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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

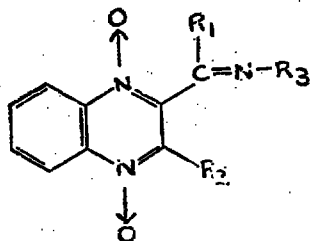
Quinoxaline Derivatives and process for their preparation

5 We, CHAS PFIZER & CO., INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235, East 42nd Street, New York 17, 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:—

10 This invention relates to a novel series of Schiff bases which are effective as urinary tract antiseptics, systemic anti-infectives, animal growth promotants and as agents for the control of chronic respiratory disease in poultry and improvement of feed efficiency in animals. More particularly, it relates to a series of Schiff bases derived from 2-formyl-quinoxaline-1,4-dioxides which are valuable

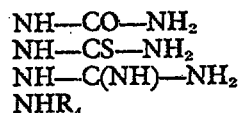
20 for the control of urinary tract and systemic infections, chronic respiratory disease in poultry, infectious sinusitis in turkeys and promotion of growth of animals.

25 The novel compounds of this invention have the general formula

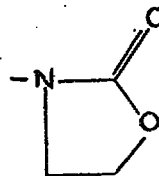


wherein each of R_1 and R_2 is individually a hydrogen atom or a lower alkyl group containing from 1 to 6 carbon atoms; R_3 is

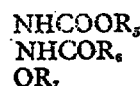
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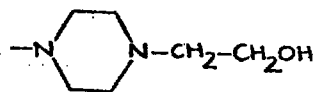
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or



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wherein R_4 is a lower alkyl group containing from 1 to 6 carbon atoms, a phenyl, benzyl or hydroxyalkyl group containing from 2 to 4 carbon atoms;

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R_5 is a lower alkyl group containing from 1 to 6 carbon atoms, a hydroxyalkyl group containing from 2 to 4 carbon atoms or a haloalkyl group containing from 2 to 4 carbon atoms;

45

R_6 is a lower alkyl group containing from 1 to 6 carbon atoms, or a phenyl group; and

50

R_7 is a hydrogen atom or a lower alkyl group containing from 1 to 6 carbon atoms.

The term "lower alkyl" as used herein includes the branched-chain as well as the straight-chain radicals of those lower alkyl

55

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groups having three or more carbon atoms.

The most convenient method of preparing the compounds of the present invention, from the standpoint of availability of materials, ease and simplicity of reaction, yield and purity of product, is the condensation of the appropriate 2-lower alkanoyl quinoxaline-1,4-dioxide with the proper amino derivative, H_2N-R_3 , wherein R_3 is as defined above.

The process comprises, in general, the reaction of the 2-lower alkanoyl quinoxaline-1,4-dioxide and the amino derivative of choice in a suitable solvent system such as acetic acid, ether and lower alcohols, especially methyl and ethyl alcohols at a temperature of from room temperature to the reflux temperature of the solvent. The addition of a small amount of an acid such as hydrochloric or acetic frequently serves to accelerate the reaction and improve the yield. The amino derivative can be used in the form of an acid addition salt, e.g., the hydrochloride, sulfate, acetate. In such a case an aqueous solution of the amine derivative to which the requisite amount of alkali, alkali bicarbonate or carbonate or an excess of alkali acetate is added is generally used. In many cases, as for example, when using semicarbazide, a concentrated aqueous solution of the semicarbazide hydrochloride is added to an alcohol or acetic acid solution of the aldehyde to give the desired semicarbazone. Potassium acetate is added to complete formation of the product. In still another modification the salt of the amino derivative, e.g., semicarbazide hydrochloride, is employed in methanol solution and added to the aldehyde to produce the desired product.

The reaction may occur almost immediately or may require periods of up to several days depending upon the reactants and reaction conditions. In most instances, however, reaction is complete in less than four hours.

The products are yellow crystalline substances for the most part which precipitate from the reaction mixture. They are collected by suitable means and dried.

The starting 2-lower alkanoylquinoxaline-1,4-dioxides, many of which are new compounds, are prepared by known methods such as selenium dioxide oxidation of the corresponding alkyl derivatives; e.g., methyl is oxidized to formyl; ethyl to acetyl; propyl to propionyl, and butyl to butyryl, according to the procedure of Seyhan, Ber. 84, 477 (1951). The method comprises, in general, oxidation of the desired 2-lower alkylquinoxaline-1,4-dioxide in a suitable solvent such as lower alkyl esters of acetic acid, especially ethyl acetate, aromatic hydrocarbons, such as toluene and the xylenes, at a temperature of from about 50° C. to the boiling point of the solvent. The selenium dioxide and lower alkylquinoxaline-1,4-dioxide are used in approximately equal quantities by weight. The oxidation is conducted for periods of from

about one hour to about three hours after which the product is recovered by suitable means. The requisite 2-lower alkylquinoxaline-1,4-dioxides are prepared by condensation of the appropriate 1,2-dicarbonyl compound, or the monoxime or bisulfite addition compound thereof, with o-phenylene diamine in a suitable solvent. Water, alcohols, acetic acid and dioxane serve as solvents for the condensation which is conducted at temperatures of from about 0° to the boiling point of the solvent.

Certain 2,3-di-lower alkylquinoxaline-1,4-dioxides, for example, 2,3-dimethyl- and 2,3-dipropyl-, can be prepared by reaction of a 2,3-dichloro-quinoxaline with the desired alkyl magnesium iodide in a 1—2 molar ratio (Ogg, et al, J. Am. Chem. Soc., 53, 1846 (1931)). Alternatively, 2,3-dipropyl-quinoxaline is prepared by reaction of the dipotassium salt of the corresponding 2,3-dimethyl compound with ethyl iodide (Ogg, et al, loc. cit.). The quinoxalines thus obtained are then oxidized by means of per acids such as hydrogen peroxide in glacial acetic acid, peracetic acid, *m*-chloropero benzoic acid, performic acid, or monoperphthalic acid to the corresponding 1,4-dioxides.

In the case of 2,3-di-(lower alkyl)quinoxaline-1,4-dioxides wherein the alkyl groups are different, selenium dioxide oxidation produces a mixture of products. The oxidation products can be separated by known methods such as chromatography or fractional crystallization. An alternative method which produces only the desired 2-lower alkanoylquinoxaline-1,4-dioxide comprises a Grignard reaction on the appropriate 2-formyl-3-lower alkyl-quinoxaline with R_1MgX ($X=Br, I$) to give upon hydrolysis the corresponding 2-(α -hydroxy lower alkyl)-3-lower alkylquinoxaline. The thus produced compound is oxidized by means of a peracid such as those enumerated above to the corresponding 2-(α -hydroxy lower alkyl)-3-lower alkylquinoxaline-1,4-dioxide. Oxidation of the secondary alcohol group by chromic oxide, potassium dichromate or potassium permanganate produces the desired 2-lower alkanoyl-3-lower alkyl-quinoxaline-1,4-dioxide.

A further method comprises the conversion of a 2-(α -bromo lower alkyl)quinoxaline to the corresponding 2-lower alkanoyl derivative by reaction with dimethyl sulfoxide at a temperature of about 20° C. to about 30° C. The reaction mixture is then poured into water, the alkanoyl derivative extracted with chloroform and recovered therefrom. Per acid oxidation of the product affords the desired 2-lower alkanoyl quinoxaline-1,4-dioxide.

