

PATENT SPECIFICATION

(11) 1 256 723

NO DRAWINGS

- (21) Application No. 31664/69 (22) Filed 23 June 1969
 (31) Convention Application No. 741 247 (32) Filed 1 July 1968 in
 (33) United States of America (US)
 (45) Complete Specification published 15 Dec. 1971
 (51) International Classification C 07 c 129/12; A 61 k 27/00
 (52) Index at acceptance

C2C 20Y 220 227 22Y 29X 29Y 30Y 311 313 314 315 31Y
 320 321 326 328 32Y 338 351 354 373 37Y 620
 650 669 694 697 699 703 746 747 74X 758 790
 79Y LA NA RH
 A5B 38Y 391 410 41Y 420 42Y 432 433 43Y 480 48Y
 492 49Y 586 58Y 64X 64Y



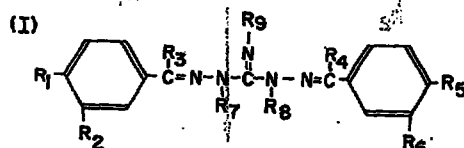
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(54) PROTOZOACIDALLY-ACTIVE SUBSTITUTED GUANIDINES

(71) We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, 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 relates to substituted guanidines which are protozoacidally-active. More particularly, this invention relates to compositions for the control of coccidiosis and other protozoan infections in warm-blooded animals other than human beings, which compositions contain protozoacidally-active substituted guanidines, and to methods for controlling coccidiosis and other protozoan infections in warm-blooded animals (other than human beings) by administering to the host animals the protozoacidally-active substituted guanidines. The present invention also relates to certain novel substituted guanidines, and to methods for preparing the substituted guanidine compounds.

The compositions of the present invention contain as the protozoacidally-active component a compound of Formula I:



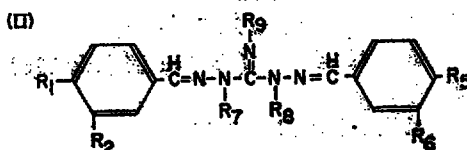
wherein each of R_1 and R_3 is halogen, trifluoromethyl or cyano, each of R_2 and R_6 is hydrogen or halogen, each of R_3 , R_4 , R_7 , and R_8 is hydrogen or (C_1-C_4) alkyl, and R_5 is hydrogen or (C_2-C_6) alkanoyl; or a pharmacologically acceptable acid-addition salt thereof.

The acid-addition salts can be, for example, nitrates, hydrochlorides, hydrobromides and methosulfates.

The term "halogen" means chlorine, bromine, fluorine, and iodine.

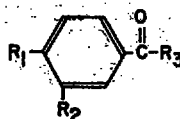
The compounds of Formula I are, in general, crystalline solids, ranging in color from white to pale yellow, slightly soluble in water and (C_1-C_4) alcohols and insoluble in benzene, toluene and chloroform.

The present invention also includes new bis(benzylideneamino)guanidines of Formula II:

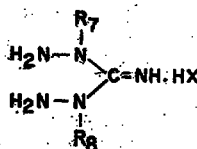


wherein R_1 , R_2 , R_3 , R_4 , R_7 , R_8 and R_9 are as defined hereinbefore, and pharmacologically acceptable acid salts thereof.

Those active components and novel compounds wherein R_1 and R_5 are the same, R_2 and R_6 are the same, R_3 and R_4 are the same and R_9 is hydrogen can be prepared by reacting a compound of the formula:

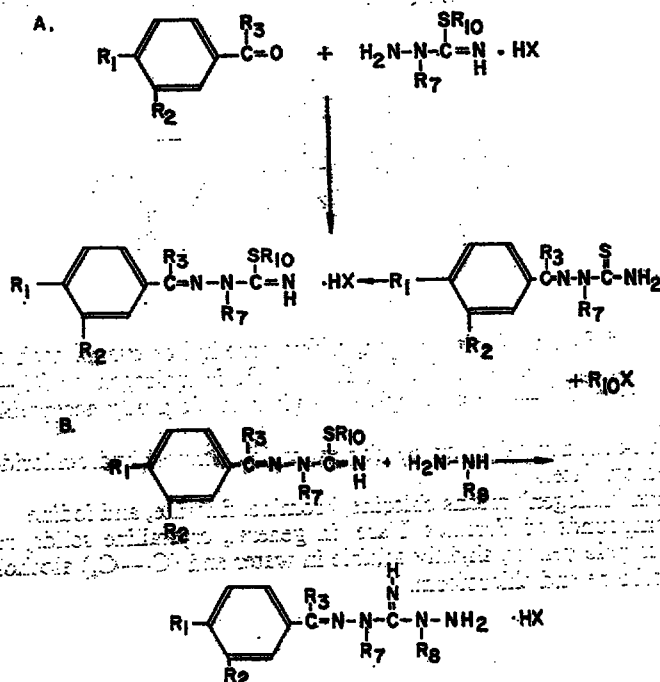


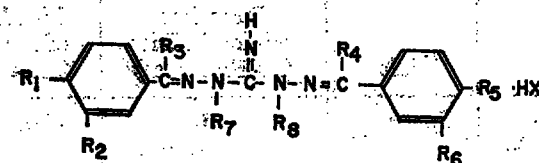
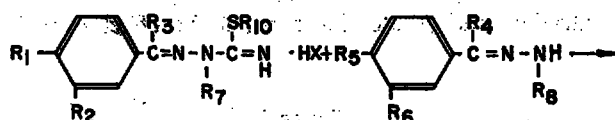
wherein R_1 , R_2 and R_3 are as hereinabove described, dissolved in a water miscible organic solvent, with an aqueous or aqueous alcoholic solution of a compound of the formula:



wherein R_7 and R_8 are as hereinabove described and X is the anion of a pharmacologically acceptable acid. Preferably, the reaction mixture is heated to from 50°C to the boiling point of the solvent and held there for from one to ten minutes and then cooled to room temperature. The precipitated product is collected, washed with ethanol and/or ether and dried.

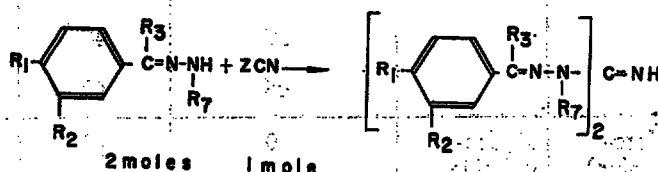
Other methods of preparing the active components and novel compounds are illustrated by the equations which follow:





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The active components and novel compounds of the present invention are highly active antiprotozoal agents in warm-blooded animals. For example, these compounds have anticoccidial activity against *Eimeria tenella* as shown by the following test: The animals were Peterson cross cockerels, 7 days old and of approximately equal size and weight. These cockerels were divided into groups and the groups were placed in separate cages with wire floors. Medicated and control diets were then presented to the groups of birds 2 days before inoculation while they were still in uncontaminated quarters. During the entire period of the tests, the birds ate and drank *ad libitum*. Control groups were maintained on a standard unmedicated commercial type chicken diet. Test groups were maintained on the same standard diet in which a measured concentration of test compound had been incorporated homogeneously. The cockerels were inoculated once orally with sporulated oocysts of *Eimeria tenella*. The number of oocysts inoculated directly into the crops of all cockerels in the tests was sufficient to produce high mortality in the untreated controls. The quantity necessary to produce high mortality was determined prior to the times of inoculation by giving graded quantities of oocysts to comparable birds. Seven days following inoculation the tests were terminated and the mortality rate was recorded for each group. The results of these tests appear in Table I and show conclusively that these compounds are highly effective as anticoccidial agents. The tests represent very severe laboratory challenges, and lower concentrations than those shown would be effective under practical field conditions.

TABLE I

Compound	Salt	Parts Per Million in Diet (As Free Base)	Number of Birds Treated	% Survival
1,3-Bis(4-chloro-benzylideneamino)-guanidine	Nitrate	0	100	32
		15	70	77
		30	70	96
		45	30	100
1,3-Bis(4-chloro-benzylideneamino)-guanidine	Metho-sulfate	0	40	28
		15	39	59
		30	40	90
		45	40	98
1,3-Bis(4-chloro-benzylideneamino)-guanidine	Hydro-chloride	0	20	20
		7.5	20	45
		15	20	75
		30	20	100
1,3-Bis(4-bromo-benzylideneamino)-guanidine	Nitrate	0	20	45
		15	20	80
		30	20	95
1,3-Bis(4-chloro- α -methylbenzylidene-amino)guanidine	Nitrate	0	20	40
		60	10	80
		250	10	100

TABLE I (Continued)

