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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Anti-Coccidial Compositions comprising Nitrofuran Derivatives

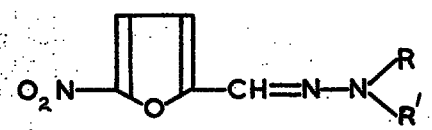
We, THE NORWICH PHARMACAL COMPANY, a Company organised under the Laws of the State of New York, United States of America, of Norwich, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is for improvements in or relating to the control of coccidiosis in poultry and has for an object to provide a new composition having anticoccidial properties to facilitate combatting coccidiosis in poultry by providing an anticoccidial poultry feed.

The disease of poultry commonly referred to "coccidiosis" is widespread. It is caused by species of the genus Eimeria. A particularly troublesome member is *Eimeria tenella* which lodges in the caecum of chickens and is responsible for severe, and often fatal, infections. The morbidity and mortality occasioned by this infection create an extensive economic loss if left untreated or unchecked. Particularly obnoxious in connection with this disease is the appearance of "bloody droppings" from the chickens provoked by rupture of their caecal mucosal tissue.

In the last decade, several drugs have been developed which possess anticoccidial properties but none of them is without some shortcomings. Apart from anticoccidial activity *per se*, other factors such as tolerability at effective dose levels of the drug, feed efficiency and conversion resulting when a drug-containing diet is employed, emergence of drug-resistant mutants, effect of drug on egg production and hatchability, permissive development of natural immunity in the presence of drug, activity at tolerable levels to combat and overcome massive infections sometimes encountered and economy of treatment, must be considered in poultry husbandry.

We have discovered that it is possible to combat coccidiosis in poultry by means of certain nitrofuran derivatives that can be combined with feedstuff administered to the poultry so that such feedstuff serves as an inert carrier therefor. These nitrofuran derivatives are fully tolerable at effective dose levels, can be employed for extensive time periods with generally beneficial effect upon the growth and development of the birds, are substantially non-toxic and are relatively inexpensive. They are readily consumed by poultry when combined with poultry feed. The nitrofuran derivatives that we employ in the practice of this invention are 5-nitro-2-furfurylidene hydrazine compounds that may be represented by the following general formula:



in which

R represents a hydrogen atom or a lower alkyl group, and

R^1 represents a hydrogen atom or a lower alkyl or lower alkanoyl group, the expression "lower" meaning that the group contains from 1 to 5 carbon atoms.

While each of the 5-nitro-2-furfurylidene hydrazine compounds defined by the foregoing general formula is distinguished by its anticoccidial activity, the individual compounds differ from each other somewhat in degree of anticoccidial effectiveness. The preferred compound for the purpose of the present invention is 1-acetyl-1-methyl-2-(5-nitro-2-furfurylidene) hydrazine.

In accordance with the present invention, there is provided a composition comprising a compound of the above general formula and an inert carrier, as hereinafter defined.

The term "inert carrier" as used herein means any non-toxic substance which is inert towards the active nitrofuran compounds other than water or other common solvents when used alone in association with the active com-

[*Price 4s. 6d.*]

pounds. Examples of carriers which are commonly used in poultry husbandry are ground oyster shells, Attapulgus clay, commercial poultry feeds, urea, corn meal, ground corn, citrus meal, fermentation residues, soya bean oil and distillers' dried grains. The mixing of the active ingredient with the carrier is accomplished by commonly-used methods such as stirring, tumbling and grinding. In this way, it is possible to prepare compositions of varying concentration to suit particular needs or desires. Premixes, *i.e.*, concentrates, so prepared and containing from 1% to 25% by weight of the active ingredient can then be added to poultry rations in amounts necessary to provide desirable drug levels of from 0.003% to 0.02% by weight.