In still another method, a Bockalheide type rearrangement is employed. This method comprises conversion of a 2-lower alkyl or 2,3-di-lower alkyl quinoxaline to the mono-N-oxide followed by treatment of the N-oxide with acetic anhydride to produce the cor-

responding 2-(α -acetoxy lower alkyl) compound. Oxidation by means of a per acid followed by acid hydrolysis gives the desired 2-(α -hydroxy lower alkyl)quinoxaline-1,4-dioxide which is then oxidized to the α -lower alkanoyl derivative as described above.

The novel compounds of this invention exhibit activity as urinary tract and systemic anti-infectives in animals, including man, against a wide variety of microorganisms including gram-positive and gram-negative bacteria. They are especially valuable against gram-negative infections both *in vitro* and *in vivo*. Their surprising activity can be demonstrated by *in vitro* tests against various organisms in a brain-heart infusion medium by the usual two-fold serial dilution technique.

The *in vivo* activity of the compounds of this invention can be demonstrated by two procedures. The first procedure is the urinary excretion test which is an acute test conducted on healthy animals. This test entails giving the test animals a single massive dose of the test compound. Then, after a given time interval, the urine of the animal is collected and assayed for antibacterial activity by an *in vitro* procedure, for example, the growth inhibition of *E. coli*, *P. vulgaris* and *P. aeruginosa* is measured. The other *in vivo* procedure employed is the urinary tract infection test which is a chronic test conducted on sick animals. Here, a surgical incision is made into the bladder of the experimental animal and a dose of an infectious organism plus a pellet of zinc about 2 mm. in diameter are inserted into the bladder. The zinc pellet acts as a focus of the infection and over a period of 2 weeks, infection in control animals normally becomes quite serious. During this period of time, however, the test animal is allowed to imbibe *ad libitum* on a feed which contains incorporated therein a compound of this invention at a predetermined concentration, such as 0.2%. At the end of this period, the control and test animals are sacrificed and the kidney and bladder are examined to determine the extent of the infection. The urine of said animals is also examined to determine the bacterial count. The compounds of this invention are found to be surprisingly effective in suppressing kidney and bladder infections and in controlling the bacterial count of the urine.

As previously mentioned these novel compounds are also effective in the control of chronic respiratory disease of poultry, especially of chickens, and of infectious sinusitis in turkeys. The primary causative organisms responsible for these respiratory infections belong to the genus *Mycoplasma*, especially *M. gallisepticum*, *M. gallinarum*, *M. iners*, *M. synoviae*, and type N-PPLO. The field condition commonly known as "air sac" disease, airsacculitis or complicated respiratory disease is not due to *Mycoplasma* alone but to concomitant secondary infections, especially to

coliform, *Proteus* and *Micrococcus* species. The term "chronic respiratory disease" as used in this application also includes complicated chronic respiratory disease and infectious sinusitis.

It should be noted that these valuable compounds are effective for the control, that is the treatment and prevention, e.g. prophylaxis, of the herein described infections. For such purposes many modes of administration of the novel compounds of this invention are possible including the oral and parenteral routes of administration, the method of choice being dictated by the type and severity of the infection. These compounds may be administered alone or, preferably, in combination with a pharmaceutical carrier and, as such, can be given in single or multiple doses. More particularly, they may be administered in suitable dosage forms to provide a dosage unit of active ingredients in an amount that is adjusted to the particular needs of the individual. When large doses of these compounds are to be used, it is preferable to administer two or more doses at various time intervals.

When used for such purposes these novel compounds can be administered orally or parenterally, e.g. by subcutaneous or intramuscular injection, at a dosage of from 1 mg./kg. to 100 mg./kg. of body weight. For parenteral administration dosages of from 10 mg./kg. to 100 mg./kg. of body weight are preferred. Vehicles suitable for parenteral injection may be either aqueous such as water, isotonic saline, isotonic dextrose, Ringer's solution, or non-aqueous such as fatty oils of vegetable origin (cotton seed, peanut oil, corn, sesame), dimethylsulfoxide and other non-aqueous vehicles which will not interfere with the therapeutic efficiency of the preparation and are non-toxic in the volume or proportion used (glycerol, propylene glycol, sorbitol). Additionally, compositions suitable for extemporaneous preparation of solutions prior to administration may advantageously be made. Such compositions may include liquid diluents, for example, propylene glycol, diethyl carbonate, glycerol and sorbitol, buffering agents, hyaluronidase, local anesthetics and inorganic salts to afford desirable pharmacological properties. For oral administration dosages of from 1 mg./kg. to 60 mg./kg. of body weight are favored. This can be achieved by a number of methods including dosage unit formulations such as capsules, tablets, lozenges, troches, liquid mixtures and solutions. In the case of poultry and domestic animals other methods include mixing with the feed, the preparation of feed concentrates and supplements. Additionally, dilute solutions or suspensions, e.g., a 0.1% solution, can be supplied for drinking purposes.

Further, these compounds may be combined with feeds or with various pharmaceutically acceptable inert carriers in the form

of capsules, tablets, lozenges, troches, dry mixes, suspensions, solutions, elixers, and parenteral solutions or suspensions. The carriers employed include solid diluents, aqueous vehicles and non-toxic organic solvents. In general, the compounds of this invention are present in various dosage forms at concentration levels ranging from 0.5% to 90% by weight of the total composition.

10 For purposes of oral administration, tablets containing various excipients such as citric acid, sucrose, starch and lactose may be employed along with various disintegrants such as alginic acid and certain complex silicates together with binding agents such as polyvinyl-pyrrolidone, gelatin and acacia. In addition, lubricating agents such as magnesium stearate, sodium metaphosphate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in soft elastic and hard shelled gelatin capsules. Preferred materials in this connection would also include polyethylene glycol and glycerines they not only may be used in this particular type of pharmaceutical dosage form as diluents but also as plasticizing agents serving to protect the capsule against any leakage that might possibly occur due to denaturing of the gelatin protein.

30 When aqueous suspensions and elixers are desired for oral administration, the compounds of this invention may be combined with various sweetening and flavoring agents, coloring matter or dyes, and if so desired, emulsifying and suspending agents together with such diluents as water, ethyl alcohol, propylene glycol, glycerin and various combinations thereof. For the control of chronic respiratory disease it is convenient to provide the active ingredient admixed with a nutritionally balanced feed or a food concentrate.

45 Solutions or suspensions of these valuable compounds in pyrogen-free sterile distilled water containing a preservative such as butylparaben, chlorobutanol, phenol and the like, may be utilized for parenteral administration by the subcutaneous, intramuscular or intravenous route of injection.

Further, the addition of a low level of one or more of the herein described Schiff bases to the diet of animals, both ruminant and non-ruminant, such that these animals receive the product over an extended period of time, at a level of from about 1 mg./kg. to about 100 mg./kg. of body weight per day, especially over a major portion of their active growth period, results in an acceleration of the rate of growth and improved feed efficiency. Included in these two classes of animals are poultry (chickens, ducks, turkeys), cattle, sheep, dogs, cats, swine, rats, mice, horses, goats, mules, rabbits, mink, etc. The beneficial effects in growth rate and feed efficiency are over and above what is normally obtained with complete nutritious diets containing all the

nutrients, vitamins, minerals and other factors known to be required for the maximum healthy growth of such animals. The animals thus attain market size sooner and on less feed.

The herein described feed compositions have been found to be particularly valuable and outstanding in the case of such animals as poultry, rats, hogs, swine, lambs and cattle. In some instances the degree of response may vary with respect to the sex of the animals. The products may, of course, be administered in one component of the feed or they may be blended uniformly throughout a mixed feed; alternatively as noted above, they may be administered in an equivalent amount via the animal's water ration. It should be noted that a variety of feed components may be of use in the nutritionally balanced feeds.