Compound	Salt	Parts Per Million in Diet (As Free Base)	Number of Birds Treated	% Survival
1,3-Bis(3,4-dichlorobenzylideneamino)guanidine	Nitrate	0	20	30
		60	10	100
1,3-Bis(4-cyanobenzylideneamino)guanidine	Nitrate	0	20	20
		30	10	80
		60	10	100
1,3-Bis(4-iodobenzylideneamino)guanidine	HCl	0	20	0
		30	20	55
1,3-Bis(4-fluorobenzylideneamino)guanidine	Nitrate	0	20	45
		93	5	80
1,3-Bis(4-trifluoromethylbenzylideneamino)guanidine hydrochloride	Hydrochloride	0	20	70
		120	10	100

The active components of the present invention have high activity against other coccidial species in chickens. Thus, 1,3-bis(4-chlorobenzylidene amino)guanidine completely protected treated chickens from mortality due to *Eimeria necatrix*, and from poor weight gains due to *E. acervulina*, *E. brunetti*, *E. maxima* or *E. mivati*. Methods used were essentially identical with those previously cited with appropriate modifications. Weight gains were determined 7 days after single experimental inoculations with the designated species of coccidia. The results are summarized in Table II.

TABLE II
Anticoccidial Activity of 1,3-Bis(4-chlorobenzylideneamino)-guanidine

<i>Eimeria</i> Spp.	Ppm. in Diet	No. Birds	% Survival	% control Weight gain	Salt
parvovulva	0	19	21	31	metho-sulfate
	15	20	100	80	
	30	20	100	103	
acervulina	0	20	100	57	nitrate
	45	20	100	99	
brunetti	0	20	100	76	hydro-chloride
	15	20	100	100	
	30	20	100	95	
maxima	0	20	100	58	hydro-chloride
	15	20	100	101	
	30	20	100	95	
	45	20	100	100	
mivati	0	20	95	52	hydro-chloride
	15	20	100	86	
	30	20	100	91	
	45	20	100	100	

It is anticipated that the active components of this invention will prove widely useful in a variety of vehicles, modes or means of administration or dispersal for the purpose of minimizing, preventing, controlling, treating, ameliorating or curing protozoal infections with sensitive organisms. One of these infections is coccidiosis which is a protozoan parasitic disease widespread in animals, causing a greater economic loss among domestic and game animals in temperate climates than any other protozoan disease. Coccidiosis is the most important animal parasitic disease of chickens, the causative agents being protozoa of the genus *Eimeria*, and is also important in other domestic animals such as turkeys, sheep, cattle and pigs.

The present compositions and novel compounds are active in warm-blooded animals as anti-malarial agents. When tested in mice in the range of from 150 mg./kg. to 300 mg./kg. they show an activity comparable to quinine.

Although administration of the active components for coccidiosis will generally be most practical in or with the feed, or in the drinking water, the active components may also be administered to individual hosts in the form of tablets, drenches or capsules, or by injection. These latter methods of administration are, of course, less practical for treatment of large groups of animals than they are for treating limited numbers of animals, but they are quite practical for use on a small scale or on an individual basis.

In accordance with this invention, medicated feeds are usually prepared by thoroughly admixing 0.0005 to 0.05% by weight and preferably 0.0015 to 0.025% by weight of active compound with a nutritionally balanced animal feed, as for example, the chick feed described in the examples hereinafter.

Where it is desirable to prepare a concentrate or premix for ultimate dilution in feed to the above levels, generally 1% to 25% and preferably 3% to 10% by weight of medicament is blended with an edible organic or inorganic carrier, e.g., corn meal or corn and soybean meal, or alfalfa, or mineral salts containing a small amount of an edible dusting oil such as, for example, corn oil, or soybean oil. The thus prepared premix may then be added to the complete animal poultry feed prior to administration.

The invention is illustrated by the Examples which follow:

EXAMPLE 1

Preparation of 1,3-Bis(4-chlorobenzylideneamino)guanidine nitrate, hydrochloride and methosulfate.

A boiling solution of 14.1 grams of 4-chlorobenzaldehyde (slight excess) in 250 milliliters of ethanol is stirred vigorously as a solution of 6.1 grams of 1,3-diaminoguanidine nitrate and 0.5 milliliters of concentrated nitric acid in 50 milliliters of water is added in one portion. The reaction mixture is stirred as the temperature recedes to room temperature. The reaction mixture is then allowed to stand for several hours. The precipitate which forms is collected, washed with hot ethanol, air-dried and finally dried at 60°C. under reduced pressure. The yield is 14.0 grams of product and the melting point is 198°C. with decomposition.

