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VETERINARY COMPOSITIONS CONTAINING A QUINOLINE-3-CARBOXYLIC ESTER

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U.S. Cl. 424—258 **13 Claims**

ABSTRACT OF THE DISCLOSURE

Veterinary compositions containing, as the essential active component, derivatives of 4-hydroxy-quinoline-3-carboxylic esters in which the 7-position of the quinoline nucleus bears a benzyloxy, chlorobenzyloxy or N

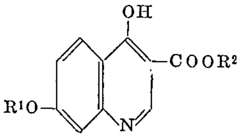
$C_{12}H_{25}O$—

group and the 6-position is optionally substituted. These derivatives are disclosed as useful in the prophlatic treatment of coccidiosis in poultry or other domestic animals. Representative of the disclosed active components is methyl 7 - benzyloxy-6-n-butyl-4-hydroxyquinoline-3-carboxylate.

This application is a division of our application Ser. No. 526,694, now U.S. Pat. No. 3,414,576.

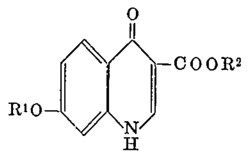
This invention relates to heterocyclic compounds and more particularly it relates to quinoline derivatives which possess anti-coccidial activity.

According to the invention we provide quinoline derivatives of the formula:



wherein R¹ stands for an alkyl, aryl or aralkyl radical, any of which may optionally be substituted, R² stands for an alkyl radical, and wherein the quinoline nucleus may optionally bear one or more additional substituents, provided that when the quinoline nucleus bears no additional substituents, and when R_2 stands for the ethyl radical, R¹ does not stand for the methyl or phenyl radical, and provided that when both R¹ and R² stand for alkyl radicals of not more than 4 carbon atoms, then the quinoline nucleus does not bear as sole additional substituent, an alkoxy radical of not more than 4 carbon atoms in the 6-position.

It is to be understood that the above definition of quinoline derivatives encompasses the quinoline derivatives when they are present in the tautomeric structure having the formula:



A preferred group of compounds of the invention comprises those quinoline derivatives wherein R¹ stands for a benzyl radical, optionally substituted by one or more halogen atoms, R² stands for the methyl or ethyl radical, and the quinoline nucleus is substituted in the 6-

position by an alkyl radical of not more than 6 carbon atoms, or an alkenyl or alkoxy radical of not more than 4 carbon atoms.

Another preferred group of compounds of the invention comprises those quinoline derivatives wherein R¹ stands for an alkyl radical containing at least 12 and not more than 14 carbon atoms, R² stands for the methyl or ethyl radical, and the quinoline nucleus is substituted in the 6-position by an alkyl radical of not more than 6 carbon atoms.

As a suitable value for R¹ when it stands for an alkyl radical there may be mentioned, for example, a straight- or branched-chain alkyl radical containing not more than 15 carbon atoms, for example the isopropyl, n-dodecyl or n-tetradecyl radical. As a suitable value for R¹ when it stands for an aryl radical there may be mentioned, for example, the phenyl radical, optionally substituted by one or more alkyl radicals of not more than 5 carbon atoms, for example methyl radicals. As a suitable value for R¹ when it stands for an aralkyl radical there may be mentioned, for example, an aralkyl radical of not more than 9 carbon atoms, optionally substituted by one or more halogen atoms, for example chlorine atoms, alkyl radicals of not more than 3 carbon atoms, for example methyl radicals, or nitro radicals. Thus a specific value for R¹ when it stands for an aralkyl radical is, for example, the benzyl, 4-methylbenzyl, 2-chlorobenzyl, 4-chlorobenzyl, 2,4-dichlorobenzyl, 4-nitrobenzyl or 3-phenylpropyl radical.

As a suitable value for R² there may pe mentioned, for example, a straight- or branched-chain alkyl radical of not more than 4 carbon atoms, for example the methyl ethyl, n-propyl or isopropyl radical.

As suitable additional substituents which may be present on the quinoline nucleus, there may be mentioned, for example, one or more substituents selected from alkyl radicals of not more than 10 carbon atoms, alkenyl and alkoxy radicals of not more than 6 carbon atoms, and haolgen atoms. Thus specific additional substituents which may be present on the quinoline nucleus are, for example, the methyl, ethyl, n-propyl, n-butyl, isobutyl, n-hexyl, n-octyl, allyl, α-methylallyl, methoxy, ethoxy, n-propoxy, isopropoxy and chloro substituents.

