1,184,426

PATENT SPECIFICATION

NO DRAWINGS

1,184,426

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International Classification:—A 61 k 27/00

COMPLETE SPECIFICATION

A Composition for the Treatment and Prevention of Coccidiosis

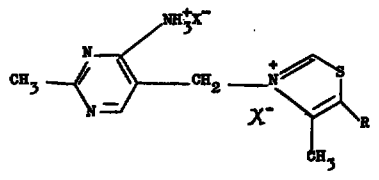
We TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA (TAKEDA CHEMICAL INDUSTRIES LTD), a body corporate organised under the laws of Japan, of 54, 4-chome, Jusonishino-cho, Higashiyodogawa-ku, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a composition for the treatment and/or prevention of coccidiosis in poultry, and to methods for the treatment and/or prevention of coccidiosis in poultry.

Coccidiosis is a fatal infectious poultry disease and the treatment and prevention of the disease are one of the most important problems in the poultry industry.

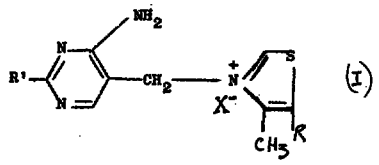
Up to the present, attempts have been made to treat the disease by means of various anti-coccidial agents. These known anti-coccidial agents, however, have such defects as weak activity and strong, unfavourable side effects.

In our copending application No. 10153/66 (now Serial No. 1,143,634) we claimed a composition for the treatment and/or prevention of coccidiosis in poultry which comprises a carrier or diluent and a thiazolium salt of the formula:



wherein R is a "lower alkyl" group with from 1 to 3 carbon atoms and X^- is an inorganic anion, the concentration of the latter salt in the composition being from 0.0016% to 0.025% by weight.

We have now found that thiazolium quaternary monosalts of formula (I):



(I)

wherein R and R' are the same or different and are alkyl groups with from 1 to 3 carbon atoms, and X^- is an inorganic or organic acid radical consisting of NO_3^-, NO_2^-, I^-, SCN^-, ClO_4^- or rhodanate have a remarkable preventive and curative action against coccidiosis equal to (or greater than) that of the above-mentioned di-salt as well as the following advantageous characteristics:

(1) they have a higher storage stability than the di-salt;
(2) they are less hygroscopic than the di-salt; and
(3) as they do not have electrostatic properties,

they can be easily admixed with the normal poultry diet.

The present invention has been accomplished upon the basis of these new-findings. That is to say, the present invention provides a composition for the treatment and/or prevention of coccidiosis in poultry, which comprises a carrier and/or a diluent and a thiazolium salt of the above-mentioned formula (I), the concentration of the salt in the composition being from 0.001% to 0.05% by weight. The invention also provides a method of treating and/or preventing coccidiosis in poultry, in which an anti-coccidial amount of the thiazolium salt of the above-mentioned formula (1) is administered to poultry.

In the formula (1), R and R' are the same

[*Price 5s. 0d.*]

or different and represents alkyl groups having 1 to 3 carbon atoms, and exemplified by methyl, ethyl, propyl, and isopropyl.

X^- represents an inorganic or organic acid radical consisting of NO_3^-, NO_2^-, I^-, SCN^-, ClO_4^- or rhodanate. Typical compounds represented by the foregoing formula (1) may be exemplified by:

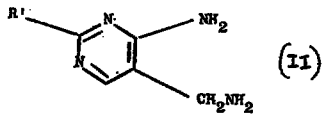
3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium mono salt,

3 - (2 - ethyl - 4 - aminopyrimidinyl - 5 - methyl - 4,5 - dimethyl thiazolium mono salt,

3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4 - methyl - 5 - ethylthiazolium mono salt,

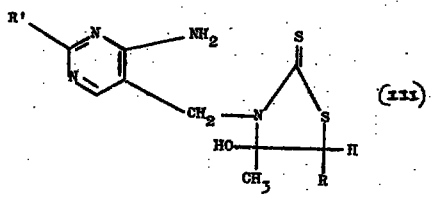
3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4 - methyl - 5 - propyl thiazolium mono salt.

The compound of the formula (1) can be successfully obtained for example, by a method which comprises reacting a compound of the Formula (II):



(II)

with carbon disulphide and 3-halogeno butanone-2 in the presence of a basic compound such as aqueous ammonia, an alkali metal hydroxide or an alkali metal carbonate to give 3 - (2 - lower alkyl - 4 - amino - pyrimidinyl - 5 - methyl) - 4 - hydroxy - 4 - methyl - 5 - methyl thiazolizine - 2 - thione of the formula (III):



(III)

wherein R' is as above defined, subjecting the compound of the formula (III) to treatment with an inorganic acid such as hydrochloric acid, sulphuric acid or nitric acid or an organic acid such as acetic acid or formic acid, and then treating the resulting 3 - (2 - lower alkyl - 4 - aminopyrimidinyl - 5 - methyl) - 4 - methyl - 5 - methylthiazole - 2 - thione with an oxidising agent such as hydrogen peroxide, bromine, potassium permanganate or potassium hypochlorite. The resulting mixture is reacted with the appropriate salt to give a compound of the formula I.

A composition according to the present invention comprises a thiazolium quaternary monosalt of the formula (I) as an active anti-coccidial ingredient dispersed in, or admixed with, a suitable carrier or diluent. A composition may be administered orally in such forms as powders, granules, tables, suspension, emulsion or by injection or by admixing with poultry diet or by dissolving in water depending on various conditions such as the kind of poultry, the state of poultry or the age of poultry. The carrier or diluent preferably does not react with the active ingredient and must be administered with safety to poultry. Carriers or diluents suitable in the present compositions include, for example, wheat shorts, wheat flour, corn meal, soybean mill feed, soybean flour, vegetables, ground shells, fish meal, soybean grits, dried grains, fermentation residues, rice-bran, potato starch, lactose, sucrose, glucose, fructose, molasses solubles, antibiotic mycelia, vitamins, crushed limestone and clay.

The optimum concentration of the present composition depends to some extent on the kind of thiazolium salt employed, the kind of poultry or the purpose of the administration of the composition, that is prevention or curing. A composition of any desired concentration may be prepared by selecting proper diluents and by determining the proper ratio of carrier to active ingredient. In general, formulations containing from 0.001% to 0.05%, preferably from 0.005% to 0.025% by weight (based on the feed) of the active ingredient (I) in poultry diets or water are suitable for the treatment and prevention of the disease. When the thiazolium quaternary mono salts (I) are employed as therapeutic agents, the higher concentrations of 0.0125% to 0.05% by weight are preferably used. Intermediate formulations of a certain concentration are preferably prepared in advance by using suitable diluents or carriers, and added to the finished feed in administration to poultry in the required proportions. 1% to 30% by weight of the thiazolium quaternary mono salt is convenient as the concentration of the intermediate formulations.

For the purpose of giving those skilled in the art a better understanding of the invention, the following illustrative experiments are given. In the following examples of formulations of the composition, part (parts) or percent are shown on weight basis, otherwise stated. Parts by weight mean the same relation to parts by volume as do grams to millilitres.

Experiment 1 (anti-coccidial action).

Test Procedure

(1) *Chicks*: Nine-day-old white leghorn males

(2) *Infectious coccidium*: Sporulated oocysts of *Eimeria tenella*

(3) *Administered compounds*: As a test compound, mononitrate and monorhodanate

salts of 3 - (2 - methyl - 4 - amino - pyrimidinyl - 5 - methyl) - 4,5 - dimethyl-thiazolium (I) are employed each in a concentration of 0.0063% by weight in a diet. As a control compound, 3 - (2 - methyl - 4 - amino - pyrimidinyl - 5 - methyl) - 4,5 - dimethyl - thiazolium chloride hydrochloride (di-salt) is used in a concentration of 0.0063% by weight in the diet.

(4) *Method of test:* The above-mentioned chicks are bred in isolation for 8 days and their condition of health is observed. They are weighed and divided into several groups consisting of five chicks each. The mean weight of each group is arranged to be equal. One each of the chick groups is applied to test groups and to a control group. To the infectious and non-infectious groups, one group is applied. After division into groups, the test group and control group are bred by the diet containing said compounds and infectious and non-infectious groups are bred by the normal diet. After such breeding is carried out for 24 hours, each chick except the non-infectious group is inoculated orally with 100,000 oocysts of *Eimeria tenella.*

(5) *Observations:* Mortality and blood droppings in each group are recorded daily until the end of the test. Eight days after oocyst inoculation, all the survivors are sacrificed and examined pathologically.

(6) Explanation of findings set forth in Table 1:

$$\text{Growth rate} = \left(\frac{\text{Average body weight at the Finish}}{\text{Average body weight at the Start}} - 1\right) \times 100$$

$$\text{Rate of growth rate} = \frac{\text{growth rate of test group}}{\text{growth rate of control group}} \times 100$$

Bloody droppings: Average drops of blood excreted from the intestine of each chick belonging to a group.

(7) Index of efficacy by Johnson J. E., *et al.*

Index of efficacy is calculated as follows:

A.

Caecal lesions	Equivalents
None	0
Trace	1
Slight	2
Moderate	4
Severe	8

B.

Oocysts in diluted caecal contents*	Equivalents
None per 20 fields	0
1—5 per field	1
6—50 per field	2
51—150 per field	4
150 and above per field	8

The "field" is the field of view of the microscope used to study the caecal contents.

*Caecal contents are diluted 10 times and observed with a microscope.

x : Average A. rating + average B. rating in infectious group.

y : Average A. rating + Average B. rating in test groups

$$\text{Index of Efficacy} = \frac{x - y}{x} \times 100$$

*When the value of "x—y" is a negative value, the index of efficacy is deemed to be "0".

TABLE 1

	% by weight of compound in diet	Rate of growth rate of body weight (%)	Bloody droppings day after			Index of efficacy
			4	5	6	
Test group	mono nitrate 0.0063	103.9	0	0	0	71.1
	mono rhodanate 0.0063	98.6	0	0	0	80.3
	Chloride hydrochloride (di-salt) 0.0063	92.4	0	0	0	61.3
Control group	Infectious control	65.7	3.2	6.0	3.1	
	Non-infectious control	100.00	0	0	0	

As shown in the Table, it is observed that the 3 - (2 - methyl - 4 - amino-pyrimidinyl - 5 - methyl) - 4,5 - dimethyl-thiazolium mononitrate and monorhodanate of the present invention are substantially equal to the di-salt, effective against *Eimeria tenella* and that the test compounds no not cause any unfavourable effect on poultry.

Experiment 2.

Test Procedures:

(1) *Chicks*: Twelve-day-old white leghorn males.

(2) *Infectious coccidium*: Sporulated oocysts of *Eimeria tenella.*

(3) *Administered compounds*: As a test compound, (a) 3 - (2 - ethyl - 4 - amino - pyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium mono-nitrate is employed in concentrations of 0.0031%, 0.0063% and 0.0125% by weight in a conventional poultry feed.

(4) *Method of test*: The chicks are raised in isolation for 11 days and the condition of their health is observed. They are then weighed and divided into five groups consisting of five chicks each. The mean weight of each group is arranged to be the same. Three of the five groups are test groups and two are control groups (i.e. infectious group and non-infectious group). The chicks in each test group are fed with a diet containing the above concentrations of compound (a), and the two control groups are fed with a normal poultry diet. After 24 hours, each chick except those of the non-infectious group is inoculated orally with 50,000 oocysts of *Eimeria tenella.*

(5) *Observations*: Mortality and bloody droppings in each group are recorded daily until the end of the test. Eight days after oocyst inoculation, all the survivors are sacrificed and examined pathologically.

The explanation of findings set forth in Table 2 below is the same as in Experiment 1 above regarding Table 1.

TABLE 2

	% by weight of compound in diet	Rate of growth rate of body weight (%)	Bloody droppings day after			Index of efficacy
			3	4	5	
Test Group	mono nitrate (a) 0.0031	106.9	0	0	0	98.8
	mono nitrate (a) 0.0063	105.2	0	0	0	100.0
	mono nitrate (a) 0.0125	109.1	0	0	0	98.1
Control group	Infectious control	80.7	1.0	2.4	3.6	—
	Non-infectious control	100	0	0	0	—

Experiment 3.

1. *Storage stability.*

a. Each salt of chloride hydrochloride (di-salt), mononitrate and monorhodanate of 3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium is added to a commercial grower feed in a following concentration. After these feeds are stored at 30°C for 4 weeks, at 35°C for 2 weeks and 4 weeks and at 40°C for 1 week and 2 weeks, the remaining amount of each active ingredient is examined in each group. The results are shown in Table 3 below.

TABLE 3

Active ingredient	Concentration γ/g (feed)	Remaining amount (per cent to initial amount)				
		Stored at 40°C.		Stored at 35°C.		Stored at 30°C
		After 1 week	After 2 weeks	After 2 weeks	After 4 weeks	After 4 weeks
Chloride hydrochloride (di-salt)	132	85.0	85.4	86.7	67.5	75.4
mono nitrate	111	95.4	93.2	99.8	71.7	85.7
mono rhodanate	118	92.7	86.5	91.5	76.2	79.7

b. Each of chloride hydrochloride (di-salt), mononitrate and monorhodanate of 3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium is added to each of grower feed and stater feed respectively in a concentration of 250 γ g (feed) of free 3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium.

After these feeds are stored at 40°C for 2 weeks, the remaining amount of the active ingredient in each group is examined. The result is shown in Table 4.

TABLE 4

Salt \ Feed	Remaining amount) (per cent to initial amount)	
	Stater feed	Grower feed
Chloride hydrochloride (di-salt)	67.0	67.3
mono nitrate	82.4	84.0
mono rhodanate	81.4	84.9

2. *Hygroscopic property*

After the following salts are kept standing at 4°C under a specific relative humidity for 7 days and 14 days, water content (%) of each salt is examined. The result is shown in Table 5. The thiazolium compound from which the salts are formed is 3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethyl thiazolium.

TABLE 5

Salt	Initial water content (%)	Relative humidity (%)	Water content (%)	
			After 7 days	After 14 days
Chloride hydrochloride (di-salt)	5.45	52	8.26	8.34
		63	8.42	8.48
		75	8.87	8.89
Mononitrate	0.83	52	0.50	0.70
		63	0.71	0.79
		75	0.97	1.05
Monorhodanate	6.02	52	6.06	6.00
		63	5.76	5.99
		75	5.73	5.79

N.B. Actual water content of rhodanate is 0.2 — 0.3% since rhodanate has one mole (about 5.8%) of water of crystallisation.

As shown in the results, the monosalts of the present invention have a higher storage stability and a lower hygroscopic property than the di-salt.

EXAMPLE 1

The following components are mixed together:

3 - (2 - Methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium mono rhodanate ..... 25 parts
Wheat flour ..... 75 parts

0.05 Part of the mixture is homogeneously added to 99.95 parts of conventional diet for chicks. The prepared composition is fed to chicks.

EXAMPLE 2

The following components are mixed together:

3 - (2 - Methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium mono nitrate ..... 10 parts
Soybean flour ..... 85 parts
Sucrose ..... 5 parts

0.05 Part of the mixture is homogeneously added to 99.95 parts of conventional diet for breeders.

The prepared composition is fed to breeders.

EXAMPLE 3

The following components are admixed together:

3 - (2 - Methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium mono rhodanate ..... 20 parts
Fermentation residue ..... 80 parts

0.05 Part of the mixture is homogeneously added to 99.95 parts of conventional diet for breeders.

The prepared composition is fed to breeders.

EXAMPLE 4

The following components are admixed together:

3 - (2 - Methyl - 4 - aminopyrimidinyl - 5 - methyl - 4,5 - dimethylthiazolium mono nitrite ..... 45 parts
Lactose ..... 35 parts
Sucrose ..... 20 parts

10 Parts of mixture are dissolved in 10000 parts by volume of water.

The prepared composition is fed to chicks.

EXAMPLE 5

The following components are admixed together:

3 - (2 - Methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium nitrate ..... 1 part
Grain flour ..... 88 parts
Calcium carbonate ..... 11 parts

0.03 Parts of the mixture is added to 99.97 parts of conventional diet for layer.

The prepared composition is fed to layers.

EXAMPLE 6

Preparation of active ingredient

Into 40 parts by volume of methanol, 7.5 parts of 2 - methyl - 4 - amino - 5 - aminomethylpyrimidine is dissolved. To the solution are added 23.4 parts of aqueous ammonia, 4.2 parts of carbon disulphide and then 8.1 parts of 3 - chlorobutanone - 2, and agitated for 4 hours at 50°C to allow a reaction to take place. After the reaction, methanol is distilled off under reduced pressure, and to the residue is added 7.2 parts of concentrated hydrochloric acid, followed by heating at 70°C for 1 hour. After cooling, an aqueous solution of sodium hydroxide is added to the solution and pH value is adjusted to 7 to give a solid substance. The solid substance is separated by filtration, washed with water and dried to give 13 parts of 3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazole - 2 - thione melting at 223°C. Yield 90%.

Into 100 parts by volume of water, 10 parts of 3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazole - 2 - thione is dissolved. To the solution is slowly added 10.2 parts of a 30% hydrogen peroxide under agitation while the temperature is kept at 20°C. The resulting mixture is agitated for 2 hours to allow a reaction to take place. 5.5 parts of sodium bicarbonate is added to reaction mixture to adjust pH value to neutral range, followed by adding to so-treated total mixture a concentrated aqueous solution of 2.5 parts of ammonium rhodanate to give 8.0 parts 3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium monorhodanate (Yield 80%) m.p. 188—190°C.

Elementary Analysis: $C_{12}H_{15}N_5S_2.H_2O$

	C	H	N
Calculated:	46.28	5.50	22.49
Found :	45.89	5.36	22.21

In place of the above ammonium rhodanate, a concentrated aqueous solution of 2.5 parts of sodium nitrate is employed to give 6.5 parts of 3 - (2 - methyl - 4 - aminopyrimidinyl) - 5 - methyl) - 4,5 - dimethylthiazolium mononitrate. (Yield 68%).

After recrystallising from a hot water, the nitrate becomes colourless needles melting at 185—188°C (decomposition).

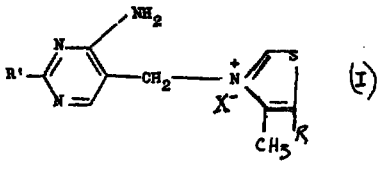
Elementary analysis: $C_{11}H_{15}N_5O_3S$

	C	H	N
Calculated:	44.43	5.08	23.55
Found :	44.26	5.20	23.35

If the effective amount, i.e. the anticoccidial amount, of the thiazolium mono-salt to be administered according to the present invention is calculated in terms of the amount per 100 grams of the body weight of poultry, it may also be expressed as 0.5 to 10 milligrams, preferably 1 to 5 milligrams, per 100 grams of the body weight of poultry.

WHAT WE CLAIM IS:—

1. A composition for the treatment and/or prevention of coccidiosis in poultry, which comprises a carrier and/or a diluent and a thiazolium salt of the formula



(I)

wherein R and R' are the same or different and are alkyl groups with from 1 to 3 carbon

* C L M S *

0.05 Part of the mixture is homogeneously added to 99.95 parts of conventional diet for breeders.

The prepared composition is fed to breeders.

EXAMPLE 3

The following components are admixed together:

3 - (2 - Methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium mono rhodanate	20 parts
Fermentation residue	80 parts

0.05 Part of the mixture is homogeneously added to 99.95 parts of conventional diet for breeders.

The prepared composition is fed to breeders.

EXAMPLE 4

The following components are admixed together:

3 - (2 - Methyl - 4 - aminopyrimidinyl - 5 - methyl - 4,5 - dimethylthiazolium mono nitrite	45 parts
Lactose	35 parts
Sucrose	20 parts

10 Parts of mixture are dissolved in 10000 parts by volume of water.

The prepared composition is fed to chicks.

EXAMPLE 5

The following components are admixed together:

3 - (2 - Methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium nitrate	1 part
Grain flour	88 parts
Calcium carbonate	11 parts

0.03 Parts of the mixture is added to 99.97 parts of conventional diet for layer.

The prepared composition is fed to layers.

EXAMPLE 6

Preparation of active ingredient

Into 40 parts by volume of methanol, 7.5 parts of 2 - methyl - 4 - amino - 5 - aminomethylpyrimidine is dissolved. To the solution are added 23.4 parts of aqueous ammonia, 4.2 parts of carbon disulphide and then 8.1 parts of 3 - chlorobutanone - 2, and agitated for 4 hours at 50°C to allow a reaction to take place. After the reaction, methanol is distilled off under reduced pressure, and to the residue is added 7.2 parts of concentrated hydrochloric acid, followed by heating at 70°C for 1 hour. After cooling, an aqueous solution of sodium hydroxide is added to the solution and pH value is adjusted to 7 to give a solid substance. The solid substance is separated by filtration, washed with water and dried to give 13 parts of 3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazole - 2 - thione melting at 223°C. Yield 90%.

Into 100 parts by volume of water, 10 parts of 3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazole - 2 - thione is dissolved. To the solution is slowly added 10.2 parts of a 30% hydrogen peroxide under agitation while the temperature is kept at 20°C. The resulting mixture is agitated for 2 hours to allow a reaction to take place. 5.5 parts of sodium bicarbonate is added to reaction mixture to adjust pH value to neutral range, followed by adding to so-treated total mixture a concentrated aqueous solution of 2.5 parts of ammonium rhodanate to give 8.0 parts 3 - (2 - methyl - 4 - aminopyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium monorhodanate (Yield 80%) m.p. 188—190°C.

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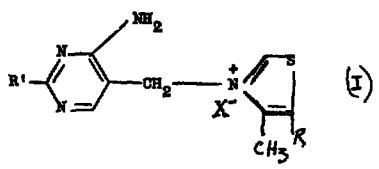
If the effective amount, i.e. the anticoccidial amount, of the thiazolium mono-salt to be administered according to the present invention is calculated in terms of the amount per 100 grams of the body weight of poultry, it may also be expressed as 0.5 to 10 milligrams, preferably 1 to 5 milligrams, per 100 grams of the body weight of poultry.

WHAT WE CLAIM IS:—

1. A composition for the treatment and/or prevention of coccidiosis in poultry, which comprises a carrier and/or a diluent and a thiazolium salt of the formula



(I)

wherein R and R' are the same or different and are alkyl groups with from 1 to 3 carbon

atoms, and X^- is an inorganic or organic acid radical consisting of NO_3^-, NO_2^-, I^-, SCN^-, ClO_4^- or rhodanate, the concentration of the latter salt in the composition being from 0.001% to 0.05% by weight.

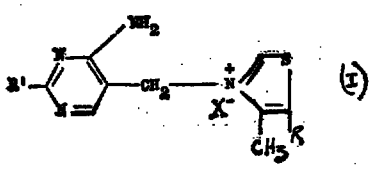
2. A composition for the treatment and/or prevention of coccidiosis in poultry, which comprises a carrier and/or diluent and 3 - (2 - methyl - 4 - amino - pyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium mononitrate, the concentration of the latter salt in the composition being from 0.001% to 0.05% by weight.

3. A composition as claimed in claim 1 for treating and/or preventing coccidiosis in poultry substantially as herein described.

4. A composition for the treatment and/or prevention of coccidiosis in poultry, substantially as herein described with reference to any of the specific examples.

5. A method for the treatment and/or prevention of coccidiosis in poultry in which a composition as claimed in any of claims 1 to 4 is administered to poultry.

6. A method of treating and/or preventing coccidiosis in poultry, in which an anticoccidial amount of a thiazolium salt of the formula



(I)

wherein R and R′ are the same or different and are alkyl groups with from 1 to 3 carbon atoms, and X^- is an inorganic or organic acid radical consisting of NO_3^-, NO_2^-, I^-, SCN^-, ClO_4^- or rhodanate, is administered to poultry.

7. A method of treating and/or preventing coccidiosis in poultry, in which an anticoccidial amount of 3 - (2 - methyl - 4 - amino - pyrimidinyl - 5 - methyl) - 4,5 - dimethylthiazolium mono nitrate is administered to poultry.

8. A method as claimed in claim 6 substantially as herein described.

9. A method of treating and/or preventing coccidiosis in poultry substantially as herein described with reference to any of the specific examples.

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