The hydrochloride or methosulfate salt may be prepared by this same procedure, substituting equivalent amounts of the appropriate guanidine salt and employing 0.5 milliliters of the appropriate acid. The hydrochloride salt melts at 289—290°C. with decomposition. The methosulfate salt melts at 217—224°C. with decomposition.

EXAMPLE 2

Preparation of 1,3-Bis(4-chlorobenzylideneamino)guanidine.

The free base of the title compound is prepared by suspending 8 g. of the nitrate salt (Example 1) in 200 ml. of anhydrous ethanol, adding 2.5 ml. of 10N sodium hydroxide solution, stirring and heating until the reaction mixture becomes homogeneous, and finally cooling the solution and filtering the resultant solid. The melting point of the free base is 187—188°C.

EXAMPLE 3

Preparation of 1,3-Bis(4-bromobenzylideneamino)guanidine Nitrate

A boiling solution of 20.0 grams of 4-bromobenzaldehyde in 250 milliliters of ethanol is stirred vigorously as a solution of 6.1 grams of 1,3-diaminoguanidine nitrate and 0.5 milliliters of concentrated nitric acid in 50 milliliters of water is added in one portion. The reaction mixture is stirred as the temperature recedes to room temperature. The reaction mixture is allowed to stand for several hours. The precipitate which forms is collected, washed with hot ethanol, air dried and finally dried at 60°C. under reduced pressure. The yield is 16.5 grams of product and the melting point is 178°—180°C. with decomposition.

EXAMPLE 4

Preparation of 1,3-Bis(3,4-dichlorobenzylideneamino)guanidine Nitrate

A boiling solution of 17.6 grams of 3,4-dichlorobenzaldehyde in 250 milliliters of ethanol is stirred vigorously as a solution of 6.1 grams of 1,3-diaminoguanidine nitrate and 0.5 milliliters of concentrated nitric acid in 50 milliliters of water is added in one portion. The reaction mixture is stirred as the temperature recedes to room temperature. The reaction mixture is then allowed to stand for several hours. The precipitate which forms is collected, washed with hot ethanol, air dried and finally dried at 60°C. under reduced pressure. The yield is 17.5 grams of product and the melting point is 195—196°C. with decomposition.

EXAMPLE 5

Preparation of 1,3-Bis(4-cyanobenzylideneamino)guanidine Nitrate

A boiling solution of 13.1 grams of 4-cyanobenzaldehyde in 250 milliliters of ethanol is stirred vigorously as a solution of 6.1 grams of 1,3-diaminoguanidine nitrate and 0.5 milliliters of concentrated nitric acid in 50 milliliters of water is added in one portion. The reaction mixture is stirred as the temperature recedes to room temperature. The reaction mixture is then allowed to stand for several hours. The precipitate which forms is collected, washed with hot ethanol, air dried and finally dried at 60°C. under reduced pressure. The yield is 15.1 grams of product and the melting point is 205°—210°C. with decomposition.

EXAMPLE 6

Preparation of 1,3-Bis(4-chloro- α -methylbenzylideneamino)guanidine Nitrate

A boiling solution of 15.4 grams of 4-chloro-acetophenone in 250 milliliters of ethanol is stirred vigorously as a solution of 6.1 grams of 1,3-diaminoguanidine nitrate and 0.5 milliliters of concentrated nitric acid in 50 milliliters of water is added in one portion. The reaction mixture is stirred as the temperature recedes to room temperature. The reaction mixture is then allowed to stand for several hours. The precipitate which forms is collected, washed with hot ethanol, air dried and finally dried at 60°C. under reduced pressure. The yield is 8.7 grams of product and the melting point is 215°C. with decomposition.

EXAMPLE 7

Preparation of 1,3-Bis(4-iodobenzylideneamino)guanidine Hydrochloride

Following the procedure of Example 1 and substituting 4-iodobenzaldehyde for 4-chlorobenzaldehyde and 1,3-diaminoguanidine hydrochloride for 1,3-diaminoguanidine nitrate the title compound is obtained. The hydrochloride has a melting point of 288°—291°C., dec.

EXAMPLE 8

Preparation of 1,3-Bis(4-fluorobenzylideneamino)guanidine Nitrate

Using the procedure of Example 1 and substituting 4-fluorobenzaldehyde for 4-chlorobenzaldehyde the title compound is obtained. The nitrate has a melting point of 169°—170°C., dec.