As specific compounds of the invention there may be mentioned, for example,

ethyl 7-benzyloxy-4-hydroxyquinoline-3-carboxylate,
ethyl 7-n-dodecycloxy-4-hydroxyquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxyquinoline-3-carboxylate,
ethyl 7-benzyloxy-4-hydroxy-6-propylquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-n-propylquinoline-3-carboxylate,
methyl 6-allyl-7-benzyloxy-4-hydroxyquinoline-3-carboxylate,
ethyl 4-hydroxy-7-isopropoxyquinoline-3-carboxylate,
methyl 7-n-dodecyloxy-4-hydroxyquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-(α-methylallyl)quinoline-3-carboxylate,
n-propyl 7-benzyloxy-4-hydroxyquinoline-3-carboxylate,
isopropyl 7-benzyloxy-4-hydroxyquinoline-3-carboxylate,
methyl 4-hydroxy-7-(3-phenylpropoxy)quinoline-3-carboxylate,
methyl 4-hydroxy-7-(4-methylbenzyloxy)quinoline-3-carboxylate,
methyl 7-(4-chlorobenzyloxy)-4-hydroxy-6-n-propylquinoline-3-carboxylate,
ethyl 7-(4-chlorobenxyloxy)-4-hydroxy-6-n-propylquinoline-3-carboxylate,
ethyl 4-hydroxy-7-(4-methylphenoxy)quinoline-3-carboxylate,

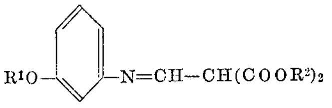
methyl 7-(2-chlorobenzyloxy)-4-hydroxy-6-n-propylquinoline-3-carboxylate,
methyl 7-(2,4-dichlorobenzyloxy)-4-hydroxy-6-n-propylquinoline-3-carboxylate,
methyl 7-dodecycloxy-4-hydroxy-6-n-propylquinoline-3-carboxylate,
methyl 4-hydroxy-7-phenoxyquinoline-3-carboxylate,
ethyl 4-hydroxy-7-(2-methylphenoxy)-quinoline-3-carboxylate,
ethyl 7-benzyloxy-4-hydroxy-6-n-hexylquinoline-3-carboxylate,
ethyl 7-benzyloxy-4-hydroxy-6-methylquinoline-3-carboxylate,
ethyl 7-benzyloxy-6-n-butyl-4-hydroxyquinoline-3-carboxylate,
ethyl 7-benzyloxy-4-hydroxy-6-n-octylquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-n-hexylquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-methylquinoline-3-carboxylate,
methyl 7-benzyloxy-6-ethyl-4-hydroxyquinoline-3-carboxylate,
methyl 7-benzyloxy-6-n-butyl-4-hydroxyquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-isobutylquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-n-octylquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-methoxyquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-ethoxyquinoline-3-carboxylate,
ethyl 7-benzyloxy-4-hydroxy-6-ethoxyquinoline-3-carboxylate,
ethyl 7-benzyloxy-4-hydroxy-6-n-propoxyquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-n-propoxyquinoline-3-carboxylate,
ethyl 7-benzyloxy-4-hydroxy-6-chloroquinoline-3-carboxylate,
ethyl 7-benzyloxy-4-hydroxy-6,8-dichloroquinoline-3-carboxylate,
methyl 7-n-tetradecyloxy-4-hydroxyquinoline-3-carboxylate,
ethyl 7-n-tetradecyloxy-4-hydroxyquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-isopropoxyquinoline-3-carboxylate,
methyl 7-(4-nitrobenzyloxy)-4-hydroxyquinoline-3-carboxylate and methyl 8-chloro-7-(2,4-dichlorobenzyloxy)-4-hydroxy-6-n-propylquinoline-3-carboxylate.

Of these, preferred compounds in respect of their anticoccidial activity are, for example,

methyl 7-benzyloxy-4-hydroxy-6-n-propylquinoline-3-carboxylate,
methyl 7-(4-chlorobenzyloxy)-4-hydroxy-6-n-propylquinoline-3-carboxylate,
methyl 7-(2-chlorobenzyloxy)-4-hydroxy-6-n-propylquinoline-3-carboxylate,
methyl 7-(2,4-dichlorobenzyloxy)-4-hydroxy-6-n-propylquinoline-3-carboxylate,
methyl 7-dodecyloxy-4-hydroxy-6-n-propylquinoline-3-carboxylate,
ethyl 7-benzyloxy-6-n-butyl-4-hydroxyquinoline-3-carboxylate,
methyl 7-benzyloxy-6-n-butyl-4-hydroxyquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-methoxyquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-ethoxyquinoline-3-carboxylate,
ethyl 7-benzyloxy-4-hydroxy-6-n-propoxyquinoline-3-carboxylate,

methyl 7-benzyloxy-4-hydroxy-6-n-propoxyquinoline-3-carboxylate,
methyl 7-benzyloxy-4-hydroxy-6-isopropoxyquinoline-3-carboxylate,
ethyl 7-(4-chlorobenzyloxy)-4-hydroxy-6-n-propylquinoline-3-carboxylate and
ethyl 7-benzyloxy-4-hydroxy-6-ethoxyquinoline-3-carboxylate.

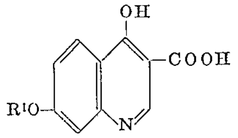
According to a further feature of the invention we provide a process for the manufacture of the quinoline derivatives of the invention which comprises the cyclisation of a compound of the formula:



wherein R^1 and R^2 have the meanings stated above, and wherein the benzene ring may optionally bear one or more additional substituents.

