1,035,179

PATENT SPECIFICATION

NO DRAWINGS

1,035,179

Date of Application and filing Complete Specification: June 9, 1965.
No. 24400/65.
Application made in United States of America (No. 380,058) on July 2, 1964.
Application made in Belgium (No. 659,237) on Feb. 3, 1965.
Application made in United States of America (No. 440,621) on March 17, 1965.
Complete Specification Published: July 6, 1966.
© Crown Copyright 1966.

Index at acceptance:—C2 C(1E1K4, 1E7C1, 1E7E1, 1E7N5, 2B3A2, 2B3B, 2B3G3, 2B30, 3A7V1A4, 3A7V1E2, 3A7V1F2, 3A7V1J1, 3A7V1K2, 3A7V1L, 3A7V1P, 3A7V3A4, 3A7V3E2, 3A7V3J3, 3A7V3P, 3A13C6B, 3A13C10D)

Int. Cl.:—C 07 d 33/38

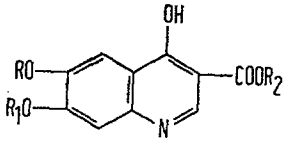
COMPLETE SPECIFICATION

Esters of 6,7-di-Substituted-4-Hydroxy-3-Quinolinecarboxylic Acid

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

This invention is concerned with certain novel esters of 6,7-di-substituted-4-hydroxy-3-quinolinecarboxylic acid and with their use in compositions having anticoccidial properties for administration to animals.

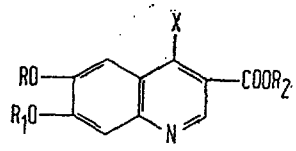
In our Specification No. 1,007,590 we have described and claimed lower alkyl esters of 6,7 - dialkoxy - 4 - hydroxy - 3 - quinolinecarboxylic acid of the formula



where R and R_1 are alkyl groups containing 3 or 4 carbon atoms or are ethyl groups when R_2 is methyl and R_2 is an alkyl group containing up to 4 carbon atoms. These compounds are distinguished by the high order of chemotherapeutic activity which they exhibit in the treatment of parasitic infections in animals when administered in far less than toxic amounts. They have proved very successful upon oral administration in combatting coccidiosis; the latter is a prevalent and economically significant disease of poultry caused by a variety of coccidia including *Eimeria tenella, Eimeria acervulina* and *Eimeria necatrix.*

We have now found that certain analogues of the compounds described in our said Application are also effective against coccidiosis.

According to the present invention we provide, as new compounds, esters of 6,7-di-substituted - 4 - hydroxy - 3 - quinolinecarboxylic acid of the formula



wherein R and R_1, which may be the same or different, are alkyl or alkenyl groups containing from 2 to 4 carbon atoms, R_2 is an alkyl group containing up to 4 carbon atoms or an allyl group, and X is acetoxy or is hydroxy when at least one of R and R_1 is an alkenyl group or when R_2 is an allyl group.

When the new compounds of this invention are mixed with an edible or potable carrier, advantageously by being incorporated in a nutritionally balanced diet at a level of from 0.006 to 0.1% by weight, and are offered to coccidially infected chickens, they overcome the mortality and morbidity usually associated with coccidial disease and accomplish a salutary effect upon growth and appearance of the birds.

The formulation of these new compounds in a form permitting convenient administration is readily accomplished by admixing them in the diet of animals as indicated above. Since the diet is a very effective and convenient means for administering medication for prophylactic or therapeutic effect, many combinations of suitable ingredients will occur to those skilled in the art as carriers for the anticoccidial compounds of this invention. Thus, commonly used ingredients comprise ground oyster shells, Attapulgus

[Price 4s. 6d.]

clay, commercial poultry feeds, urea, corn meal, ground citrus meal, fermentation residues, distiller's grains, soybean oil and lecithin.