For the prophylactic control of coccidiosis, the amount of active ingredient is extremely low, a daily intake of 0.005% by weight of the food consumed serving well; for optimum results, we prefer that the daily intake should be about 0.0075% to 0.011%, such amounts usually affording excellent protection whilst in the event that an outbreak of the disease is encountered, higher concentrations of the order of about 0.015% to about 0.02% by weight of the food may be employed.

The nitrofuran derivatives employed in carrying out the invention can be readily obtained. Their preparation involves the interaction of 5-nitro-2-furaldehyde and the appropriate hydrazine compound. For instance, 5-nitro-2-furfurylidene hydrazine may be obtained by reacting 5-nitro-2-furaldehyde with hydrazine; 1-acetyl-2-(5-nitro-2-furfurylidene) hydrazine may be prepared by reacting 5-nitro-2-furaldehyde with acethydrazide, and 1,1 - dimethyl - 2 - (5 - nitro - 2-furfurylidene) hydrazine may be secured by reacting 5-nitro-2-furaldehyde with unsymmetrical dimethyl hydrazine. In order that nitrofuran derivatives with which the present invention is concerned may be readily available to those skilled in the art, the following descriptions are given of the preparation of various members of the series of compounds.

Preparation 1: One mole of 5-nitro-2-furaldehyde is dissolved in 1 litre of ethanol and 64 g. (1.0 mole) of methyl hydrazine is added. This mixture is stirred for 2 hours then filtered and the solid so obtained is dried. The yield of 1 - methyl - 2 - (5 - nitro-2-furfurylidene) hydrazine is 106 g. (65% yield).

Preparation 2: The product of Preparation 1 is mixed with 350 cc. of acetic anhydride and heated under reflux for 15 minutes. The mixture is allowed to stand and the deposited solid is filtered and dried to yield 91 g. (68% yield) of 1 - acetyl - 1 - methyl - 2 - (5-nitro-2-furfurylidene) hydrazine.

Preparation 3: One mole of ethyl hydrazine sulphate is dissolved in 1 litre of water and treated with 450 cc. of a saturated sodium carbonate solution raising the pH to about 6. Over one-half hour, a solution of one mole of 5-nitro-2-furaldehyde in 1400 cc. of ethanol is added with vigorous stirring. The orange product is filtered to yield 151 g. (82.5% yield) of 1-ethyl-2-(5-nitro-2-furfurylidene) hydrazine (m.p. = 119°—121° C.). This product is refluxed with 500 cc. of acetic anhydride for 15 minutes, cooled to 0° C., the deposited solid filtered and thoroughly washed with methanol. There are thus obtained 170 g. (91% yield) of 1-acetyl-1-ethyl - 2 - (5 - nitro - 2 - furfurylidene) hydrazine (m.p. = 172°—174° C.).

Preparation 4: A mixture of 20 g. of dimethylhydrazine hydrochloride, 29 g. of 5-nitro-2-furaldehyde, 200 cc. of water and 600 cc. of ethanol is heated to boiling, filtered and the filtrate cooled. The precipitated solid is washed with a little cold ethanol and dried to give 32.5 g. (86% yield) of 1,1-dimethyl-2-(5-nitro-2-furfurylidene) hydrazine (m.p. 115° C.).

Preparation 5: In a flask are placed 119 g. (0.7 mole) of the product of Preparation 1, 220 cc. of butyric anhydride and 16.5 cc. of pyridine. This mixture is heated to achieve solution at 145° C. It is cooled and the deposited product collected. There are obtained 129 g. (83% yield) of 1-butyryl-1-methyl-2-(5-nitro-2-furfurylidene) hydrazine (m.p. = 124°—125° C. after recrystallisation from methanol).

Preparation 6: 31 g. of butyryl hydrazide is dissolved in 300 cc. of ethanol and 42 g. of 5-nitro-2-furaldehyde is dissolved in 250 cc. of ethanol. The two solutions are combined and stirred with heating to 70° C. for 2 hours and then cooled. The deposited crystals of 1 - butyryl - 2 - (5 - nitro - 2 - furfurylidene) hydrazine weigh 33 g. (50% yield) and have a m.p. of 168°—170° C.