The cyclisation may be carried out by, for example, heating the starting material, conveniently at a temperature above 200° C. The cyclisation reaction may be carried out in the presence of an inert diluent or solvent, for example diphenyl ether of "Dowtherm" A ("Dowtherm" is a trademark).

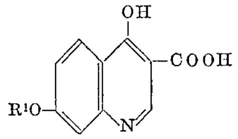
According to a further feature of the invention we provide a process for the manufacture of the quinoline derivatives of the invention which comprises the esterification of an acid of the formula:



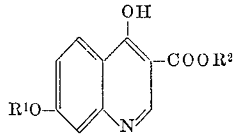
wherein R^1 has the meaning stated above, and wherein the quinoline nucleus may optionally bear one or more additional substituents.

The esterification may conveniently be carried out by conventional means, for example by the interaction of an alcohol of the formula $R^2.OH$, wherein R^2 has the meaning stated above, with the abovementioned acid in the presence of a mineral acid catalyst, for example sulphuric acid or hydrochloric acid; or by the interaction of the said alcohol of the formula $R^2.OH$, with an activated derivative of the abovementioned acid, for example the acid halide, for example the acid chloride.

The abovementioned acid of the formula:



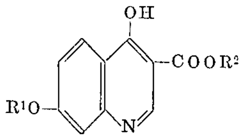
used as starting material in the above process may be obtained by the hydrolysis of the corresponding ester of the formula:



wherein R^1 and R^2 have the meanings stated above, and the quinoline nucleus may optionally bear one or more additional substituents.

The hydrolysis may be carried out under acidic conditions, for example, in the presence of an inorganic acid, for example hydrochloric acid, or it may be carried out under basic conditions, for example, in the presence of an inorganic base, for example an alkali metal hydroxide, for example sodium hydroxide or potassium hydroxide. The hydrolysis may conveniently be carried out in the presence of a diluent or solvent, for example ethanol, water or acetone, and it may be accelerated or completed by the application of heat.

According to a further feature of the invention we provide a process for the manufacture of those of the quinoline derivatives of the invention wherein the quinoline nucleus bears one or more halogen substituents, which comprises the halogenation of a compound of the formula:

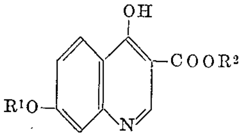


wherein R¹ and R² have the meanings stated above, and the quinoline nucleus has at least one unsubstituted position in the carbocyclic ring of the quinoline nucleus.

The halogenation may be effected by the use of an N-halogenated amide, for example an N-halosuccinimide, for example N-chlorosuccinimide, and it may be carried out in an inert diluent or solvent, for example dimethylformamide. The reaction may be accelerated or completed by the application of heat.

As stated above, the quinoline derivatives of this invention possess valuable anti-coccidial properties. They are especially active against the intestinal species *Eimeria brunetti,* and certain of them are also active against the caecal species *E. tenella* and *E. necatrix.* They are therefore useful as the active ingredient in veterinary compositions such as concentrated food pre-mixes or medicated foodstuffs for the prophylactic treatment of coccidiosis in poultry or other domestic animals.

According to a further feature of the invention, therefore, we provide veterinary compositions comprising one or more quinoline derivatives of the formula.



wherein R¹ stands for an alkyl, aryl or aralkyl radical, any of which may optionally be substituted, R² stands for an alkyl radical, and wherein the quinoline nucleus may optionally bear one or more additional substituents, provided that when both R¹ and R² stand for alkyl radicals of not more than 4 carbon atoms, then the quinoline nucleus does not bear as sole additional substituent, an alkoxy radical of not more than 4 carbon atoms in the 6-position, together with a non-toxic diluent or carrier.

The veterinary compositions may be, for example, concentrated food pre-mixes wherein the active ingredient is mixed with an inert diluent, for example kaolin, talc, calcium carbonate, fuller's earth, attapulgus clay or ground oyster shells, or is mixed with a foodstuff as diluent, for example whole ground corn, corn distillers dry grain, wheat shorts or corn cob meal. It is intended that the said pre-mixes should be further diluted with an animal foodstuff in order to provide a suitable medicated foodstuff which can be eaten directly by poultry or other domestic animals. It is preferred that such medicated foodstuff compositions intended for direct feeding to poultry should contain between about 0.00005% and about 0.1% by weight of active ingredient in the composition, and more particularly between 0.0001% and 0.001% by weight in the food of the preferred active ingredients. It is likewise preferred that the concentrated pre-mixes should contain between about 0.1% and about 25% by weight of the active ingredient and more particularly between 0.2% and 2% by weight of the preferred active ingredients.

The compositions of the invention may additionally contain one or more other compounds of known veterinary utility, for example one or more known anthelmintics, or growth promotors, antibacterials or tranquilisers.

The invention is illustrated but not limited by the following examples in which the parts are by weight:

EXAMPLE 1

93 parts of diethyl 3-benzyloxyanilinomethylenemalonate are added gradually to 450 parts of boiling diphenyl ether. The mixture is heated under reflux for 30 mins. and then cooled. The solid product is filtered off, washed with carbon tetrachloride, and crystallised from dimethylformamide. There is thus obtained ethyl 7-benzyloxy-4-hydroxyquinoline-3-carboxylate, M.P. 295° C.