The resulting new feed compositions have marked effects on the rate of growth and feed efficiency. Feed efficiency, an extremely important economic factor in raising animals, may be defined as the number of pounds of feed required to produce a pound gain in weight. The novel feed supplements of this invention permit the use of higher energy, higher protein diets to obtain improved feed/gain ratios and the use of feedstuffs that at present are not utilized efficiently. Simply stated, the compositions of this invention when fed to animals are more efficiently converted to animal body weight than prior art compositions. Any animal feed composition may be prepared to comprise the usual nutritional balance of energy, proteins, minerals, and vitamins together with one or more of the quinoxaline-di-N-oxides described above. Some of the various components are commonly grains such as ground grain, and grain by-products; animal protein substances, such as meat, and fish by-products; vitaminaceous mixtures, e.g. vitamin A and D mixtures, riboflavin supplements and other vitamin B complexes; and bone meal, limestone, and other inorganic compounds to provide minerals.

The relative proportions of the quinoxaline-di-N-oxides in feeds and feed concentrates may vary somewhat, depending upon the compound, the feed with which they are employed and the animal consuming the same. These substances are advantageously combined in such relative proportions with edible carriers to provide concentrates which may readily be blended with standard nutritionally balanced feeds or which may be used themselves as an adjunct to the normal feedings.

Dry pre-mixes containing these compounds are prepared containing from 0.10 to about 10% of the active ingredient mixed with salt (sodium chloride) and other minerals which it is desired to incorporate into the poultry ration. This can then be fed on an *ad libitum* basis by adjusting the proportion of active

ingredient in the mixture to the average daily consumption per bird so as to provide the proper daily dose as specified above. If prepared feed supplements are employed, the material can be administered in admixture with the feed. Again a concentration range of about 0.10 to 10% of the drug in the feed is employed. However, higher proportions can be satisfactorily employed depending upon the palatability of the product to the poultry. This can be readily determined by simple experimentation. It is sometimes convenient to mix the daily dose with only a portion of the average daily allotment to insure complete consumption of the dose. The balance of the daily feed supplement can then be fed after consumption of the medicated portion in the usual fashion. These methods are particularly useful for prophylactic treatment, but similar compositions can be employed for therapeutic use. Concentrations of drug in the feed or mineral mixture up to from 0.1 to 10%, depending again upon the palatability of the material, are sometimes useful.

In the preparation of concentrates a wide variety of carriers may be employed containing the aforesaid drugs. Suitable carriers include the following: soybean oil meal, corn gluten meal, cotton seed oil meal, sunflower seed meal, linseed oil meal, cornmeal, limestone and corncob meal. The carrier facilitates uniform distribution of the active materials in the finished feed with which the concentrate is blended. This is especially important because only a small proportion of these potent materials are required. The concentrate may be surface coated, if desired, with various proteinaceous materials or edible waxes, such as zein, gelatin, microcrystalline wax and the like to provide a protective film which seals in the active ingredients. It will be appreciated that the proportions of the drug preparation in such concentrates are capable of wide variation since the amount of active materials in the finished feed may be adjusted by blending the appropriate proportion of concentrate with the feed to obtain the desired degree of supplementation. In the preparation of high potency concentrates, i.e. premixes, suitable for blending by feed manufacturers to produce finished feeds or concentrates of lower potency, the drug content may range from about 0.1 g. to 50 g. per pound of concentrate. A particularly useful concentrate is provided by blending 2 g. of drug with 1 pound of limestone or 1 pound of limestone-soybean oil meal (1:1). Other dietary supplements, such as vitamins, minerals, etc. may be added to the concentrates in the appropriate circumstances.

The high potency concentrates may be blended by the feed manufacturer with proteinaceous carriers, such as soybean oil meal, to produce concentrated supplements which are suitable for direct feeding to animals. In such

instances the animals are permitted to consume the usual diet of corn, barley and other fibrous grains. The proportion of the drug in these supplements may vary from 0.1 to 10 g. per pound of supplement.

The concentrates described may also be added to animal feeds to produce a nutritionally balanced, finished feed containing from 10 to 125 g. of the quinoxaline-di-N-oxide per ton of finished feed. In the case of ruminants, the finished feed should contain protein, fat, fiber, carbohydrate, vitamins and minerals, each in an amount sufficient to meet the nutritional requirements of the animal for which the feed is intended. Most of these substances are present in naturally occurring feed materials, such as alfalfa hay or meal, cracked corn, whole oats, soybean oil meal, corn silage, ground corn cobs, wheat bran, and dried molasses. Bone meal, limestone, iodized salt and trace minerals are frequently added to supply the necessary minerals, and urea to provide additional nitrogen.

As is well known to those skilled in the art, the types of diets are extremely variable depending upon the purpose, type of feeding operation, species, etc. Specific diets for various purposes are listed by Morrison in the Appendix of "Feeds and Feeding", the Morrison Publishing Company, Clinton, Iowa, 1959.

In the case of non-ruminant animals, such as hogs, a suitable feed may contain from about 50 to 80% of grains, 3 to 10% animal protein, 5 to 30% vegetable protein, 2 to 4% of minerals, together with supplementary vitaminaceous sources.

Additionally, many of the compounds described herein have unexpectedly significant activity *in vivo* against a variety of small and medium viruses such as the myxoviruses and especially against influenza PRS and BGL. Care should, of course, be exercised when using these compounds for this purpose. Therapeutic dosages and regimens commensurate with the therapeutic index of these compounds can be administered without substantial adverse effect.

Furthermore, many of these compounds are highly active anthelmintic agents by the oral and parenteral routes of administration and compare with piperazine sulfate in their activity and dosage regimen.

In all these various formulations the active agents can be one or a plurality of the compounds of this invention. These compounds may also be advantageously employed in combination with other pharmaceutically acceptable compounds such as the tetracycline-type antibiotics, carbomycin, neomycin, bacitracin, tylosin, sulfamethazine and penicillin-type antibiotics. In this manner it is possible to obtain mixtures which will combat disease and produce an over-all well being in the patient.

The PD_{50} values (the dosage which will bring about 50% survival of the test animals)

of representative compounds within the scope of this invention against a systemic gram-negative infection in mice and the minimum effective dose necessary to cure a *Proteus* urinary tract infection (UTI) in rats are tabulated below and compared with "Furadantin". The word "Furadantin" is a Registered Trade Mark.