As a matter of facility it is customary to supply a premix or concentrate containing the edible or potable carrier and from 5 to 50% by weight of the active ingredient and adapted to be extended with other suitable edible or potable carriers to the desired dilution for use which, as stated above, is usually from 0.006 to 0.1% of active ingredient. Such a premix is readily and commonly prepared by admixing the active ingredient in the selected edible or potable carrier by tumbling, grinding or stirring. A representative premix comprises:

	%	Per Pound
Active ingredient	22.05	100.00
Lecithin	2.00	9.07
Soybean oil	2.00	9.07
Corn meal	73.95	335.45

This may be diluted by the addition of combinations of the aforementioned ingredients to prepare the requisite diet for administration to the infected or potentially infected host. The new compounds can also, if desired, be incorporated in tablets, gelatin capsules, suspensions or like compositions consisting of suitable carriers and adjuvants common to the pharmaceutical art.

The method which is preferred for the preparation of the new compounds of this invention consists of reducing a 1,2-dialkoxy or dialkenyloxy-4-nitrobenzene in the presense of an inert solvent, such as ethanol, to obtain the corresponding amino compound, adding diethyl ethoxymethylene or dimethyl methoxymethylene malonate to the solution of the amino compound obtained, removing the solvent, adding a liquid temperature regulating medium, such as "Dowtherm" (trade mark), to the mixture, and heating the latter at a temperature of from 200° to 250°C to effect ring closure and formation of a quinoline structure. Alternatively, instead of using "Dowtherm," cyclisation leading to the formation of a 4-halo-quinoline compound can be effected by heating the product obtained by reaction of the amino compound and the malonate, with a phosphorus oxyhalide, such as phosphorus oxychloride, and this product can be hydrolysed to replace the 4-halo substituent by a 4-hydroxy substituent by heating in the presence of an acid medium.

The foregoing processes give the methyl or ethyl esters, and other esters, that is alkyl esters containing 3 or 4 carbon atoms in their alkyl groups or allyl esters, can be prepared by the saponification of the methyl or ethyl ester product, followed by subjecting the acid formed to re-esterification by the Fisher-Speier or Schotten-Baumann reaction. Another method of preparing the other esters consists in the transesterification technique whereby one alcohol moiety is exchanged for another.

The preparation of compounds wherein X is an acetoxy group is readily carried out by treating the corresponding quinolinol with an acetylating agent, such as acetic anhydride.

In order that this invention may be more fully understood, the following examples are given by way of illustration only:—

Example I

Ethyl 6,7 - diisobutoxy- 4 - hydroxy - 3 - quinolinecarboxylate

To a solution of 197 g. (1.8 M) of catechol in 730 ml of ethanol is added 143 g. (3.6 M) of sodium hydroxide pellets in a nitrogen atmosphere. When salt formation is complete, 490 g. (3.6 M) of isobutyl bromide is added dropwise at 55—65°. The nitrogen inlet tube is removed, and this mixture is refluxed for 17 hours. The sodium bromide is removed by filtration and the filtrate concentrated. The tar-like residue is taken up in 2 l. of water and extracted with 2 l. and then 1 l. of ether. These ether extracts are combined and washed with 2×500 ml. of a 10% sodium hydroxide solution and then with 2×1 l. of H_2O. After drying the ether solution over $MgSO_4$ it is concentrated to a residue weighing 125 g. (33%).

While maintaining the temperature below 25° with an ice bath, 105 g. (.47 M) of 1,2-diisobutoxybenzene is added dropwise to a 1:1 solution of water and concentrated nitric acid. On completion of the addition, cooling is continued until the reaction is no longer exothermic. The mixture is poured into 2 l. of ice water with stirring. The resulting brown solid is filtered, washed well with water until washings are no longer acid, dissolved in slightly warm methanol and filtered. A little water is added to induce crystallisation. The recrystallised material weighs 49 g. (39%), m.p. 68—72°C.