EXAMPLE 9

Preparation of Methyl thiocarbazimidate hydrochloride

Excess methyl chloride is collected in a dry ice-acetone-cooled trap and added to a tared pressure vessel containing 91.1 g. of powdered thiosemicarbazide in 600 ml. of anhydrous ethanol. Weighing the vessel plus contents shows that 53 g. of methyl chloride has been added. The reaction mixture is magnetically stirred while heating in an oil bath temperature of 77 to 110°C. for 48 minutes. After 33 minutes, the reaction has become homogeneous. It is cooled in ice and the resultant rose-white solid filtered and dried in a vacuum oven. The yield of the title compound is 121 g. melting point 154—155°C.

Substitution of dimethyl sulfate, ethyl iodide or propyl bromide for methyl chloride and allowing the reactions to proceed in refluxing anhydrous ethanol instead of under pressure, results in the preparation of methyl thiocarbazimidate methosulfate, ethyl thiocarbazimidate hydroiodide, and propyl thiocarbazimidate hydrobromide, respectively.

EXAMPLE 10

Preparation of Methyl 3-(4-chlorobenzylidene)thiocarbazimidate hydrochloride

A solution of 3.8 g of 4-chlorobenzaldehyde in 10 ml. of warm absolute ethanol is added all at once to a stirred solution of 5 g. of methyl thiocarbazimidate hydrochloride in 100 ml. of warm absolute alcohol. The reaction mixture is stirred at room temperature for about 15 minutes and cooled in ice. The white solid product is filtered off and air dried; melting point 212—214°C.

The following are prepared in like manner: methyl 3-(4-bromobenzylidene)thiocarbazimidate methosulfate from 4-chlorobenzaldehyde and methyl thiocarbazimidate methosulfate, ethyl 3-(4-cyanobenzylidene)thiocarbazimidate hydroiodide from 4-cyanobenzaldehyde and ethyl thiocarbazimidate hydroiodide, and propyl 3-(3,4-dichlorobenzylidene)thiocarbazimidate hydrobromide from 3,4-dichlorobenzaldehyde and propyl thiocarbazimidate hydrobromide.

EXAMPLE 11

Preparation of Methyl 3-(4-chlorobenzylidene)thiocarbazimidate hydrochloride

A 10% molar excess of methyl chloride is added 2.14 g. of 4-chlorobenzaldehyde thiosemicarbazone and 25 ml of anhydrous ethanol in a pressure vessel. The reaction mixture is magnetically stirred and heated in an oil bath for 1 1/2 hour. The crystalline title compound separates on cooling and is filtered off and air dried.

EXAMPLE 12

Preparation of 1,3-Bis(4-chlorobenzylideneamino)guanidine hydrochloride

A solution of 101 g. of 4-chlorobenzaldehyde in 40 ml. of warm 95% ethanol is added portionwise to a stirred solution of 1,3-diaminoguanidine hydrochloride in 450 ml. of 90% ethanol at 70°C. Addition of the first portion causes rapid boiling and the reaction mixture is cooled to a little above room temperature before the remainder

of the 4-chlorobenzaldehyde solution is added. Stirring is continued for 15 minutes and the reaction mixture is cooled in ice, filtered, and air dried. The yield is 122 g of solid, melting point 295°C. with decomposition.

The same product is obtained when 1-amino-3-(4-chlorobenzylideneamino)guanidine hydrochloride (Example 13) is allowed to react under similar conditions as above with an equimolar amount of 4-chlorobenzaldehyde.

The same product is also obtained from the reaction of methyl 3-(4-chlorobenzylidene)thiocarbazimidate (Example 10) with the hydrazone of 4-chlorobenzaldehyde in refluxing 95% ethanol. The hydrazone of 4-chlorobenzaldehyde is prepared according to the procedure for the synthesis of hydrazones of aromatic aldehydes and ketones outlined in G. Newkome and D. Fishel, J. Org. Chem., 31, 677 (1966).

EXAMPLE 13

Preparation of 1-Amino-3-(4-chlorobenzylideneamino)guanidine hydrochloride

To a solution of 2.6 g. of methyl 3-(4-chlorobenzylidene)thiocarbazimidate in 10 ml. of boiling absolute ethanol is added 0.6 g. of hydrazine hydrate. The reaction mixture is cooled in ice and the solid 1-amino-3-(4-chlorobenzylideneamino)guanidine removed by filtration.