1. [2 - Formyl - 3 - methylquinoxaline-1,4 - dioxide] N - [3 - (2 - oxazolidonyl)-imine]
2. 2 - Formyl - 3 - methylquinoxaline - 1,4-dioxide semithiocarbazone
3. 2 - Formyl - 3 - methylquinoxaline - 1,4-dioxide carbomethoxyhydrazone
4. 2 - Formyl - 3 - methylquinoxaline - 1,4-

dioxide oxime

5. 2 - Formyl - 3 - methylquinoxaline - 1,4-dioxide acetylhydrazone
6. 2 - Formyl - 3 - methylquinoxaline - 1,4-dioxide - N - methylhydrazone
7. 2 - Formylquinoxaline - 1,4-dioxide semicarbazone
8. 2 - Formylquinoxaline - 1,4 - dioxide oxime
9. [2 - Formylquinoxaline - 1,4 - dioxide] N - [3 - (2 - oxazolidonyl)imine]
10. 2 - Formyl - 3 - methylquinoxaline - 1,4-dioxide carbethoxyhydrazone
11. 2 - Formylquinoxaline - 1,4 - dioxide carbethoxyhydrazone
12. N - (5 - nitro - 2 - furfurylidene) - 1-aminohydantoin "Furadantin"

Compound	PD ₅₀ (mg./kg.) Pasteurella		Minimum Effective Dose (mg./kg.)
	Oral	SQ*	UTI**
1	28	16	25
2	400	55	12.5
3	8.3	9.4	25
4	21	24	6.25
5	42	44	25
6	85	50	25
7	23	35	1.56—3.12
8	60	100	> 25
9	13	13	1.56
10	35	35	12.5
11	110	150	< 12.5
12	—	—	25—50

* SQ = Subcutaneous injection

** Infecting organism in *Proteus* 59

The following examples are solely for the purpose of illustration only and are not to be construed as limitations of this invention.

EXAMPLE I.

2-Formylquinoxaline-1,4-Dioxide Carbomethoxyhydrazone.

A solution of methylcarbazate (48.0 g.) in methanol (250 ml.) is added all at once at room temperature to a well stirred solution of 2-formyl-quinoxaline-1,4-dioxide (100 g.) in

methanol (2.5 liters). Two drops of concentrated hydrochloric acid are added. The mixture is stirred for 3 hours then filtered to remove the yellow crystalline product. The crystals are washed with methanol then air dried; m.p. 234.5—236° C. (dec.). Yield= 121.8 g.

The product is purified by refluxing in chloroform for 2 hours, followed by filtration and air drying; m.p. 239.5—240° C. (dec.).

Analysis
Calcd for C₁₁H₁₀O₄N₂: C, 50.38; H, 3.84; N, 21.37%
Found: C, 50.36; H, 3.91; N, 21.17%

EXAMPLE II.

2-Formyl-3-Methylquinoxaline-1,4-Dioxide Semicarbazone.

To a solution of 2-formyl-3-methylquinoxaline-1,4-dioxide (100 g.) in methanol (3 liters) there is added a warm solution (40—

yellow crystalline product is separated by fil-

50° C.) of semi-carbazide hydrochloride (55 g.) yellow crystalline product is separated by filtration in methanol (3 liters). The mixture is stirred with hot methanol and air for 3 hours at the end of which time the dried; m.p. 240—241° C. (dec.). Yield=70 g.

Analysis
Calcd. for $C_{11}H_{11}O_3N_3$: C, 50.57; H, 4.24; N, 26.81%
Found: C, 50.59; H, 4.28; N, 26.50%

10

EXAMPLE III.

The following Schiff bases are prepared by the procedures of the preceding examples. Percent data on the products are tabulated below.

TABLE I — Analysis

R_1	R_2	R_3	%C		%H		%N		M.P. (°C.)	U.V. (mu.)		I.R. (u)
Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	λ_{max}	ϵ	
H	CH ₃	—NHCOOCH ₃	52.17	52.42	4.38	4.31	20.28	20.56	245—7 (dec.)	241	10,750*	5.70
										243	32,000	
										364	15,700	
H	CH ₃	—NECOOCH(CH ₃)CH ₂ OH	52.49	52.39	5.04	4.87	17.49	17.66	214—5 (dec.)	240	15,850	5.80
										302	29,000	
										375	10,600	
H	CH ₃	—OH	54.79	54.84	4.14	4.25	19.17	19.07	213—4 (dec.)	241	18,350	
										283	29,200	
										373	10,190	
H	CH ₃	—NH—COCH ₃	55.38	55.41	4.65	4.62	21.53	21.56	240—2 (dec.)	241	19,500*	5.97
										295	29,300	
										364	15,500	
H	CH ₃	—NHCH ₃	56.89	56.77	5.21	5.50	24.13	24.03	174.5— 5.5 (dec.)	236	16,100	
										305	19,400	
										337	27,200	
										386	14,700	

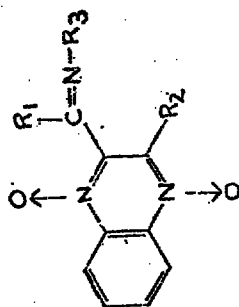
TABLE I — Analysis (continued)

R ₁	R ₂	R ₃	%C		%H		%N		M.P. (°C.)	U.V. (mμ)		I.R. (u)
			Calcd.	Found	Calcd.	Found	Calcd.	Found		λ Max.	ε	
H	H	—NHCOCH ₃	53.66	53.68	4.09	4.02	22.76	22.75	252—3 (dec.)	236 253 305 373	12,300 11,200 38,800 17,500	5.95
H	H	—OH	52.68	52.78	3.44	3.46	20.48	20.31	236—8 (dec.)	248~ 293 378	17,600 31,100 11,300	
H	H	3-(2-oxazolidonyl)	52.55	52.88	3.68	3.85	20.43	20.90	253—5 (dec.)	240 310 380	14,300 39,000 13,200	5.71
H	H	—NH—COOCH(CH ₃)CH ₂ OH	50.98	51.03	4.61	4.65	18.29	18.18	249—50 (dec.)	244 308 379	13,800 38,000 13,800	5.81
H	CH ₃	—NHCOOC ₂ H ₅	53.79	53.81	4.86	4.67	19.30	19.35	236—7 (dec.)	240 292 364	19,000* 40,000 15,000	5.74
H	H	—NHCOOC ₂ H ₅	52.17	52.07	4.38	4.28	20.28	20.35	245—6 (dec.)	254 305 370	13,200* 37,400 13,700	5.70

* U.V. data obtained in water as solvent; the remaining data is determined in methanol solution.

EXAMPLE IV.

Following the procedures of Examples I and II, products having the formula shown are prepared.



R ₁	R ₂	R ₃	R ₁	R ₂	R ₃
CH ₃	H	NHCOOCH ₃	i-C ₃ H ₇	H	OH
H	H	NHCOOC ₂ H ₅	H	n-C ₃ H ₇	OH
H	H	NHCOOC ₄ H ₉	C ₂ H ₅	C ₂ H ₅	OH
C ₄ H ₉	C ₂ H ₅	NHCOOC ₆ H ₁₃	CH ₃	CH ₃	OCH ₃
n-C ₄ H ₉	H	NHCOOCH ₃	H	H	OC ₄ H ₉
C ₆ H ₁₃	CH ₃	NHCOOC ₂ H ₅	CH ₃	CH ₃	OC ₆ H ₁₃
CH ₃	n-C ₄ H ₉	NHCOOCH ₃	CH ₃	CH ₃	NHCONH ₂
H	C ₂ H ₅	NHCOOCH ₃	n-C ₆ H ₁₃	H	NHCONH ₂
H	n-C ₆ H ₁₃	NHCOO-t-C ₄ H ₉	C ₂ H ₅	C ₂ H ₅	NHCONH ₂
CH ₃	H	NHCOOCH ₃	I	n-C ₄ H ₉	NHCONH ₂
i-C ₃ H ₇	H	NHCH ₃	CH ₃	CH ₃	NHCSNH ₂
H	CH ₃	NHCH ₃	n-C ₆ H ₁₃	H	NHCSNH ₂
H	CH ₃	NHC ₆ H ₅	CH ₃	CH ₃	NHC(NH)NH ₂
H	H	NHC ₂ H ₅	n-C ₄ H ₉	H	NHC(NH)NH ₂
n-C ₆ H ₁₁	H	NHCH ₂ CH ₂ OH	CH ₃	CH ₃	3-(2-oxazolidonyl)
CH ₃	n-C ₆ H ₁₃	NH-i-C ₃ H ₇	n-C ₄ H ₉	H	3-(2-oxazolidonyl)
		NHCH ₃	CH ₃	CH ₃	