To 2 g. of 5% palladium-on-carbon containing 50% water is added 16 g. (.06 M) of 3,4-diisobutoxynitrobenzene and 200 ml. of ethanol. On shaking in a hydrogen atmosphere for 20 minutes the theoretical amount of hydrogen is consumed. The catalyst is removed by filtration, and the filtrate is added to 13 g. (.06 M) of diethyl ethoxymethylene malonate and refluxed in a nitrogen atmosphere for 1 hour. White crystals of the anil separate upon cooling to room temperature, 18 g. (74%), m.p. 77—79°C.

A 56 g. sample of the anil prepared in this way is added to 600 ml. of "Dowtherm"

and the solution refluxed for 1 hour. The solid product is washed with hexane, giving 31 g. (81%), m.p. 282—284°C. Two recrystallisations from dimethylformamide yield 25 g. of ethyl 6,7-diisobutoxy-4-hydroxy-3-quinolinecarboxylate, m.p. 288—291°C.

	C	H	N
Calc. for $C_{20}H_{27}NO_5$:	66.46	7.53	3.87
Found:	66.53	7.24	4.13

EXAMPLE II

Methyl 6,7 - diisobutoxy - 4 - hydroxy - 3 - quinolinecarboxylate

To a solution of 3,4-diisobutoxyaniline is added 41 g. of dimethyl methoxymethylene malonate. The solution is heated under reflux for 2 hours and concentrated *in vacuo* to a viscous residue. This residue is warmed on a steam bath and added to 800 ml. of boiling "Dowtherm." The mixture is boiled for 20 minutes and then cooled. The product is filtered off, washed with "Dowtherm," then with acetone and dried. The yield of crude methyl 6,7 - diisobutoxy - 4 - hydroxy - 3 - quinolinecarboxylate is 36 g. (44%). A suspension of it in 250 ml. of methanol is boiled for 5 minutes and filtered hot; 35 g. of product was obtained, m.p. 278—281°C.

EXAMPLE III (U—1080)

Ethyl 4 - acetoxy - 6,7 - diethoxy - 3 - quinolinecarboxylate

A mixture of 50 g. (0.16 mole) of ethyl 6,7 - diethoxy - 4 - hydroxy - 3 - quinolinecarboxylate and 30 g. of anhydrous sodium acetate in 1250 ml. of acetic anhydride is heated to reflux for 2¼ hours and then allowed to cool. The solid is collected and washed with cold water and dried. The yield is 49 g. (86%) of ethyl 4-acetoxy-6,7-diethoxy-3-quinolinecarboxylate, m.p. 169—172°C. It may be recrystallised from ethanol.

	C	H	N
Calc. for $C_{18}H_{21}NO_6$:	62.23	6.09	4.23
Found:	62.19	6.08	3.89

EXAMPLE IV (U—1099)

Methyl 4 - acetoxy - 6,7 - diisopropoxy - 3 - quinolinecarboxylate

A mixture of 2 g. of the compound methyl 6,7 - diisopropoxy - 4 - hydroxy - 3 - quinolinecarboxylate and 2 g. of anhydrous sodium acetate in 50 ml. acetic anhydride is heated to reflux for 2½ hours. The mixture is then poured onto cracked ice. Oily material gradually solidifies and is collected and washed well with H_2O and dried to yield 1.8 g. of methyl 4 - acetoxy - 6,7 - diisopropoxy - 3 - quinolinecarboxylate (79.5%), m.p. 102—104°C.

	C	H	N
Calc. for $C_{19}H_{23}NO_6$:	63.14	6.42	3.88
Found:	63.03	6.44	4.00

EXAMPLE V (U—1112)

Allyl 6,7 - diethoxy - 4 - hydroxy - 3 - quinolinecarboxylate

To 1500 ml. of allyl alcohol at room temperature is added 50 g. of 6,7-diethoxy-4-hydroxy-3-quinolinecarbonyl chloride. After 2 days standing at room temperature, the slightly cloudy solution is filtered. Ether is added to the filtrate to the cloud point. After cooling, white solid separates gradually. The solid is collected, washed well with ether, triturated with H_2O and dried to yield 38 g. (71%), of allyl 6,7-diethoxy-4-hydroxy-3-quinolinecarboxylate, m.p. 250—253°C. with previous softening. It may be recrystallised from dimethylformamide.