Similarly the reaction of methyl 3-(4-bromobenzylidene)thiocarbazimidate methosulfate, ethyl 3-(4-cyanobenzylidene)thiocarbazimidate hydroiodide, and propyl 3-(3,4-dichlorobenzylidene)thiocarbazimidate hydrobromide with hydrazine yield, respectively, 1-amino-3-(4-bromobenzylideneamino)guanidine methosulfate, 1-amino-3-(4-cyanobenzylideneamino)guanidine hydroiodide, and 1-amino-3-(3,4-dichlorobenzylideneamino)guanidine hydrobromide.

The reaction of 4-chlorobenzaldehyde with a 4-fold molar excess of 1,3-diaminoguanidine hydrochloride in boiling 90% ethanol also gives 1-amino-3-(4-chlorobenzylideneamino)guanidine hydrochloride, together with a small amount of 1,3-bis(4-chlorobenzylideneamino)guanidine hydrochloride.

EXAMPLE 14

Preparation of 1-(4-Bromobenzylideneamino)-3-(4-chlorobenzylideneamino)guanidine hydrochloride

A solution of 1.85 g. of 4-bromobenzaldehyde in 10 ml. of ethanol is added to a solution of 2.48 g. of 1-amino-3-(4-chlorobenzylideneamino)guanidine hydrochloride in 25 ml. of boiling 95% ethanol. The reaction mixture is cooled and the solid product removed by filtration and air dried.

In a similar manner the reaction of 1-amino-3-(4-bromobenzylideneamino)guanidine methosulfate with 4-chlorobenzaldehyde gives the methosulfate salt of the subject compound. The reaction of 1-amino-3-(4-cyanobenzylideneamino)guanidine hydroiodide with 4-chlorobenzaldehyde gives 1-(4-chlorobenzylideneamino)-3-(4-cyanobenzylideneamino)guanidine hydroiodide. The reaction of 1-amino-3-(3,4-dichlorobenzylideneamino)guanidine hydrobromide and *p*-chlorobenzaldehyde gives 1-(4-chlorobenzylideneamino)-3-(3,4-dichlorobenzylideneamino)guanidine hydrobromide.

EXAMPLE 15

Preparation of Chick Diet

The following specific feed composition is an example of poultry feed as a carrier for the coccidiostats described hereinbefore.

Vitamin-Amino acid	0.5%
Trace Minerals	0.1%
Sodium Chloride	0.3%
Dicalcium Phosphate	1.2%
Ground Limestone	0.5%
Stabilized Fat	4%
Dehydrated Alfalfa, 17% protein	2%
Corn Gluten Meal, 41% protein	5%
Menhaden Fish Meal, 60% protein	5%
Soybean Oil Meal, 44% protein	30%
Ground Yellow Corn, Fine	To 100%

The vitamin pre-mix in the above feed composition is prepared from the following formulation. The expressions of quantity relate to units per kilogram of the feed composition.

Butylated Hydroxy toluene	125 mg.
di-Methionine	500 mg.
Vitamin A	3300 I.U.
Vitamin D ₃	1100 I.C.U.
Riboflavin	4.4 mg.
Vitamin E	2.2 I.U.
Niacin	27.5 mg.
Pantothenic Acid	8.8 mg.
Choline Chloride	500 mg.
Folic Acid	1.43 mg.
Mendadione Sodium Bisulfate	1.1 mg.
Vitamin B ₁₂	11 mcg.
Ground Yellow Corn, Fine	To 5 gm.

EXAMPLE 16

Preparation of 1,3-Bis(4-trifluoromethylbenzylideneamino)guanidine hydrochloride

A solution of 10 g. of 4-trifluoromethylbenzaldehyde in the minimum amount of 95% ethanol is added to a boiling solution of 3.6 g. of 1,3-diaminoguanidine hydrochloride in 50 ml. of 95% ethanol and a few ml. of water. The solution is stirred and allowed to cool and the solid removed by filtration and washed with 95% ethanol and ether. The yield is 9.6 g. of white solid with a melting point of 272—273.5° with decomposition.

EXAMPLE 17

Preparation of 1,3-Bis(4-chlorobenzylideneamino)-1,3-dimethylguanidine hydrobromide

A mixture of 14.1 grams of 4-chlorobenzaldehyde, 4.6 grams of methylhydrazine and 500 ml. of dried benzene is stirred at reflux in a continuous water removal apparatus until no further separation of water is noted. The benzene solution of the resultant methylhydrazone of 4-chlorobenzaldehyde is cooled to room temperature and treated with a solution of 5.3 grams of cyanogen bromide in 100 ml. of benzene. The reaction mixture is stirred at reflux for four hours, a white precipitate separating out during this time. The precipitate is filtered from the hot solution, washed and dried. It is recrystallized from ethanol to yield 4.0 grams of the pure compound melting at 223°—225°C. with decomposition.

The same compound is obtained when two molar equivalents of 4-chlorobenzaldehyde and one molar equivalent of 1,3-diamino-1,3-dimethylguanidine hydrobromide are refluxed in ethanol solution in the presence of a little 48% aqueous hydrobromic acid for a few minutes.

EXAMPLE 18

Preparation of 1,3-Bis(4-chlorobenzylideneamino)-1,3-di-n-butylguanidine hydrobromide

The preparation of the above compound is carried out by the procedure of Example 17, an equivalent of n-butylhydrazine replacing the methylhydrazine. The isolated product after recrystallization from ethanol-diethyl ether decomposes about 150°C.

EXAMPLE 19

Preparation of 1,3-Bis(4-Chlorobenzylideneamino)-1-methylguanidine hydrobromide

The preparation of the title compound is carried out essentially by the procedure of Example 1, 7.3 grams of 1,3-diamino-1-methylguanidine hydrobromide replacing the 1,3-diaminoguanidine nitrate and 0.5 ml. of 48% HBr being employed as catalyst. The yield of product is 15.4 grams and the melting point is 276—278°C.

EXAMPLE 20

Preparation of 2-Acetyl-1,3-bis(4-chlorobenzylideneaminoguanidine

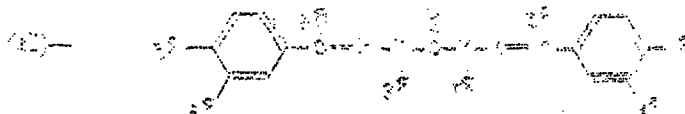
A mixture of 20 g. of 1,3-bis(p-chlorobenzylideneamino)guanidine free base and 9 ml. of acetic anhydride in 300 ml. of anhydrous ether is stirred at reflux for 16 hours, then filtered to give a solid containing starting material and acetylated material. The solid is reacted with an additional 3 ml. of acetic anhydride in 300 ml. of toluene for 1 hour, cooled to room temperature and filtered. The solid (14 g.) is dissolved in 100 ml. of chloroform and treated with 50 ml. of 3 N hydrochloric acid, and the resulting solid is filtered, the crude product is slurried in 100 ml. of boiling chloroform, filtered, and dried to give 7.2 g. of 2-acetyl-1,3-bis(4-chlorobenzylideneamino)guanidine hydrochloride, melting point 193—4°C.

The hydrochloride salt is partitioned between chloroform and aqueous sodium bicarbonate, and the chloroform layer is dried and evaporated to give 2-acetyl-1,3-bis(4-chlorobenzylideneamino)guanidine, melting point 197—200°C. (dec.).

The reaction of 1,3-bis(p-chlorobenzylideneamino)guanidine free base with acetyl chloride in ether gives the same acetyl derivative according to thin layer chromatographic evidence, along with recovered starting material.

When 1,3-bis(p-chlorobenzylideneamino)-1,3-dimethylguanidine free base is submitted to the above reaction conditions with acetic anhydride, there is obtained the corresponding 2-acetyl-1,3-bis(4-chlorobenzylideneamino)-1,3-dimethylguanidine.

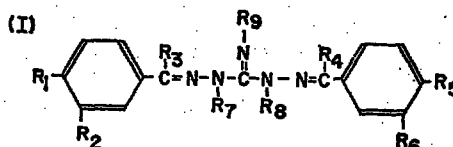
Similarly, the reaction of 1,3-bis(4-cyanobenzylideneamino)guanidine and propionic anhydride in refluxing ether gives 1,3-bis(4-cyanobenzylideneamino)-2-propionylguanidine.



It is to be understood that the present invention is not limited to the specific examples and chemical structures herein disclosed, but is intended to cover all modifications and equivalents within the scope of the following claims.

WHAT WE CLAIM IS:—

1. A composition for the control of coccidiosis and other protozoan infections in warm-blooded animals other than human beings, comprising an edible carrier and from 0.0005% to 0.05% by weight of a compound of Formula I:



wherein each of R_1 and R_5 is halogen, trifluoromethyl or cyano, each of R_2 and R_6 is hydrogen or halogen, each of R_3 , R_4 , R_7 and R_8 is hydrogen or (C_1-C_4) alkyl, and R_9 is hydrogen or (C_2-C_5) alkanoyl; or a pharmaceutically acceptable acid-addition salt thereof.

2. A composition according to Claim 1 containing from 0.0015% to 0.025% by weight of said compound of Formula I.

3. A composition for adding to an animal feed for the control of coccidiosis and other protozoan infections in warm-blooded animals other than human beings, comprising an edible carrier and from 1% to 25% by weight of a compound of Formula I as defined in Claim 1.

4. A composition according to Claim 3 containing from 3% to 10% by weight of said compound of Formula I.

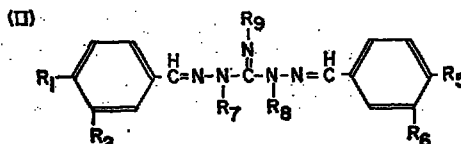
5. A composition according to any preceding claim, wherein R_7 , R_8 and R_9 are each hydrogen.

6. A composition according to Claim 5, wherein said compound of Formula I is 1,3-bis(4-chlorobenzylideneamino)guanidine hydrochloride.

7. A method of controlling coccidiosis and other protozoan infections in warm-blooded animals other than human beings, comprising administering orally or parenterally to the host animal a protozoacidally effective amount of a compound of Formula I as defined in Claim 1.

8. A method according to Claim 7, wherein R_7 , R_8 and R_9 are each hydrogen.

9. A substituted guanidine of Formula II:



wherein each of R_1 and R_5 is halogen, trifluoromethyl or cyano, each of R_2 and R_6 is hydrogen or halogen, each of R_7 and R_8 is hydrogen or (C_1-C_4) alkyl, and R_9 is hydrogen or (C_2-C_5) alkanoyl, or a pharmacologically acceptable acid-addition salt thereof.

10. A 1,3-bis(4-halobenzylideneamino)guanidine.

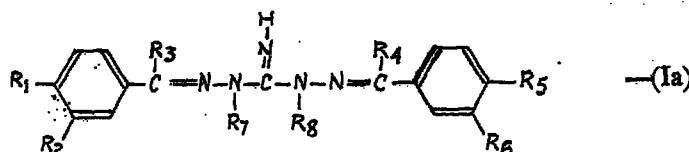
11. 1,3-bis(4-Chlorobenzylideneamino)guanidine.

12. 1,3-bis(4-Bromobenzylideneamino)guanidine.

13. 1,3-bis(3,4-Dichlorobenzylideneamino)guanidine.

14. A compound according to Claim 9, wherein R_7 , R_8 and R_9 are each hydrogen.

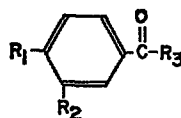
15. A method of preparing a compound of Formula Ia:



wherein R_1 and R_5 are the same and are halogen, trifluoromethyl or cyano, R_2 and R_6 are the same and are hydrogen or halogen, R_3 and R_4 are the same and are hydrogen or (C_1-C_4) alkyl, and R_7 and R_8 are the same and are hydrogen or (C_1-C_4) alkyl;



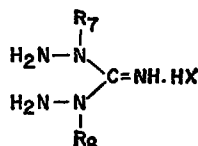
or a pharmacologically acceptable acid salt thereof, which method comprises reacting a compound of the formula:



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in which R_1 , R_2 and R_3 are as defined above, dissolved in a water-miscible organic solvent, with an aqueous or aqueous alcoholic solution of a compound of the formula:

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in which R_7 and R_8 are as defined above and X is the anion of a pharmacologically acceptable acid, and recovering said compound therefrom.

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16. A method according to Claim 15, wherein R_7 and R_8 are each hydrogen.

17. A composition for the control of coccidiosis and other protozoan infections in warm-blooded animals other than human beings, substantially as hereinbefore described.

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18. A method for controlling coccidiosis and other protozoan infections in warm-blooded animals other than human beings, substantially as hereinbefore described.

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19. A substituted guanidine according to Claim 9 and substantially as hereinbefore described.

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20. A substituted guanidine according to Claim 14 and substantially as hereinbefore described.

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21. A method of preparing a substituted guanidine, according to Claim 15 and substantially as hereinbefore described.

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