concentration $\mu\text{g/ml}$)
C ₂ H ₄ OH	CH ₃	OH	O	1(100) 1(25)
n-C ₄ H ₉	CH ₃	OH	O	3(25) 1(6.25)
CH ₃	H	C ₆ H ₅	O	3(25) 0(6.25)
CH ₃	H	C ₆ H ₄ OH(4)	O	3(25) 2(6.25)

Claims

1. A compound of the formula (I):



(I)

- or a tautomer or salt thereof, wherein R¹ is a benzyl group, or a lower (C₁ to C₄) alkyl group optionally substituted by a hydroxy group; R² is a hydrogen atom, a hydroxy group, a methyl group, a hydroxymethyl group, a benzyl group optionally substituted in the phenyl ring with a nitro group or one or two lower (C₁ to C₄) alkoxy groups, a phenacyl group optionally substituted in the phenyl ring with one or more hydroxy or lower (C₁ to C₄) alkoxy groups, a group CH(Y)CO₂Z in which Y is a hydrogen atom, a lower (C₁—C₄) alkyl group, or a benzyl group, where Z is a hydrogen atom or a lower (C₁—C₄) alkyl group; R³ is a hydroxy group, a methyl group, or a phenyl group optionally substituted with a hydroxy group; and X is an oxygen atom or a group NH; provided that:

- (i) R³ is a methyl group only when R² is a methyl or hydroxy group;
 (ii) R³ is a phenyl group optionally substituted with a hydroxy group only when R² is a hydrogen atom;
 (iii) when R³ is a hydroxy group, R² is other than a hydrogen atom or a hydroxy group; and
 (iv) when R¹ is a methyl group and R³ is a hydroxy group X is NH.

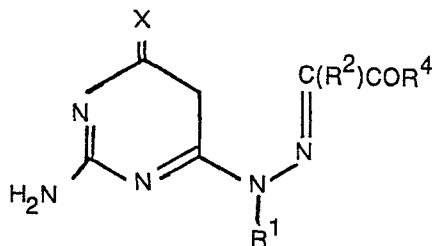
2. A compound of formula (I) as claimed in claim 1 wherein R² is a hydrogen atom, a hydroxy group, a methyl group, a hydroxymethyl group, a benzyl group optionally substituted in the phenyl ring with a nitro or one or two lower alkoxy groups, a phenacyl group optionally substituted in the phenyl ring with one or more lower alkoxy groups, or a group CH(Y)CO₂Z in which Y and Z are the same or different and each is a hydrogen atom or a lower alkyl group.

3. A compound according to either claim 1 or 2 wherein R¹ is a methyl group; R² is a methyl group or a hydrogen atom and R³ is a hydroxy or a phenyl group optionally substituted with a hydroxy group.

4. A compound according to claim 1 wherein R¹ is a lower (C₁ to C₄) alkyl group optionally substituted with a hydroxy group, or a benzyl group; and Z is a hydrogen atom or a lower (C₁ to C₄) alkyl group.

5. A compound according to either claim 1 or 4 wherein R¹ is a methyl or *n*-butyl group and R² is a hydrogen atom, a hydroxy group, a methyl group, a benzyl group optionally substituted in the phenyl ring with two methoxy groups, or a phenacyl group substituted in the phenyl ring with two methoxy groups.

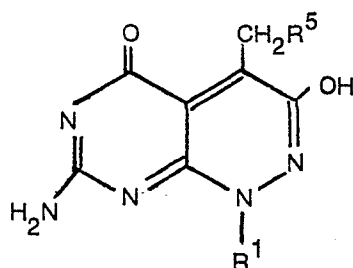
6. A process for the preparation of a compound of the formula (I) or a tautomer or salt thereof as defined in claim 1 which comprises the cyclisation of a compound of the formula (II):



(II)

10 or a tautomer or salt thereof, wherein X, R¹ and R² are as hereinbefore defined and R⁴ is a lower (C₁ to C₄) alkoxy group, or a group R³ as hereinbefore defined apart from a hydroxy group, and thereafter wherein X is an oxygen atom and R³ is an acyloxymethyl group, hydrolysing R³ to a hydroxymethyl group.