	C	H	N
Calc. for $C_{17}H_{19}NO_5$:	64.34	6.04	4.41
Found:	64.10	6.12	4.48

EXAMPLE VI (U—1252)

Allyl 6,7 - diisobutoxy - 4 - hydroxy - 3 - quinolinecarboxylate

A. A mixture of 37.5 g. (0.104 M) of the compound of Example I in 200 ml. of 10%NaOH is heated to reflux for 3¾ hours. Upon slight cooling, jellylike material separates which is dissolved by the addition of more base and a large amount of H_2O with heating. The solution is filtered hot and the cloudy hot filtrate is acidified with concentrated HCl. After cooling, the solid is collected and washed well with H_2O. The yield is 30.5 g. (85%), of 6,7-diisobutoxy-4-hydroxy-3-quinolinecarboxylic acid hydrate, m.p. 243—250°C. It may be purified by dissolving in NaOH solution, filtering, acidifying, filtering again and recrystallising from dimethylformamide, m.p. 256—257°C.

B. A suspension of 19 g. (0.057 M) of the acid of A. in 600 ml. benzene in a 1 l. 3-necked flask fitted with a stirrer and a Dean-Stark trap is refluxed for an hour. A small amount of H_2O is separated. Then 4.5 ml. (10% excess) of $SOCl_2$ is added and the reaction mixture is refluxed with stirring for 9½ hours and cooled overnight. Solid is collected, washed with benzene, then ether and dried in 100°C. oven for 10 minutes. The yield is 18 g. (90%) of acid chloride, m.p. 252—255°C.

C. A mixture of 6.0 g. (0.017 M) of 6,7 - diisobutoxy - 4 - hydroxy - 3 - quinolinecarbonyl chloride in 300 ml. allyl alcohol is heated on a steam bath for about 10 minutes. The solution is neutralised to pH 7—8 with concentrated NH_4OH and solid separates. Ether is added and the reaction

mixture cooled. Solid is collected, washed well with ether and triturated well with H_2O, filtered and dried in 100°C. oven. The yield of allyl 6,7-diisobutoxy-4-hydroxy-3-quinolinecarboxylate is 4.6 g. (72.5%), m.p. 235—236°C.

	C	H	N
Calc. for $C_{21}H_{27}NO_5$:	67.54	7.29	3.75
Found:	67.74	7.24	3.95

EXAMPLE VII (U—1280)

Ethyl 4 - hydroxy - 6,7 - bis - (2 - methylallyloxy) - 3 - quinolinecarboxylate

A. *o-Bis-(2-methylallyloxy)benzene*

To a solution of 110 g. of catechol in 4 l. of dimethylformamide is added 110 g. of $NaOCH_3$ powder in about 10 minutes with stirring. The reaction mixture is stirred for ½ hour with slight warming. Then heating is stopped and 182 g. of methallyl chloride is added in about 5 minutes at 37°C. The temperature gradually rises to 46°C. in about ½ hour. The reaction mixture is stirred overnight and then heated to 45—50°C. for an additional hour. The reaction mixture is cooled and filtered. The filtrate is acidified to pH 6, poured into H_2O and extracted with 16 x 200 ml. of benzene. The benzene extract is washed with 10% NaOH solution followed by H_2O until the washings are neutral. After drying over $MgSO_4$ and distilling, 156 g. (72%) of A. is obtained, distilling at 91°C/0.35 mm.