The diethyl 3-benzyloxyanilinomethylenemalonate used as starting material may be obtained as follows:

A mixture of 45 parts of 3-benzyloxyaniline and 51 parts of diethyl ethoxymethylenemalonate is heated at 100° C. for 1 hour. The solid reaction product is crystallised from ethanol. There is thus obtained diethyl 3-benzyloxyanilinomethylenemalonate, M.P. 71° C.

EXAMPLE 2

17 parts of 3-n-dodecyloxyaniline and 13.5 parts of diethyl ethoxymethylenemalonate are heated at 100° C. for 2 hours, and the crude diethyl 3-n-dodecyloxyanilinomethylenemalonate so obtained is added gradually to 100 parts of boiling diphenyl ether. The mixture is heated under reflux for 30 minutes and then cooled. The solid product is filtered off, washed with carbon tetrachloride, and crystallised from dimethylformamide. There is thus obtained ethyl 7-n-dodecyloxy-4-hydroxyquinoline - 3-carboxylate, M.P. 255° C.

EXAMPLE 3

A mixture of 4 parts of 3-benzyloxyaniline and 3.5 parts of dimethyl methoxymethylenemalonate is heated at 100° C. for 2 hours, and the crude dimethyl 3-benzyloxyanilinomethylenemalonate so obtained is added gradually to 40 parts of stirred, boiling diphenyl ether. The mixture is stirred and heated under reflux for 30 minutes, and then cooled. The solid product is filtered off, washed with carbon tetrachloride, and recrystallised from dimethylformamide. There is thus obtained methyl 7-benzyloxy-4-hydroxyquinoline-3-carboxylate, M.P. 273° C.

EXAMPLE 4

A mixture of 3.5 parts of 3-benzyloxy-4-n-propylaniline and 3.4 parts of diethyl ethoxymethylenemalonate is heated at 100° C. for 2 hours, and the crude diethyl 3-benzyloxy-4-n-propylanilinomethylenemalonate so obtained is added in one portion to 35 parts of stirred, boiling diphenyl ether. The mixture is stirred and heated under reflux for 5 minutes, and then cooled. The solid product is filtered off, washed with petroleum ether (B.P. 40–60° C.), and recrystallised from dimethylformamide. There is thus obtained ethyl 7-benzyloxy-4-hydroxy-6-n-propylquinoline-3-carboxylate, M.P. 299° C.

The 3-benzyloxy-4-n-propylaniline used as starting material may be obtained as follows:

A mixture of 10 parts of 3-hydroxy-4-n-propylacetanilide, 7.2 parts of benzyl chloride, 20 parts of potassium carbonate and 120 parts of acetone is heated under reflux for 18 hours. The mixture is cooled and filtered, and the filtrate is evaporated under reduced pressure. The residue so obtained is dissolved in chloroform, and the solution washed successively with dilute sodium hydroxide solution and saturated sodium chloride solution. The chloroform solution is then dried and evaporated, and the residue is recrystallised from petroleum ether (B.P. 60–80° C.). There is thus obtained 3-benzyloxy-4-n-propylacetanilide, M.P. 85° C. 9 parts of this latter compound are heated under reflux for 6 hours with 20 parts of potassium hydroxide in a mixture of 10 parts of water and 100 parts of ethanol. The solution is then cooled and evaporated under reduced pressure, and the residue is partitioned between water and ether. The ethereal layer is separated, washed with saturated sodium chloride solution, dried and evaporated. There is thus obtained 3-benzyloxy-4-n-propylaniline as an oil.

EXAMPLE 5

The procedure described in Example 4 is repeated except that the 3.4 parts of diethyl ethoxymethylenemalonate are replaced by 2.7 parts of dimethyl methoxymethylenemalonate. There is thus obtained methyl 7-benzyloxy-4-hydroxy-6-n-propylquinoline-3-carboxylate, M.P. 292° C.

EXAMPLE 6

A mixture of 5 parts of 7-benzyloxy-4-hydroxyquinoline-3-carboxylic acid and 35 parts of thionyl chloride is heated under reflux for 2 hours with a catalytic amount of pyridine. The excess of thionyl chloride is evaporated, 25 parts of benzene are added, and the mixture evaporated to dryness. The solid acid chloride so obtained is heated under reflux for 1 hour with 50 parts of dry methanol, and the solution is then evaporated. The solid residue is heated at 100° C. for a few minutes with 50 parts of water, and the resulting mixture cooled and filtered. The solid product is recrystallised from dimethylformamide. There is thus obtained methyl 7-benzyloxy-4-hydroxyquinoline-3-carboxylate, M.P. 273° C.

The 7-benzyloxy-4-hydroxyquinoline - 3 - carboxylic acid used as starting material may be obtained as follows:

A mixture of 34 parts of ethyl 7-benzyloxy-4-hydroxyquinoline-3-carboxylate and 200 parts of 10% w./v. potassium hydroxide solution is heated under reflux for 2 hours. A little charcoal is added, and the hot mixture is filtered. The filtrate is acidified with hydrochloric acid, and the precipitated solid is filtered off, washed with water, dried in vacuo at 100° C. for 18 hours, and recrystallised from 2-ethoxyethanol. There is thus obtained 7-benzyloxy-4-hydroxyquinoline-3-carboxylic acid, M.P. 273° C.

EXAMPLE 7

The procedure described in Example 6 is repeated except that the 5 parts of 7-benzyloxy-4-hydroxyquinoline-3-carboxylic acid are replaced by 5 parts of 7-benzyloxy-4-hydroxy-6-n-propylquinoline-3-carboxylic acid. There is thus obtained methyl 7-benzyloxy-4-hydroxy-6-n-propylquinoline-3-carboxylate, M.P. 292° C.

The 7 - benzyloxy-4-hydroxy-6-n-propylquinoline-3-carboxylic acid used as starting material may be obtained as follows:

A mixture of 5.5 parts of ethyl 7-benzyloxy-4-hydroxy-6-n-propylquinoline-3-carboxylate and 45 parts of 10% w./v. sodium hydroxide solution is heated under reflux for 2 hours. A little charcoal is added, and the hot mixture is filtered. The filtrate is acidified with hydrochloric acid, and the precipitated solid is filtered off, washed with water and dried in vacuo at 100° C. for 18 hours. There is thus obtained 7-benzyloxy - 4 - hydroxy-6-n-propylquinoline-3-carboxylic acid, M.P. 271° C.

EXAMPLE 8

A mixture of 5 parts of 4-allyl-3-benzyloxyaniline and 3.85 parts of dimethyl methoxymethylenemalonate is heated at 100° C. for 2 hours. The solid reaction product is crystallised from a mixture of benzene and petroleum ether, B.P. 60–80° C. There is thus obtained dimethyl 4-allyl-3-benzyloxyanilinomethylenemalonate, M.P. 92° C. 5 parts of this latter compound are added in one portion to 50 parts of stirred, boiling diphenyl ether. The mixture is stirred and heated under reflux for 5 minutes, and then cooled. The solid product is filtered off, washed with petroleum ether (B.P. 40–60° C.), and recrystallised from dimethylformamide. There is thus obtained methyl 6-allyl-7-benzyloxy-4-hydroxyquinoline-3-carboxylate, M.P. 283° C.

The 4-allyl-3-benzyloxyaniline used as starting material may be obtained as follows:

A mixture of 16.5 parts of 4-allyl-3-hydroxyacetanilide, 11 parts of benzyl chloride, 30 parts of potassium carbonate and 150 parts of acetone is heated under reflux for 18 hours. The mixture is cooled and filtered, and the filtrate is evaporated under reduced pressure. The residue so obtained is dissolved in chloroform, and the solution washed successively with dilute sodium hydroxide solution and saturated sodium chloride solution. The chloroform solution is then dried and evaporated, and there is thus obtained 4-allyl-3-benzyloxyacetanilide, M.P. 82° C. 14.2 parts of this latter compound are heated under reflux for 6 hours with 33 parts of potassium hydroxide in a mixture of 16 parts of water and 160 parts of ethanol. The solution is then cooled and evaporated under reduced pressure, and the residue is partitioned between water and ether. The ethereal layer is separated, washed with saturated sodium chloride solution, dried and evaporated. There is thus obtained 4-allyl-3-benzyloxyaniline as an oil.

EXAMPLE 9

The process of Example 2 is repeated except that the 17 parts of 3-n-dodecyloxyaniline are replaced by 9.3 parts of 3-isopropylaniline. There is thus obtained ethyl 4-hydroxy-7-isopropoxyquinoline-3-carboxylate, M.P. 246° C.

EXAMPLE 10

8 parts of 3-n-dodecyloxyaniline and 4.5 parts of dimethyl methoxymethylenemalonate are heated at 100° C. for 2 hours. The solid reaction product is crystallised from petroleum ether (B.P. 40–60° C.) 8 parts of the dimethyl 3-n-dodecyloxyanilinomethylenemalonate, M.P. 58° C. so obtained are added to 80 parts of boiling diphenyl ether. The mixture is heated under reflux for 20 minutes and then cooled. The solid product is heated in boiling carbon tetrachloride, and the mixture is then cooled and filtered. The solid product is crystallised from dimethyl formamide, and there is thus obtained methyl 7-n-dodecycloxy-4-hydroxyquinoline-3-carboxylate, M.P. 255° C.

EXAMPLE 11

6 parts of 3-benzyloxy-4-(α-methylallyl)aniline and 4.2 parts of dimethyl methoxymethylenemalonate are heated at 100° C. for 2 hours, and the crude dimethyl 3-benzyloxy-4-(α-methylallyl)anilinomethylenemalonate so obtained is added gradually to 50 parts of stirred, boiling diphenyl ether. The mixture is heated under reflux for 5 minutes and then cooled. The solid product is filtered off, washed with carbon tetrachloride and crystallised from dimethyl formamide. There is thus obtained methyl 7-benzyloxy-4-hydroxy-6-(α-methylallyl)quinoline-3-carboxylate, M.P. 283° C.