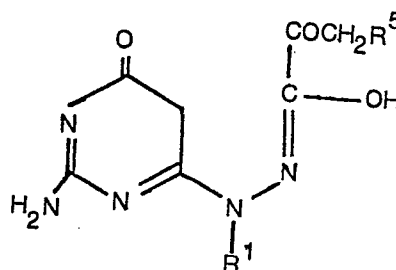
15 7. A process for the preparation of a compound of the formula (I) wherein R¹ is as defined in claim 1, X is an oxygen atom, R³ is a methyl group and R² is a hydroxy group which comprises the hydrolysis of a compound of the formula (IV):



(IV)

30 wherein R⁵ is an aryl group.

8. A process for the preparation of a compound of the formula (IV), as defined in claim 7, which comprises the cyclisation of a compound of the formula (V):



(V)

45 wherein R¹ and R⁵ are as defined in claim 7.

9. A compound of the formula (IV) as defined in claim 7.

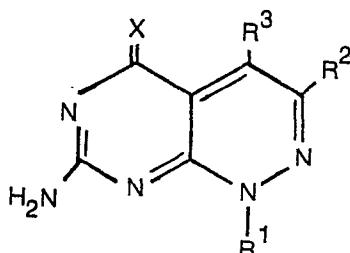
10. A veterinary composition which comprises a compound of the formula (I), or a tautomer or veterinary acceptable salt thereof, as defined in claim 1, together with a veterinary acceptable carrier.

11. A veterinary composition according to claim 10 in unit dose form.

50 12. A poultry feed which comprises a non-toxic effective anticoccidial treatment amount of a compound of the formula (I), or a tautomer or veterinary acceptable salt thereof.

Revendications

55 1. Les composés de formule générale (I)



(I)

ainsi que leurs tautomères et sels, formule dans laquelle R¹ représente un groupe benzyle ou un alkyle inférieur (en C₁₋₄) pouvant porter éventuellement un hydroxyle; R² est un atome d'hydrogène, un hydroxyle, un méthyle, un hydroxyméthyle, un benzyle éventuellement substitué sur le cycle phénylique par un groupe nitro ou un ou deux alcoxy inférieurs (en C₁₋₄), un phénacyle éventuellement substitué sur le cycle phénylique par un ou plusieurs hydroxyles ou alcoxy inférieurs (en C₁₋₄), ou un groupe —CH(Y)CO₂Z, Y étant un atome d'hydrogène, un alkyle inférieur (en C₁₋₄) ou un benzyle, et Z l'hydrogène ou un alkyle inférieur en (C₁₋₄); R³ est un hydroxyle, un méthyle ou un phényle éventuellement substitué par un hydroxyle; et X représente un atome d'oxygène ou un groupe NH; avec les conditions que:

- (1) R³ ne soit un méthyle que si R² est un méthyle ou un hydroxyle;
- (2) R³ ne soit un phényle éventuellement substitué par un hydroxyle que si R² est un atome d'hydrogène;
- (3) si R³ est un hydroxyle, R² n'est ni l'hydrogène ni un hydroxyle; et
- (4) si R¹ est un méthyle et R³ un hydroxyle, X est un groupe NH.

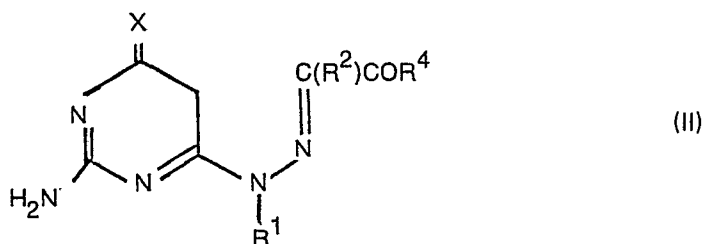
2. Composé selon la revendication 1 dans lequel R² est un atome d'hydrogène, un hydroxyle, un méthyle ou un hydroxyméthyle, un benzyle éventuellement substitué sur le cycle phénylique par un groupe nitro ou un ou deux groupes alcoxy, un phénacyle éventuellement substitué sur le cycle phénylique par un ou plusieurs alcoxy, ou encore un groupe —CH(Y)CO₂Z, Y et Z, qui peuvent être identiques ou différents l'un de l'autre, désignant chacun l'hydrogène ou un alkyle inférieur.

3. Composé selon la revendication 1 ou 2 dans lequel R¹ est un méthyle, R² un méthyle ou un atome d'hydrogène et R³ un hydroxyle ou un phényle éventuellement hydroxylé.

4. Composé selon la revendication 1 dans lequel R¹ est un alkyle en C₁₋₄ éventuellement substitué par un hydroxyle, ou un benzyle, et Z un atome d'hydrogène ou un alkyle en C₁₋₄.

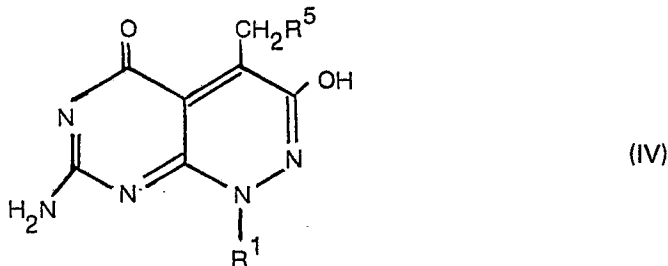
5. Composé selon l'une quelconque des revendications 1 à 4 dans lequel R¹ est un groupe méthyle ou n-butyle et R² un atome d'hydrogène, un hydroxyle, un méthyle, un benzyle éventuellement substitué sur le cycle phénylique par deux groupes méthoxy, ou un phénacyle portant sur le cycle phénylique deux groupes méthoxy.

6. Procédé de préparation des composés de formule (I) et de leurs tautomères ou sels, selon la revendication 1, procédé suivant lequel on cyclise un composé de formule (II)



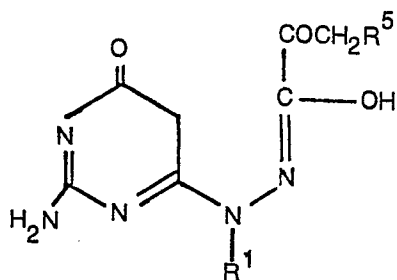
ou un tautomère ou sel de celui-ci, R⁴ étant un alcoxy en C₁₋₄ ou un groupe R³ tel que défini à la revendication 1, à l'exception d'un hydroxyle, puis, si X est un atome d'oxygène et R³ un groupe acyloxy-méthyle, on hydrolyse le groupe R³ en un groupe hydroxyméthyle.

7. Procédé de préparation des composés de formule (I) selon la revendication 1 dans lesquels X est un atome d'oxygène, R³ un groupe méthyle et R² un hydroxyle, procédé suivant lequel on hydrolyse un composé de formule (IV)



dans laquelle R⁵ est un groupe aroyle.

8. Procédé de préparation des composés de formule IV selon la revendication 7, suivant lequel on cyclise un composé de formule (V)



(V)

le symbole R^5 ayant la signification donnée à la revendication 7.

9. Les composés de formule (IV) selon la revendication 7.

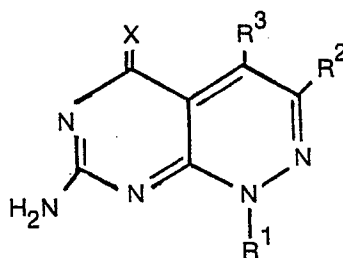
10. Composition vétérinaire comprenant un composé de formule (I), un tautomère de ce composé ou un sel acceptable pour des usages vétérinaires, selon la revendication 1, avec un véhicule pour usages vétérinaires.

11. Composition selon la revendication 10 sous forme d'unités de prise.

12. Aliment pour volailles, comprenant une dose anti-coccidiose non toxique d'un composé de formule (I) selon la revendication 1, ou d'un tautomère ou sel de celui-ci acceptable pour un usage vétérinaire.

Patentansprüche

1. Verbindung der Formel (I)



(I)

oder ein Tautomeres oder ein Salz davon, worin R^1 eine Benzylgruppe oder eine niedrigmolekulare (C_1-C_4)-Alkylgruppe, die gegebenenfalls durch eine Hydroxylgruppe substituiert ist; R^2 ein Wasserstoffatom, eine Hydroxylgruppe, eine Methylgruppe, eine Hydroxymethylgruppe, eine Benzylgruppe, die gegebenenfalls am Phenylring mit einer Nitrogruppe oder einer oder zwei niedrigmolekularen (C_1-C_4)-Alkoxygruppen substituiert ist, eine Phenacylgruppe, die gegebenenfalls am Phenylring mit einer oder mehreren Hydroxylgruppen oder niedrigmolekularen (C_1-C_4)-Alkoxygruppen substituiert ist, eine Gruppe der Formel $CH(Y)CO_2Z$, worin Y für ein Wasserstoffatom, eine niedrigmolekulare (C_1-C_4)-Alkylgruppe oder eine Benzylgruppe Z für ein Wasserstoffatom oder eine niedrigmolekulare (C_1-C_4)-Alkylgruppe stehen; R^3 eine Hydroxylgruppe, eine Methylgruppe oder eine Phenylgruppe, die gegebenenfalls mit einer Hydroxylgruppe substituiert ist; und X ein Sauerstoffatom oder eine NH-Gruppe mit der Maßgabe bedeuten, daß

(i) R^3 nur dann eine Methylgruppe bedeutet wenn R^2 eine Methylgruppe oder eine Hydroxylgruppe darstellt;

(ii) R^3 nur dann eine gegebenenfalls mit einer Hydroxylgruppe substituierte Phenylgruppe bedeutet, wenn R^2 ein Wasserstoffatom darstellt;

(iii) R^2 von einem Wasserstoffatom oder einer Hydroxylgruppe verschieden ist, wenn R^3 eine Hydroxylgruppe darstellt; und

(iv) wenn R^1 eine Methylgruppe und R^3 eine Hydroxylgruppe darstellen, X eine NH-Gruppe bedeutet.

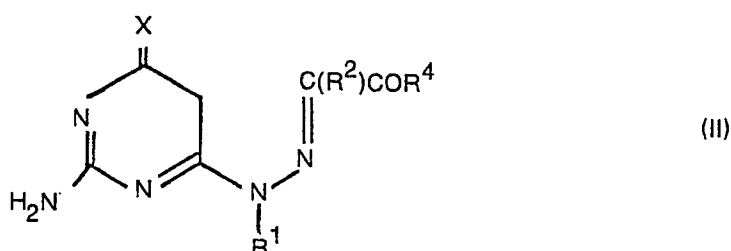
2. Verbindung der Formel (I) gemäß Anspruch 1, worin R^2 ein Wasserstoffatom, eine Hydroxylgruppe, eine Methylgruppe, eine Hydroxymethylgruppe, eine Benzylgruppe, die gegebenenfalls am Phenylring mit einer Nitrogruppe oder einer oder zwei niedrigmolekularen Alkoxygruppen substituiert ist, eine Phenacylgruppe, die gegebenenfalls am Phenylring mit einer oder mehreren niedrigmolekularen Alkoxygruppen substituiert ist oder eine Gruppe der Formel $CH(Y)CO_2Z$, in der Y und Z gleichartig oder verschieden sind und jeweils Wasserstoffatome oder niedrigmolekulare Alkylgruppen darstellen, bedeutet.

3. Verbindung nach den Ansprüchen 1 oder 2, worin R^1 eine Methylgruppe; R^2 eine Methylgruppe oder ein Wasserstoffatom und R^3 eine Hydroxylgruppe oder eine gegebenenfalls mit einer Hydroxylgruppe substituierte Phenylgruppe bedeuten.

4. Verbindung nach Anspruch 1, worin R^1 eine niedrigmolekulare (C_1-C_4)-Alkylgruppe, die gegebenenfalls mit einer Hydroxylgruppe substituiert ist, oder eine Benzylgruppe; und Z ein Wasserstoffatom oder eine niedrigmolekulare (C_1-C_4)-Alkylgruppe bedeuten.