B. *3,4-Bis-(2-methylallyloxy)nitrobenzene*

Eleven grams of 1,2-bis-(2-methylallyloxy) benzene is added to 25 ml. of concentrated nitric acid over a 30-minute period at 10—20°C. with stirring. After stirring an additional 30 minutes, the solid mass is broken up and poured into 300 ml. of ice water. The solid is filtered, suspended in fresh water, filtered again, washed well with water, then with a little cold methanol and air dried; 11 g. (82%) of 3,4-bis-(2-methylallyloxy)nitrobenzene is obtained; m.p. 78—81°C.

C. *3,4-Bis-(2-methylallyloxy)aminobenzene*

To a mixture of 92 g. of 3,4-bis-(2-methylallyloxy)nitrobenzene in 2100 ml. of ethanol and 550 ml. of H_2O is added a solution of 27 g. $CaCL_2$ in 100 ml. of H_2O together with 500 g. of Zn dust. The mixture is heated to reflux with stirring for 4 hours, filtered while still warm, and the Zn dust is washed with ethanol. The filtrate is concentrated *in vacuo* to a dark syrupy residue. Water and some concentrated HCl is added to this residue and solid separates upon standing. The solid is triturated with about 6 l. of H_2O and filtered. The filtrate is made alkaline to pH 8—9 with concentrated NH_4OH and then extracted with ether. After drying over $MgSO_4$, ether is distilled off to give 57 g. (70%) of C.

D. *Ethyl 4-chloro-6,7-bis-(2-methylallyloxy) - 3 - quinolinecarboxylate*

The amine of C. is heated to reflux with 52.8 g. (0.24 M) of diethyl ethoxymethylene malonate in 150 ml. of ethanol for 2 hours. The solution is concentrated *in vacuo* to give a viscous liquid which solidifies upon cooling. The yield of anil is 98 g. (99.5%). A mixture of 97 g. of the anil and 400 ml. of $POCl_3$ is heated on a steam bath for 2 hours. The excess $POCl_3$ is then distilled off *in vacuo* and the residue poured onto cracked ice. The cold mixture is made slightly basic with concentrated NH_4OH and solid separates. The solid is collected, washed well with H_2O and air dried to give 87 g. (96.5%) of D., gradually melting to a red liquid above 85°C.

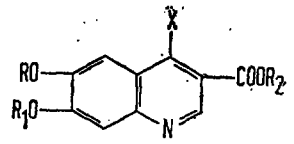
E. *Ethyl 4-hydroxy-6,7-bis-(2-methylallyloxy)-3-quinolinecarboxylate*

A mixture of 87 g. of ethyl 4-chloro-6,7-bis - (2 - methylallyloxy) - 3 - quinolinecarboxylate and 30 g. of anhydrous sodium acetate in 1 l. of acetic acid is heated to boiling for 45 minutes. After cooling, the solid is collected, washed well with ether and dried to give 44 g. of E. It may be recrystallised from dimethylformamide with decomposition.

	C	H	N
Calc. for $C_{20}H_{23}NO_5$:	67.21	6.49	3.92
Found:	67.02	6.38	4.06

WHAT WE CLAIM IS:—

1. Esters of 6,7-di-substituted-4-hydroxy-3-quinolinecarboxylic acid of the formula



wherein R and R_1, which may be the same or different, are alkyl or alkenyl groups containing from 2 to 4 carbon atoms, R_2 is an alkyl group containing up to 4 carbon atoms or an allyl group, and X is acetoxy or is hydroxy when at least one of R and R_1 is an alkenyl group or when R_2 is an allyl group.

2. Ethyl 6,7 - diisobutoxy - 4 - hydroxy-3 - quinolinecarboxylate.

3. Methyl 6,7 - diisobutoxy - 4 - hydroxy-3 - quinolinecarboxylate.

4. Ethyl 4 - acetoxy - 6,7 - diethoxy - 3 - quinolinecarboxylate.

5. Methyl 4 - acetoxy - 6,7 - diisopropoxy - 3 - quinolinecarboxylate.

6. Allyl 6,7 - diethoxy - 4 - hydroxy - 3 - quinolinecarboxylate.

mixture cooled. Solid is collected, washed well with ether and triturated well with H_2O, filtered and dried in 100°C. oven. The yield of allyl 6,7-diisobutoxy-4-hydroxy-3-quinolinecarboxylate is 4.6 g. (72.5%), m.p. 235—236°C.