EXAMPLE IV (Continued)

R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
H	H	NHC ₆ H ₁₃	CH ₃	n-C ₆ H ₁₃	3-(2-oxazolidonyl)
H	H	NH(CH ₂) ₄ OH	CH ₃	C ₂ H ₅	NHCOOCH ₃
CH ₃	H	OH	n-C ₃ H ₇	n-C ₂ H ₅	NHCOOCH ₃
CH ₃	H	OCH ₃	CH ₃	C ₂ H ₅	OH
CH ₃	H	OC ₄ H ₉	C ₂ H ₅	n-C ₃ H ₇	OH
H	CH ₃	OCH ₃			
i-C ₃ H ₇	H	OCH ₃			
H	n-C ₃ H ₇	O-i-C ₃ H ₇			
C ₂ H ₅	C ₂ H ₅	OC ₂ H ₅			
CH ₃	CH ₃	NHCOOCH ₂ CH ₂ OH			
C ₂ H ₅	H	NHCOO(CH ₂) ₃ OH			
C ₄ H ₉	C ₄ H ₉	NHCOOCH ₂ CH ₂ OH			
CH ₃	H	1-[4-(β-hydroxyethyl)piperazine]			
CH ₃	H	1-[4-(β-hydroxyethyl)piperazine]			
H	H	1-[4-(β-hydroxyethyl)piperazine]			
C ₄ H ₉	H	1-[4-(β-hydroxyethyl)piperazine]			
H	C ₆ H ₁₃	1-[4-(β-hydroxyethyl)piperazine]			

PREPARATION A.

Preparation of 2-Lower Alkanoylquinoxaline-1,4-dioxides.

5 Method A—Selenium Dioxide Oxidation of Alkyl to Alkanoyl Groups.

2,3-Dimethylquinoxaline 1,4-dioxide (20 gm.) is dissolved in ethyl acetate (250 ml.), selenium dioxide (15 gm.) added, and the

10

mixture refluxed and stirred for 90 minutes. The ethyl acetate is removed by vacuum distillation and the residue triturated with methylene chloride. Concentration of the methylene chloride solution yields crude 2-formyl-3-methyl-quinoxaline-1,4-dioxide (Circa 15 g.).

15

Recrystallization from ethyl acetate/methylene chloride mixture yields the pure product; m.p. 186—187° C. (decomp.).

Analysis

Calcd. for C₁₄H₁₀O₂N₂: C, 58.82; H, 3.95; N, 13.72
Found: C, 58.77; H, 3.93; N, 13.78

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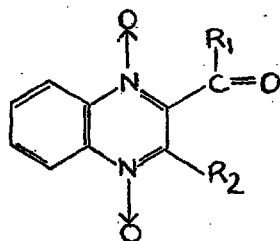
25

30

35

40

In like manner the following 2-lower alkanoyl-1,4-dioxides are produced from the appropriate 2-lower alkylquinoxaline-1,4-dioxides.



5

	R_1	R_2
	CH ₃	H
	C ₂ H ₅	C ₂ H ₅
10	n-C ₄ H ₉	H
	n-C ₆ H ₁₃	CH ₃
	CH ₃	n-C ₄ H ₉
	H	C ₂ H ₅
	H	C ₆ H ₁₃
15	i-C ₃ H ₇	H
	n-C ₅ H ₁₁	H
	CH ₃	n-C ₆ H ₁₃
	H	n-C ₈ H ₁₇
	CH ₃	CH ₃
20	n-C ₈ H ₁₇	H
	H	n-C ₈ H ₁₇

Method B—Oxidation of 2-(α -Hydroxy Lower Alkyl)-Quinoxaline.

A solution of 2-(α -hydroxyethyl)-3-ethylquinoxaline (8.7 g.) in 500 ml. benzene is mixed with a solution of chromium trioxide (4.0 g.) in 100 ml. water. The mixture is stirred vigorously for two hours, the benzene layer separated, washed twice with water and dried with anhydrous sodium sulfate. Removal of the solvent *in vacuo* provides the crude alkanoyl derivative which is then converted to the 1,4-dioxide by oxidation with *m*-chloroperbenzoic acid as described in Preparation B, Method A.

The remaining products of Preparation B are similarly converted to their respective 2-lower alkanoyl-1,4-dioxides.

Method C—From 2-(α -Bromo Lower Alkyl)Quinoxaline.

2-(α -Bromocethyl)quinoxaline (10 g.) is dissolved in dry dimethyl sulfoxide (200 ml.) and allowed to stand at room temperature for 48 hours. The mixture is then poured into an excess of water and the product extracted

therefrom with chloroform. The chloroform extract is back-washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give 2-acetylquinoxaline.

Oxidation of the product with *m*-chloroperbenzoic acid as described in Preparation B, Method A gives 2-acetyl-quinoxaline-1,4-dioxide.

The 2-(α -bromoethyl)quinoxaline is prepared by adding to a solution of 2-ethylquinoxaline (15.8 g.) in acetic acid (100 ml.) a solution of bromine (16 g.) in acetic acid (100 ml.) dropwise at room temperature during 6 hours. The reaction mixture is then poured into excess water and the product extracted with chloroform. The chloroform extract is backwashed with water, dried (Na₂SO₄) and evaporated *in vacuo* to give the bromo component.

In like manner the following 2-lower alkanoyl-quinoxaline-1,4-dioxides are prepared from the appropriate 2-lower alkyl quinoxaline:

2-propionyl-
2-butyryl-
2-valeryl-
2-caproylquinoxaline-1,4-dioxide

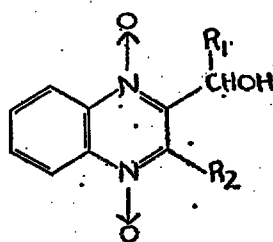
PREPARATION B.

2-(α -Hydroxy Lower Alkyl)Quinoxaline-1,4-Dioxides.

Method A. 2-Formyl-3-(lower alkyl)quinoxaline (0.5 mole) (a product obtained from the selenium dioxide oxidation of 2-methyl-3-lower alkyl quinoxaline) in diethyl ether is treated with a solution of lower alkyl magnesium bromide (1 mole) in diethylether. After stirring for 1 hour at room temperature the mixture is treated with a saturated solution of ammonium chloride. The product, 2-(α -hydroxy lower alkyl)-3-(lower alkyl)quinoxaline, isolated by removal of the solvent, is crystallized from chloroform/hexane.

2-(α -Hydroxy lower alkyl)-3-(lower alkyl)quinoxaline (0.25 mole) in chloroform is treated with *m*-chloroperbenzoic acid (0.5 mole) and the mixture allowed to stand at room temperature for 3 days. The precipitated *m*-chlorobenzoic acid is filtered off and the chloroform solution washed with saturated sodium bicarbonate solution. The product, 2-(α -hydroxy lower alkyl)-3-lower alkyl-quinoxaline-di-1,4-dioxide, obtained by removal of the chloroform, is crystallized from acetone.

By means of this procedure the following compounds having the formula shown are prepared from the appropriate reactants.



R ₁	R ₂	R ₁	R ₂
C ₂ H ₅	C ₂ H ₅	CH ₃	n-C ₆ H ₁₃
n-C ₄ H ₉	CH ₃	CH ₃	CH ₃
n-C ₆ H ₁₃	CH ₃	n-C ₄ H ₉	n-C ₄ H ₉
CH ₃	n-C ₄ H ₉		

Method B. 2,3-Di-lower alkylquinoxaline (1 mole) in chloroform is treated with *m*-chloroperbenzoic acid (1 mole) for 3 days at room temperature. The precipitated *m*-chlorobenzoic acid is filtered off and the chloroform solution washed with saturated sodium bicarbonate solution. The chloroform solution is dried (Na₂SO₄) and concentrated under vacuum. The product, 2,3-di-lower alkyl-quinoxaline mono-N-oxide, crystallizes from chloroform/hexane.

2,3-Di-lower alkylquinoxaline mono-N-oxide (0.5 mole) in excess acetic anhydride is refluxed for 30 minutes and then the acetic anhydride removed *in vacuo*. The solid residue is purified by recrystallization from ether/hexane to give pure 2-(α -acetoxy lower alkyl)-3-lower alkylquinoxaline.

2-(α -Acetoxy lower alkyl)-3-lower alkylquinoxaline (0.25 mole) in chloroform is treated with *m*-chloroperbenzoic acid (0.5 mole) as described in Method A to give 2-(α -acetoxy lower alkyl)-3-lower alkylquinoxaline-1,4-dioxide as yellow crystals from chloroform/hexane.

2-(α -acetoxy lower alkyl)-3-lower alkylquinoxaline-1,4-dioxide (0.2 mole) is allowed to stand in a mixture of methanol (3 liters) and 20% H₂SO₄ (500 ml.) for 8 days. The product, 2-(α -hydroxy lower alkyl)-3-lower alkylquinoxaline-1,4-dioxide, which deposits as yellow needles, is separated and purified by recrystallization from chloroform/hexane.

The following compounds having the above formula are thus prepared.

R ₁	R ₂
CH ₃	C ₂ H ₅
n-C ₆ H ₁₃	n-C ₄ H ₉
C ₂ H ₅	n-C ₃ H ₇

EXAMPLE V.

2-Formylquinoxaline-1,4-Dioxide Carbo-(β -Chlorethoxy) Hydrazone.

2-Formylquinoxaline (1 mole) obtained by the selenium dioxide oxidation of 2-methylquinoxaline by a method similar to that described above, for the preparation of 2-formylquinoxaline-1,4-dioxide, in methanol (2 l.) is treated with β -hydroxyethylcarbazate (1 mole) and 2 drops of concentrated hydrochloric acid. The mixture is stirred overnight, the methanol removed under vacuum to give the product, 2-formylquinoxaline carbo-(β -hydroxyethoxy) hydrazone, as a solid residue.

The thus produced carbo-(β -hydroxyethoxy)hydrazone (0.5 mole) and thionyl chloride (freshly distilled) (0.6 mole) in tetrahydrofuran (1 l.) is stirred at room temperature for 48 hours. The product, 2-formylquinoxaline carbo-(β -chloroethoxy)hydrazone, is obtained by pouring the entire reaction mixture into excess water and extracting the product with chloroform. The chloroform solution is washed with a saturated solution of sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The product is converted to the 1,4-dioxide title compound by oxidation in chloroform with two molecular equivalents of *m*-chlorobenzoic acid using the method described above in Preparation B.

EXAMPLE VI.

2-Formylquinoxaline-1,4-Dioxide Carbo-(β -Chloroethoxy) Hydrazone.

2-Formylquinoxaline-1,4-dioxide carbo-(β -hydroxyethoxy)hydrazone (prepared as in Example IV) (0.1 mole) in tetrahydrofuran (1 l.) and thionyl chloride (0.15 mole) are stirred at room temperature for 90 hours. The product, 2-formylquinoxaline-1,4-dioxide

carbo-(β -chloroethoxy)hydrazone, is obtained by pouring the reaction mixture into 3 liters of water and extracting with chloroform. The chloroform solution is washed with saturated sodium bicarbonate solution, dried (Na_2SO_4) and the solvent removed under reduced pressure to give the solid product.

In like manner the following compounds are prepared from the appropriate 2-formylquinoxaline-1,4-dioxide carbo-(hydroxy lower alkoxy) hydrazones of Example IV.

2 - acetyl - 3 - methylquinoxaline - 1,4-dioxide carbo-(β - chloroethoxy)hydrazone

2 - valerylquinoxaline - 1,4 - dioxide carbo-(γ - chloropropoxy)hydrazone

2 - valeryl - 3 - n - butylquinoxaline - 1,4-dioxide carbo-(β -chloroethoxy)hydrazone

EXAMPLE VII.

Substitution of thionyl bromide for thionyl chloride in the procedure of Example VI produces the corresponding bromo compounds.

EXAMPLE VIII.

The efficacy of several of the herein described quinoxaline-di-N-oxides in improving broiler chick and turkey poult performance is summarized in the following table. Supplementation of the rations with said compounds at various levels brought about economically significant gains in growth and feed efficiency.

The experimental birds and dietary treatments are assigned pens in accordance to randomized block designs. Each observation reported is an average of 6 pen replications, each pen containing 10 birds. The experiments are conducted in battery brooders for from 1 to 28 days of bird age. Controls are run using, of course, unsupplemented rations. For convenience in reporting results the per cent change in the weight, feed efficiency and feed consumption over the corresponding values for the controls are reported. In each case, the control is assigned a value of 100%. An increase in performance for a given compound is then represented by a + value; e.g. +6.3% weight gain indicates an increase in weight amounting to 106.3% relative to 100% for the controls.

% Above or Below Controls

Quinoxaline-di-N-Oxide	Supplementation g./ton	Weight	Feed Efficiency	Feed Consumption	Birds
2-formyl-3-methyl- carboethoxyhydrazone	125	+ 4.2	+2.6	+2.0	Chicks
	20	+ 1.0	+1.3	-2.2	Chicks
2-formyl-3-methyl- methylhydrazone	125	+ 3.3	+4.1	+0.5	Chicks
	20	- 1.2	+1.1	-2.2	Chicks
2-formyl-carbo- methoxyhydrazone	20	+ 3.3	+1.9	—	Chicks
	20	+12.2	+7.1	—	Poults
	10	+ 2.3	+1.9	—	Chicks
	10	+11.6	+6.4	—	Poults

EXAMPLE IX.

In further tests the compounds of Example VIII are added to the standard balanced animal feed compositions normally given sheep, steer, goats, dogs and mink at levels of from 10, 20, 50, 100 and 125 g./ton of feed. Each species is observed to undergo accelerated growth, particularly at the lower levels of supplement used.

EXAMPLE X.

In this experiment 48 four-week-old early weaned pigs, 4 castrated males and 4 females, are divided into 6 equal groups and each group assigned to a pen. Three of the groups serve as controls and are fed only a standard,

pre-starter, non-supplemented ration until an average line weight of 25 lbs. is attained. At this point the pigs are placed on a standard starter ration for the duration of the trial which is terminated at an average live weight of 50 lbs. The remaining three groups are fed the same standard, prestarter and starter ration supplemented with 2-formylquinoxaline-1,4-dioxide carbo-methoxyhydrazone at 20 g./ton according to the same schedule.

The total amount of the basal ration to be fed to each treatment group and to each pen is listed below. Each pen is to receive the entire amount of the pre-starter so that the weight back at the end of the trial will be starter ration.