The 3-benzyloxy-4-(α-methylallyl)aniline used as starting material may be prepared as follows:

A mixture of 40 parts of 3-acetylaminophenol, 36 parts of crotyl bromide, 39 parts of potassium carbonate and 200 parts of acetone is heated under reflux for 18 hours. The mixture is cooled and filtered, and the filtrate is evaporated under reduced pressure. The resulting oil is dissolved in chloroform and washed successively with dilute sodium hydroxide solution and saturated sodium chloride solution. The chloroform solution is dried and evaporated to yield the crotyl ether, M.P. 68° C.

40 parts of the crotyl ether are refluxed in 135 parts of N,N-dimethylaniline under nitrogen for 4½ hours. The cooled solution is diluted with an equal volume of petroleum ether (B.P. 60–80° C.) and the precipitated oil is dissolved in boiling benzene. Addition of petroleum ether (B.P. 60–80° C.) to the cooled benzene solution precipitates a solid mixture of the two isomers formed in the rearrangement. The required isomer is separated by its greater solubility in benzene, and there is thus obtained 3-hydroxy-4-(α-methylallyl)acetanilide, M.P. 137° C.

16.5 parts of the latter compound are then used in the process described in the second part of Example 8. There is thus obtained 3-benzyloxy-4-(α-methylallyl)aniline as an oil.

EXAMPLE 12

The procedure described in Example 6 is repeated except that the 50 parts of methanol are replaced by 50 parts of n-propanol. There is thus obtained n-propyl

7 - benzyloxy - 4 - hydroxyquinoline-3-carboxylate, M.P. 293° C.

EXAMPLE 13

The procedure described in Example 6 is repeated except that the 50 parts of methanol are replaced by 50 parts of isopropanol. There is thus obtained isopropyl 7 - benzyloxy - 4 - hydroxyquinoline - 3 - carboxylate, M.P. 297° C.

EXAMPLE 14

4 parts of 3-(3-phenylpropoxy)aniline and 3 parts of dimethyl methoxymethylenemalonate are heated at 100° C. for 3 hours, and the crude dimethyl 3-(3-phenylpropoxy)anilinomethylenemalonate so obtained is added to 40 parts of boiling diphenyl ether. The mixture is heated under reflux for 5 minutes and then cooled. The solid product is filtered off, washed with petroleum ether (B.P. 40–60° C.), and crystallised from 2-ethoxyethanol. There is thus obtained methyl 4-hydroxy-7-(3-phenylpropoxy)quinoline-3-carboxylate, M.P. 255° C.

The 3-(3-phenylpropoxy)aniline used as starting material may be obtained as follows:

A mixture of 40 parts of 3-acetylaminophenol, 41 parts of cinnamyl chloride, 39 parts of potassium carbonate and 200 parts of acetone is heated under reflux for 18 hours. The mixture is cooled and filtered, and the filtrate is evaporated to dryness. The residue is dissolved in chloroform, and the solution washed successively with dilute sodium hydroxide solution and saturated sodium chloride solution. The chloroform is evaporated and the residue crystallised from aqueous ethanol to give 3-cinnamyloxyacetanilide, M.P. 158° C.

12 parts of the latter compound are dissolved in 300 parts of a mixture of equal parts of dioxane and ethanol and hydrogenated at room temperature under 10 atmospheres pressure using 0.25 part of platinum oxide as catalyst. When reduction is complete the catalyst is filtered off, the product is recovered by evaporation of the filtrate and is crystallised from aqueous ethanol. There is thus obtained 3-(3-phenylpropoxy)acetanilide, M.P. 120° C. 14.2 parts of this latter compound are heated under reflux for 6 hours with 33 parts of potassium hydroxide in a mixture of 16 parts of water and 160 parts of ethanol. The solution is then cooled and evaporated under reduced pressure, and the residue is partitioned between water and ether. The ethereal layer is separated, washed with saturated sodium chloride solution, dried and evaporated. There is thus obtained 3-(3-phenylpropoxy)aniline as an oil.

EXAMPLE 15

8.5 parts of 3-(4-methylbenzyloxy)aniline and 7 parts of dimethyl methoxymethylenemalonate are heated at 100° C. for 3 hours, and the crude dimethyl 3-(4-methylbenzyloxy anilinomethylenemalonate so obtained is added to 80 parts of boiling diphenyl ether. The mixture is heated under reflux for 20 minutes, cooled, and diluted with 100 parts of petroleum ether (B.P. 60–80° C.). The solid which separates is filtered off, and boiled with methanol and then crystallised from dimethylformamide. There is thus obtained methyl 4-hydroxy-7-(4-methylbenzyloxy)quinoline-3-carboxylate, M.P. 254° C.