	C	H	N
Calc. for $C_{21}H_{27}NO_5$:	67.54	7.29	3.75
Found:	67.74	7.24	3.95

EXAMPLE VII (U—1280)

Ethyl 4 - hydroxy - 6,7 - bis - (2 - methylallyloxy) - 3 - quinolinecarboxylate

A. *o-Bis-(2-methylallyloxy)benzene*

To a solution of 110 g. of catechol in 4 l. of dimethylformamide is added 110 g. of $NaOCH_3$ powder in about 10 minutes with stirring. The reaction mixture is stirred for ½ hour with slight warming. Then heating is stopped and 182 g. of methallyl chloride is added in about 5 minutes at 37°C. The temperature gradually rises to 46°C. in about ½ hour. The reaction mixture is stirred overnight and then heated to 45—50°C. for an additional hour. The reaction mixture is cooled and filtered. The filtrate is acidified to pH 6, poured into H_2O and extracted with 16 x 200 ml. of benzene. The benzene extract is washed with 10% NaOH solution followed by H_2O until the washings are neutral. After drying over $MgSO_4$ and distilling, 156 g. (72%) of A. is obtained, distilling at 91°C/0.35 mm.

B. *3,4-Bis-(2-methylallyloxy)nitrobenzene*

Eleven grams of 1,2-bis-(2-methylallyloxy) benzene is added to 25 ml. of concentrated nitric acid over a 30-minute period at 10—20°C. with stirring. After stirring an additional 30 minutes, the solid mass is broken up and poured into 300 ml. of ice water. The solid is filtered, suspended in fresh water, filtered again, washed well with water, then with a little cold methanol and air dried; 11 g. (82%) of 3,4-bis-(2-methylallyloxy)nitrobenzene is obtained; m.p. 78—81°C.

C. *3,4-Bis-(2-methylallyloxy)aminobenzene*

To a mixture of 92 g. of 3,4-bis-(2-methylallyloxy)nitrobenzene in 2100 ml. of ethanol and 550 ml. of H_2O is added a solution of 27 g. $CaCL_2$ in 100 ml. of H_2O together with 500 g. of Zn dust. The mixture is heated to reflux with stirring for 4 hours, filtered while still warm, and the Zn dust is washed with ethanol. The filtrate is concentrated *in vacuo* to a dark syrupy residue. Water and some concentrated HCl is added to this residue and solid separates upon standing. The solid is triturated with about 6 l. of H_2O and filtered. The filtrate is made alkaline to pH 8—9 with concentrated NH_4OH and then extracted with ether. After drying over $MgSO_4$, ether is distilled off to give 57 g. (70%) of C.

D. *Ethyl 4-chloro-6,7-bis-(2-methylallyloxy) - 3 - quinolinecarboxylate*

The amine of C. is heated to reflux with 52.8 g. (0.24 M) of diethyl ethoxymethylene malonate in 150 ml. of ethanol for 2 hours. The solution is concentrated *in vacuo* to give a viscous liquid which solidifies upon cooling. The yield of anil is 98 g. (99.5%). A mixture of 97 g. of the anil and 400 ml. of $POCl_3$ is heated on a steam bath for 2 hours. The excess $POCl_3$ is then distilled off *in vacuo* and the residue poured onto cracked ice. The cold mixture is made slightly basic with concentrated NH_4OH and solid separates. The solid is collected, washed well with H_2O and air dried to give 87 g. (96.5%) of D., gradually melting to a red liquid above 85°C.