Ration Fed	% Crude Protein	Approximate Weight Range	Amount of Ration	
			Per Treatment	Per Pen
Pre-starter	20	10 to 25 lbs.	750 lbs.	250 lbs.
Starter	18	25 to 50 lbs.	1500 lbs.	500 lbs.

The supplement is added to the appropriate rations replacing corn to give the desired level of drug.

The basal ration formulations are as follows:

Ingredients	Pre Starter 750 lb. Mix	Starter 1500 lb. Mix
Ground Yellow Corn	382.9 lbs.	364.75 lbs.
Cane Sugar	37.5 lbs.	—
Soybean Meal (50% C.P.)*	175.5 lbs.	293.25 lbs.
Dried Skim Milk	75.0 lbs.	75.0 lbs.
Dried Whey	37.5 lbs.	150.0 lbs.
Dehydrated Alfalfa Meal (17% C.P.)*	—	37.5 lbs.
Stabilized Animal Fat	18.75 lbs.	37.5 lbs.
Linestone	5.25 lbs.	9.0 lbs.
Dicalcium Phosphate	9.4 lbs.	16.5 lbs.
Iodized Salt	3.75 lbs.	7.5 lbs.
Vitamin Premix ¹	3.75 lbs.	7.5 lbs.
Delamix ²	0.75 lbs.	1.5 lbs.
	750.00 lbs.	1500.00 lbs.

*C.P. = Crude Protein

¹ Vitamin Premix	% of Premix
Vitamin A	10
Vitamin D ₃	10
Choline Chloride (25%)	35.25
Niacin	0.55
Calcium Pantothenate (45%)	10
Riboflavin	0.39
Vitamin B ₁₂	0.2
² Delamix	%
Manganese	12
Iodine	0.24
Iron	4.0
Copper	0.4
Zinc	4.0
Cobalt	0.04

An average increase of 12.2% in growth improvement and 5.7% in feed efficiency is observed in the three test groups over the three control groups.

Further such tests conducted with compounds of Example III provide similar improvement in growth and feed efficiency.

EXAMPLE XI.

The procedure of Example X is repeated

but using the following basal ration formulations and a combination of 2-formyl quin-oxaline-1,4-dioxide carbomethoxyhydrazone (20 g./ton) and bacitracin (50 g./ton) as the drug in lieu of the formulations and drug of Example X. The bacitracin is added as the resin adsorbate 116 g. bacitracin/lb. adsorbate.

BASAL RATION FORMULATION

27

Ingredients	Pre-Starter 750 lb. Mix	Starter 1500 lb. Mix
Ground Yellow Corn	382.2 lbs.	865.5 lbs.
Cane Sugar	37.5 lbs.	—
Soybean Meal (50% C.P.)	175.5 lbs.	293.25 lbs.
Dried Skim Milk	75.0 lbs.	75.0 lbs.
Dried Whey	37.5 lbs.	150.0 lbs.
Dehydrated Alfalfa Meal (17% C.P.)	—	37.5 lbs.
Stabilized Animal Fat	18.75 lbs.	37.5 lbs.
Limestone	5.25 lbs.	9.0 lbs.
Dicalcium Phosphate	9.4 lbs.	16.5 lbs.
Iodized Salt	3.75 lbs.	7.5 lbs.
Vitamin Premix	3.75 lbs.	7.5 lbs.
Delamix	0.37 lbs.	0.75 lbs.
Zinc Carbonate	29.5 grams	59 grams
	750.0 lbs.	1500.0 lbs.

A 25.5% average increase in growth response and an 8.1% average increase in feed efficiency is obtained.

- 5 Substitution of the compounds of Example III in place of 2-formyl-quinoxaline-1,4-dioxide carbomethoxy-hydrazone produces similar significant responses.

EXAMPLE XII.

- 10 The efficacy of 2-formylquinoxaline-1,4-dioxide carbomethoxyhydrazone in promoting growth and improving the feed efficiency of broilers is illustrated below.

- 15 In this test, one group of 168 male and one group of 168 female one-day-old chicks of

the Cobbs strain are each divided into 12 pens of 14 chicks per pen. One-half the pens of each sex serve as control and are fed a basal, non-supplemented diet. The other half is fed a basal diet supplemented with 20 g./ton of 2-formyl-quinoxaline-1,3-dioxide carbomethoxyhydrazone. The supplement is added to the basal diet at the expense of the corn meal.

At 13 days of age all chicks are individually weighed and the two lightest and the two heaviest birds removed from each pen. The remainder of the trial, through 29 days of age, is conducted with ten chicks per pen.

BASAL DIET

Ingredient	% of Mix
Ground Yellow Corn	52.15
Soybean Oil Meal, 50%	28.10
Meat Scraps, 50%	4.00
Fish Solubles (100—S), 52%	2.00
Alfalfa Meal, 17%	2.00
Stabilized Animal Fat	8.00
Multi-fos (Dicalcium Phosphate)	2.00
Limestone (38% Ca)	.25
Iodized Salt	.50
Vitamin Premix	.50
Choline Chloride, 25%	.36
Vigofac 6*	.15
Delamix	.05

* Vigofac 6 is the registered trademark of Chas. Pfizer & Co., Inc. for unidentified poultry and livestock growth factors obtainable from Streptomyces fermentation sources.

The chicks on the supplemented diet are, on the average, 4.4% heavier than the chicks received the control ration and demonstrated

a 5.4% increase in feed efficiency over the controls

A similar experiment conducted with poults

but using 2-formyl-quinoxaline-1,4-dioxide carbomethoxyhydrazone at levels of 10 g. and

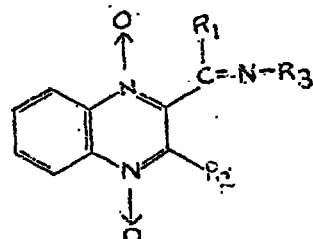
20 g./ton of basal diet demonstrated the following significant results.

5

Supplement	Weight	% Above Controls Feed Efficiency
10 g./ton	+ 8.4	+0.6
20 g./ton	+ 11.9	+4.9

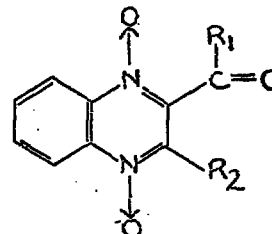
WHAT WE CLAIM IS:—

1. A process for the preparation of compounds having the general formula:



I

R₁ is a hydrogen atom or a lower alkyl group containing from 1 to 6 carbon atoms, comprising reacting a compound having the formula:



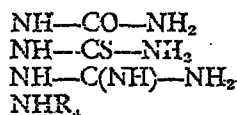
... II

10 wherein each of R₁ and R₂ is individually a hydrogen atom or a lower alkyl group containing from 1 to 6 carbon atoms; R₃ is

in which R₁ and R₂ are as above defined, with a compound having the formula:



15



or its acid addition salt, wherein R₄ is as above defined.

2. A process according to claim 1, in which the reaction is carried out in a solvent.

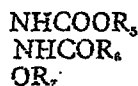
3. A process according to claim 2, in which the solvent is acetic acid, ether or a lower alcohol.

4. A process according to claim 2 or 3, in which the reaction is carried out at a temperature ranging from about room temperature to the reflux temperature of the solvent.

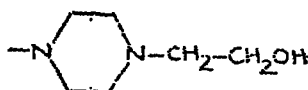
5. A process according to any one of the preceding claims, in which the reaction is carried out in the presence of a small amount of hydrochloric or acetic acid.

6. New compounds having the general formula:

or



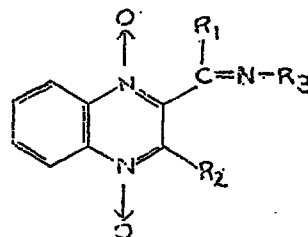
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25 wherein R₄ is a lower alkyl group containing from 1 to 6 carbon atoms, a phenyl, benzyl or hydroxyalkyl group containing from 2 to 4 carbon atoms;

30 R₅ is a lower alkyl group containing from 1 to 6 carbon atoms, a hydroxyalkyl group containing from 2 to 4 carbon atoms or a haloalkyl group containing from 2 to 4 carbon atoms;

R₆ is a lower alkyl group containing from 1 to 6 carbon atoms, or a phenyl group; and



I

wherein each of R₁ and R₂ is individually a hydrogen atom or a lower alkyl group containing from 1 to 6 carbon atoms; R₃ is



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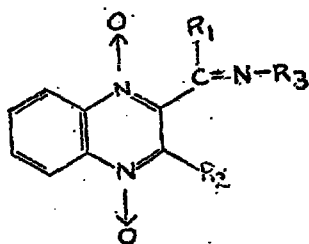
but using 2-formyl-quinoxaline-1,4-dioxide carbomethoxyhydrazone at levels of 10 g. and

20 g./ton of basal diet demonstrated the following significant results.

Supplement	Weight	% Above Controls Feed Efficiency
10 g./ton	+ 8.4	+0.6
20 g./ton	+ 11.9	+4.9

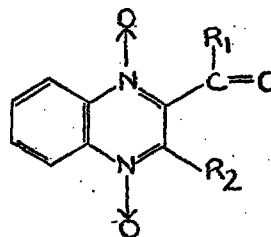
WHAT WE CLAIM IS:—

1. A process for the preparation of compounds having the general formula:



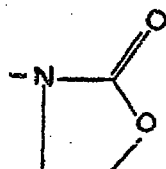
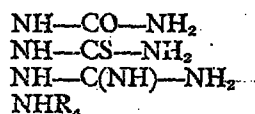
I

R₁ is a hydrogen atom or a lower alkyl group containing from 1 to 6 carbon atoms, comprising reacting a compound having the formula:

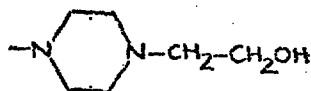
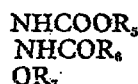


... II

wherein each of R₁ and R₂ is individually a hydrogen atom or a lower alkyl group containing from 1 to 6 carbon atoms; R₃ is



or



wherein R₄ is a lower alkyl group containing from 1 to 6 carbon atoms, a phenyl, benzyl or hydroxyalkyl group containing from 2 to 4 carbon atoms;

R₅ is a lower alkyl group containing from 1 to 6 carbon atoms, a hydroxyalkyl group containing from 2 to 4 carbon atoms or a haloalkyl group containing from 2 to 4 carbon atoms;

R₆ is a lower alkyl group containing from 1 to 6 carbon atoms, or a phenyl group; and

in which R₁ and R₂ are as above defined, with a compound having the formula:



or its acid addition salt, wherein R₃ is as above defined.

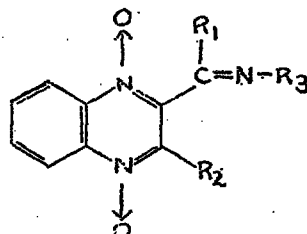
2. A process according to claim 1, in which the reaction is carried out in a solvent.

3. A process according to claim 2, in which the solvent is acetic acid, ether or a lower alcohol.

4. A process according to claim 2 or 3, in which the reaction is carried out at a temperature ranging from about room temperature to the reflux temperature of the solvent.

5. A process according to any one of the preceding claims, in which the reaction is carried out in the presence of a small amount of hydrochloric or acetic acid.

6. New compounds having the general formula:



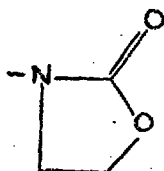
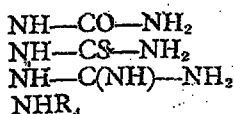
I

wherein each of R₁ and R₂ is individually a hydrogen atom or a lower alkyl group containing from 1 to 6 carbon atoms; R₃ is

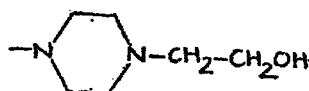
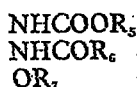


1,058,047

17



or



wherein R_1 is a lower alkyl group containing from 1 to 6 carbon atoms, a phenyl, benzyl or hydroxyalkyl group containing from 2 to 4 carbon atoms;

15 R_5 is a lower alkyl group containing from

16. A composition including one or containing from 2 to 4 carbon atoms or a halo-alkyl group containing from 2 to 4 carbon atoms;

20 R_6 is a lower alkyl group containing from 1 to 6 carbon atoms or a phenyl group; and

R_7 is a hydrogen atom or a lower alkyl group containing from 1 to 6 carbon atoms.

25 7. 2-Formyl quinoxaline-1,4-dioxide oxime.
8. 2-Formyl quinoxaline-1,4-dioxide carbomethoxy-hydrazone.

9. 2-Formyl-3-methylquinoxaline-1,4-dioxide carbo-(2-hydroxyisopropoxy)hydrazone.

30 10. 2-Formyl-3-methylquinoxaline-1,4-dioxide carbethoxyhydrazone.

11. [2-Formyl-3-methylquinoxaline-1,4-dioxide] N-[3-(2-oxazolidonyl) imine].

12. 2-Formyl-3-methylquinoxaline-1,4-dioxide semi-carbazone.

35 13. 2-Formyl-3-methylquinoxaline-1,4-dioxide acetyl-hydrazone.

14. A novel composition comprising one or more compounds having the formula I as defined in any one of claims 6 to 13 and a carrier.

15. A composition according to claim 14, in which the compound or compounds having the formula I are present in a concentration from 0.5% to 90% by weight of the total composition.

16. A composition including one or more compounds having the formula I as defined in any one of claims 6 to 13 and an antibiotic.

17. An animal feed or drink containing one or more compounds having the formula I as defined in any one of claims 6 to 13.

18. An animal feed composition containing from 0.10 to 10% of a compound having the formula I as defined in any one of claims 6 to 13.

19. An animal feed composition containing from 10 to 125 g. of a compound having the formula I as defined in any one of claims 6 to 13 per ton of the composition.

20. A process for promoting growth of animals other than human beings, including administering to the animal a compound, a composition, feed or drink as defined in any one of claims 6 to 19.

21. A process for the preparation of compounds having the general formula I substantially as hereinbefore described.

22. Compounds of formula I whenever prepared by the process of any one of claims 1 to 5 and 21.

23. Compositions containing compounds of formula I substantially as hereinbefore described.

24. Animal feed or drink containing compounds of formula I substantially as hereinbefore described.

25. A process of promoting growth of animals other than human beings including administering to the animal the compound of formula I, alone or in composition, substantially as hereinbefore described.

STEVENS, LANGNER, PARRY
& ROLLINSON,

Chartered Patent Agents,
Agents for the Applicants.

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ERRATUM

SPECIFICATION No. 1,058,047

Page 17, lines 16 and 17, delete "16. A composition including one or taining" insert "1 to 6 carbon atoms a hydroxyalkyl group containing"

THE PATENT OFFICE
6th January 1970