Preparation 7: 5-nitro-2-furfuraldehyde (5 g.) is dissolved in methanol (70 cc.) and the solution cooled by means of ice. Hydrazine hydrate (3.4 g.) is added dropwise with stirring over a period of about thirty minutes. The dark red solution is stirred for an additional ninety minutes, cooling being maintained over the entire period. It is then filtered. The filtrate is concentrated to a small volume and the precipitate formed removed by filtration. It is recrystallised from methanol in the form of bright red needles. There are obtained 3 g. of 5-nitro-2-furfurylidene hydrazine (m.p. 166°—167° C.).

The following Example is given to illustrate the preparation of a premix or concentrate in accordance with the invention.

The following ingredients were measured out and intimately admixed:—

Ground yellow corn	1200	lbs.
Fish meal	100	„
Soya bean oil	500	„
Sodium chloride	10	„
Magnesium sulphate	0.5	„
Limestone (finely ground)	20	„
Bone meal	25	„
Dehydrated alfalfa meal	50	„
Dried whey	25	„
Vitamin D_3	0.5	„

The foregoing mixture constitutes a poultry feedstuff and is medicated by the incorporation therein, during the mixing, of from 1 to 25% by weight of 1-acetyl-1-methyl-2-(5-nitro-2-furfurylidene) hydrazine.

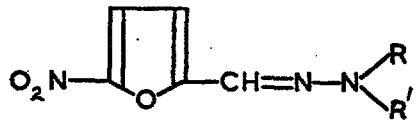
The premix or concentrate so prepared is admixed with the required quantity of the carrier ingredients above described, or with any other carrier composition to produce a desired concentration of the hydrazine compound within the limits of from 0.003 to 0.02% by weight.

It will be understood that instead of first preparing a premix or concentrate, the required amount of the drug may be directly incorporated into the desired poultry feedstuff composition to give the final medicated composition ready for use.

In place of the specific nitrofurfurylidene hydrazine compound used in the foregoing Example, there may, of course, be substituted any of the other compounds defined by the general formula above-mentioned.

WHAT WE CLAIM IS:—

1. A premix or concentrate adapted to be combined with a poultry feedstuff to provide a composition having anti-coccidial properties upon administration to poultry, comprising an inert carrier, as hereinbefore defined, and from about 1% to about 25% by weight thereof of a nitrofuran derivative represented by the following general formula:

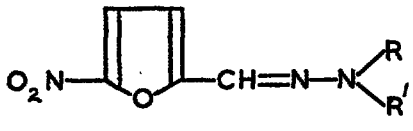


in which

R represents a hydrogen atom or a lower alkyl group and

R^1 represents a hydrogen atom or a lower alkyl or lower alkanoyl group, the term "lower" meaning that the group contains from 1 to 5 carbon atoms.

2. A composition having anticoccidial properties upon administration to poultry, comprising a poultry feedstuff having admixed therewith from about 0.003% to about 0.02% by weight thereof of a nitrofuran derivatives represented by the general formula:



in which

R represents a hydrogen atom or a lower alkyl group and

R^1 represents a hydrogen atom or a lower alkyl or lower alkanoyl group, the term "lower" meaning that the group contains from 1 to 5 carbon atoms.

3. A composition according to claim 2 wherein said nitrofuran derivative is employed in an amount of from 0.0075 to 0.011% by weight.

4. An anti-coccidial composition substantially as described in the Example.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

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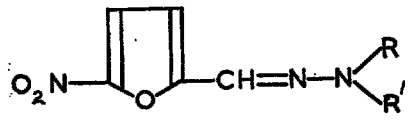
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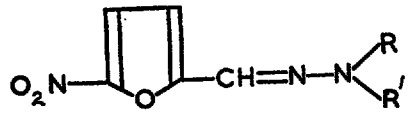


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