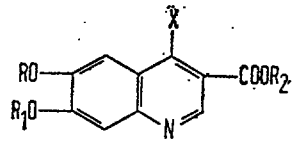
E. *Ethyl 4-hydroxy-6,7-bis-(2-methylallyloxy)-3-quinolinecarboxylate*

A mixture of 87 g. of ethyl 4-chloro-6,7-bis - (2 - methylallyloxy) - 3 - quinolinecarboxylate and 30 g. of anhydrous sodium acetate in 1 l. of acetic acid is heated to boiling for 45 minutes. After cooling, the solid is collected, washed well with ether and dried to give 44 g. of E. It may be recrystallised from dimethylformamide with decomposition.

	C	H	N
Calc. for $C_{20}H_{23}NO_5$:	67.21	6.49	3.92
Found:	67.02	6.38	4.06

WHAT WE CLAIM IS:—

1. Esters of 6,7-di-substituted-4-hydroxy-3-quinolinecarboxylic acid of the formula



wherein R and R_1, which may be the same or different, are alkyl or alkenyl groups containing from 2 to 4 carbon atoms, R_2 is an alkyl group containing up to 4 carbon atoms or an allyl group, and X is acetoxy or is hydroxy when at least one of R and R_1 is an alkenyl group or when R_2 is an allyl group.

2. Ethyl 6,7 - diisobutoxy - 4 - hydroxy-3 - quinolinecarboxylate.

3. Methyl 6,7 - diisobutoxy - 4 - hydroxy-3 - quinolinecarboxylate.

4. Ethyl 4 - acetoxy - 6,7 - diethoxy - 3 - quinolinecarboxylate.

5. Methyl 4 - acetoxy - 6,7 - diisopropoxy - 3 - quinolinecarboxylate.

6. Allyl 6,7 - diethoxy - 4 - hydroxy - 3 - quinolinecarboxylate.

* C L M S *

7. Allyl 6,7 - diisobutoxy - 4- hydroxy- 3 - quinolinecarboxylate.

8. Ethyl 4 - hydroxy - 6,7 - bis - (2-methylallyloxy) - 3 - quinolinecarboxylate.

9. A process for the preparation of a compound of the formula specified in claim 1, which comprises reducing a 1,2-dialkoxy or dialkenyloxy-4-nitrobenzene in which the alkoxy or alkenyloxy groups contain from 2 to 4 carbon atoms, in the presence of an inert solvent to obtain the corresponding amino compound, adding diethyl ethoxymethylene malonate or dimethyl methoxymethylene malonate to the solution of the amino compound obtained, removing the solvent, adding a liquid temperature regulating medium to the mixture, and heating the latter at a temperature of from 200° to 250°C to effect ring closure and formation of a quinoline structure.

10. A modification of the process according to claim 9, in which the product obtained by reaction of the amino compound and the malonate is heated with a phosphorus oxyhalide and the product so obtained is hydrolysed to introduce a 4-hydroxy substituent by heating in the presence of an acid medium.

11. A process according to claim 9 or 10, in which the methyl or ethyl ester obtained is converted into an alkyl ester containing 3 or 4 carbon atoms in its alkyl group or into an allyl ester by saponification followed by re-esterification or by transesterification.

12. A process according to any of claims 9 to 11, in which the 4-hydroxy group of the product obtained is acetylated.

13. A process for the preparation of a compound of the formula specified in claim 1 substantially as herein described in any of the Examples.

14. A composition having anticoccidial properties comprising a compound as claimed in any of claims 1 to 8 in admixture with an edible or potable carrier.

15. A composition having anticoccidial properties and suitable for administration to animals comprising from 0.006 to 0.1% by weight of a compound as claimed in any of claims 1 to 8 in admixture with an edible or potable carrier.

16. A concentrate composition comprising from 5 to 50% by weight of a compound as claimed in any of claims 1 to 8 in admixture with an edible carrier, said concentrate being adapted for dilution with one or more edible carrier to form a composition for administration according to claim 15.

A. A. THORNTON & CO.,
Chartered Patent Agents,
Northumberland House,
303—306, High Holborn,
London, W.C.1,
For the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1966. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained