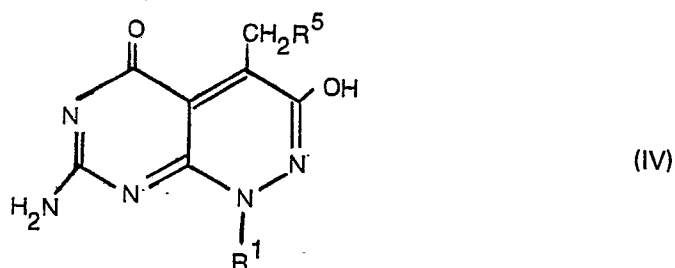
5. Verbindung nach den Ansprüchen 1 oder 4, worin R^1 eine Methylgruppe oder eine n-Butylgruppe und R^2 eine Wasserstoffatom, eine Hydroxylgruppe, eine Methylgruppe, eine gegebenenfalls am Phenylring mit zwei Methoxygruppen substituierte Benzylgruppe oder eine am Phenylring mit zwei Methoxygruppen substituierte Phenacylgruppe bedeuten.

6. Verfahren zur Herstellung einer Verbindung der Formel (I) oder eines Tautomeren oder eines Salzes davon gemäß Anspruch 1, dadurch gekennzeichnet, daß man eine Verbindung der Formel (II)



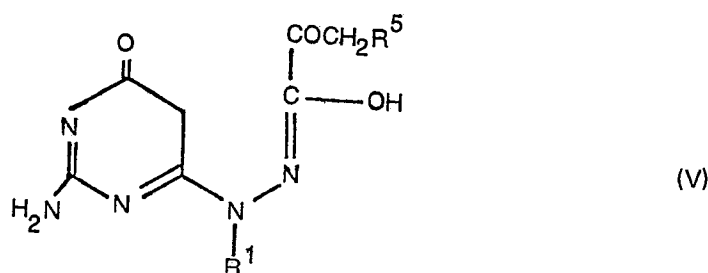
oder ein Tautomeres oder ein Salz davon, worin X, R^1 und R^2 die oben angegebenen Bedeutungen besitzen und R^4 eine niedrigmolekulare (C_1-C_4)-Alkoxygruppe oder eine Gruppe R^3 der obigen Definition mit Ausnahme der Hydroxylgruppe bedeutet, cyclisiert, und anschließend, wenn X ein Sauerstoffatom und R^3 eine Äcyloxymethylgruppe darstellen, die Gruppe R^3 zu einer Hydroxymethylgruppe hydrolysiert.

7. Verfahren zur Herstellung einer Verbindung der Formel (I) worin R^1 die in Anspruch 1 angegebenen Bedeutungen besitzt, X für ein Sauerstoffatom, R^3 für eine Methylgruppe und R^2 für eine Hydroxylgruppe stehen, dadurch gekennzeichnet, daß man eine Verbindung der Formel (IV)



worin R^5 für eine Aroylgruppe steht, hydrolysiert.

8. Verfahren zur Herstellung einer Verbindung der Formel (IV) gemäß Anspruch 7, dadurch gekennzeichnet, daß man eine Verbindung der Formel (V)



worin R^1 und R^5 die in Anspruch 7 angegebenen Bedeutungen besitzen, cyclisiert.

9. Verbindung der Formel (IV), wie sie in Anspruch 7 definiert ist.

10. Tierarzneimittel, enthaltend eine Verbindung der Formel (I) oder ein Tautomeres oder ein tiermedizinisch annehmbares Salz davon gemäß Anspruch 1 und ein tiermedizinisch annehmbares Trägermaterial.

11. Tierarzneimittel, nach Anspruch 10, dadurch gekennzeichnet, daß es in Einheitsdosisform vorliegt.

12. Geflügelfutter enthaltend eine nichttoxische für die Bekämpfung von Kokzidien wirksame Menge einer Verbindung der Formel (I) oder eines Tautomeren oder eines tiermedizinisch annehmbaren Salzes davon.