The 3-(4-methylbenzyloxy)aniline used as starting material may be prepared as follows:

A mixture of 15 parts of 3-acetylaminophenol, 19 parts of 4-methylbenzylbromide, 30 parts of potassium carbonate and 100 parts of acetone is heated under reflux for 24 hours. The filtered solution is evaporated and the residue dissolved in chloroform. The solution is washed with dilute sodium hydroxide solution and saturated sodium chloride solution. Evaporation of the dried chloroform solution gives the solid product, 3-(4-methylbenzyloxy)acetanilide. 25.3 parts of this latter compound are heated under reflux for 6 hours with 40 parts of potassium hydroxide in a mixture of 20 parts of water and 250 parts of ethanol. The solution is evaporated under reduced pressure, and the residue is partitioned between chloroform and water. The chloroform layer is washed with dilute sodium hydroxide solution followed by saturated sodium chloride solution, dried and evaporated. There is thus obtained 3-(4-methylbenzyloxy)aniline as an oil.

EXAMPLE 16

1 part of 7-benzyloxy-4-hydroxyquinoline-3-carboxylic acid is heated under reflux with 1 part of concentrated sulphuric acid in 50 parts of absolute ethanol for 24 hours. The cooled solution is diluted with water and the separated solid is washed with alcohol and crystallised from dimethylformamide. There is thus obtained ethyl 7 - benzyloxy - 4-hydroxyquinoline-3-carboxylate, M.P. 295° C.

EXAMPLE 17

A mixture of 7.6 parts of 3-(4-chlorobenzyloxy)-4-n-propylaniline and 5.7 parts of dimethyl methoxymethylenemalonate is heated at 100° C. for 2 hours and then cooled. The crude dimethyl 3-(4-chlorobenzyloxy)-4-n-propylanilinomethylenemalonate so obtained is added to 48 parts of stirred, boiling "Dowtherm" A. ("Dowtherm" is a trademark). The solution is stirred and heated under reflux for 5 mins. and then cooled. The crystalline product which separates is filtered off, washed with methanol and recrystallised from dimethyl formamide. There is thus obtained methyl 7-(4-chlorobenzyloxy)-4-hydroxy-6-n-propylquinoline-3-carboxylate, M.P. 295° C.

The 3-(4-chlorobenzyloxy)-4-n-propylaniline may be obtained as follows:

A mixture of 7 parts of 4-n-propyl-3-hydroxyacetanilide, 6.6 parts of 4-chlorobenzyl chloride, 14 parts of potassium carbonate and 100 parts of acetone is stirred and heated under reflux for 18 hours. The reaction mixture is filtered hot, and the filtrate is evaporated to dryness in vacuo. The residue is recrystallised from ethanol. The 3-(4-chlorobenzyloxy)-4-n-propyl acetanilde so obtaned melts at 112° C. It s then heated under reflux for 6 hours with a solution of 19 parts of potassium hydroxide in 10 parts of water and 115 parts of ethyl alcohol. The solvent is evaporated, and the residue is partitioned between ether and water. The ethereal solution is washed with 10% sodium hydroxide solution, and then with saturated sodium chloride solution. It is dried over magnesium sulphate and evaporated to give 3-(4-chlorobenzyloxy)-4-n-propylaniline as an oil.

The first part of the above process is repeated except that the 5.7 parts of dimethyl methoxymethylenemalonate are replaced by 5.9 parts of diethyl ethoxymethylenemalonate. There is thus obtained ethyl 7-(4-chlorobenzyloxy) 4-hydroxy-6-n-propylquinoline-3-carboxylate, M.P. 299–301° C.

EXAMPLE 18

A mixture of 5.1 parts of 3-(4-methylphenoxy)-aniline and 6.4 parts of diethyl ethoxymethylenemalonate is heated at 100° C. for 2 hours and then cooled. The crude diethyl 3 - (4 - methylphenoxy)anilinomethylenemalonate so obtained is added to 40 parts of stirred, boiling "Dowtherm" A ("Dowtherm" is a trademark). The solution is stirred and boiled for 15 mins. and then cooled. The product is filtered off, washed with ethanol and recrystallised from dimethyl formamide. There is thus obtained ethyl 4 - hydroxy - 7 - (4 - methylphenoxy)quinoline - 3 - carboxylate, M.P. 260° C.

The 3-(4-methylphenoxy)aniline may be obtained as follows:

42 parts of p-cresol are dissolved in a solution of 8.7 parts of potassium hydroxide in 65 parts of ethanol. The solvent is evaporated in vacuo, and to the residue is added 25 parts of m-bromoaniline and 0.4 part of copper bronze. The reaction mixture is stirred and heated under reflux in an oil bath at 180°–190° C. for 2 hours, cooled and partitioned between 10% aqueous potassium hydroxide

solution and chloroform. The chloroform solution is washed with 10% potassium hydroxide solution and then with saturated sodium chloride solution, dried over magnesium sulphate and evaporated to dryness. There is thus obtained 3-(4-methylphenoxy)aniline B.P. 149° C./1.0 mm.

EXAMPLE 19

The procedure described in Example 17 is repeated except that the 7.6 parts of 3-(4-chlorobenzyloxy)-4-n-propylaniline are replaced by 7.6 parts of 3-(2-chlorobenzyloxy)-4-n-propylaniline. There is thus obtained methyl 7 - (2 - chlorobenzyloxy) - 4 - hydroxy - 6 - n - propylquinoline-3-carboxylate, M.P. 283° C.

The 3-(2-chlorobenzyloxy)-4-n-propylaniline used as starting material may be obtained by repeating the second part of Example 17 except that the 6.6 parts of 4-chlorobenzyl chloride are replaced by 6.6 parts of 2-chlorobenzyl chloride. There is thus obtained 3-(2-chlorobenzyloxy)-4-n-propylaniline, M.P. 46° C.

EXAMPLE 20

The procedure described in Example 17 is repeated except that the 7.6 parts of 3-(4-chlorobenzyloxy)-4-n-propylaniline are replaced by 8.5 parts of 3-(2,4-dichlorobenzyloxy)-4-n-propylaniline or 5.3 parts of 3-phenoxyaniline. There is thus obtained methyl 7-(2,4-dichlorobenzyloxy)-4-n-propylaniline, 8.8 parts of 3-dodecyloxy-4-n-propylaniline or 5.3 parts of 3-phenoxyaniline. There is thus obtained methyl 7 - (2,4 - dichlorobenzyloxy)-4-hydroxy-6-n-propylquinoline-3-carboxylate, M.P. 299° C., methyl 7-dodecyloxy - 4 - hydroxy-6-n-propylquinoline-3-carboxylate, M.P. 256° C. or methyl 4 - hydroxy-7-phenoxyquinoline-3-carboxylate, M.P. 269° C. respectively.

The starting materials used in the above procedure may be obtained by repeating the second part of Example 17 except that the 6.6 parts of 4-chlorobenzyl chloride are replaced by 8 parts of 2,4-dichlorobenzyl chloride or 9.8 parts of dodecyl bromide. There is thus obtained 3-(2,4 - dichlorobenzyloxy) - 4 - n - propylaniline or 3 - dodecycloxy-4-propylaniline respectively as oils.

EXAMPLE 21

The process of Example 18 is repeated except that the 5.1 parts of 3-(4-methylphenoxy)aniline are replaced by 5.1 parts of 3-(2-methylphenoxy)aniline. There is thus obtained ethyl 4-hydroxy-7-(2-methylphenoxy)quinoline-3-carboxylate, M.P. 259° C.

The 3-(2-methylphenoxy)aniline, B.P. 126–136° C./0.6 mm. may be obtained by repeating the process described in the second part of Example 18 except that the 42 parts of p-cresol are replaced by 42 parts of o-cresol.

EXAMPLE 22

A mixture of 5.4 parts of 3-benzyloxy-4-n-hexyl aniline and 4.4 parts of diethyl ethoxymethylenemalonate are heated at 100° C. for 1 hour and the crude diethyl 3-benzyloxy-4-n-hexylanilinomethylenemalonate so obtained is added in one portion to 10 parts of stirred, boiling diphenyl ether. The mixture is stirred and heated under reflux for 5 minutes, and then cooled. The solid product is filtered off, washed with carbon tetrachloride, and recrystallised from dimethylformamide. There is thus obtained ethyl 7-benzyloxy-4-hydroxy-6-n-hexylquinoline-3-carboxylate, M.P. 283–285° C.

The 3-benzyloxy-4-n-hexylaniline used as starting material may be obtained as follows:

A mixture of 17 parts of 3-hydroxy-4-n-hexylacetanilide, 9 parts of benzyl chloride, 15 parts of potassium carbonate and 300 parts of acetone is heated under reflux for 24 hours. The mixture is cooled and filtered, and the filtrate evaporated under reduced pressure. The residue is recrystallised from methylene chloride-petroleum ether (B.P. 40–60° C.). There is thus obtained 3-benzyloxy-4-n-hexylacetanilide, M.P. 90–92° C. 21 parts of this latter compound are heated under reflux for 12 hours with 63 parts of potassium hydroxide in a mixture of 40 parts of water and 300 parts of ethanol. The solution is then cooled, and evaporated under reduced pressure, and the residue is partitioned between water and ether. The ethereal layer is separated, washed with saturated sodium chloride solution, dried and evaporated. There is thus obtained 3-benzyloxy-4-n-hexylaniline as an oil.

EXAMPLE 23

The proceduce described in Example 22 is repeated except that the 5.4 parts of 3-benzyloxy-4-n-hexylaniline are replaced by 4.4 parts of 3-benzyloxy-4-methylaniline, 6.1 parts of 3-benzyloxy-4-n-butylaniline, or 5.8 parts of 3-benzyloxy-4-n-octylaniline. There is thus obtained ethyl 7-benzyloxy-4-hydroxy-6-methylquinoline-3 - carboxylate, M.P. 321–323° C., ethyl 7-benzyloxy-6-n-butyl-4-hydroxyquinoline-3-carboxylate, M.P. 297–298° C., or ethyl 7-benzyloxy-4-hydroxy-6-n-octylquinoline - 3 - carboxylate, M.P. 261–262° C. respectively.

The 3-benzyloxy - 4 - alkylaniline derivatives used as starting materials may be obtained by repeating the process described in the second part of Example 22, except that the 17 parts of 3-hydroxy-4-n-hexylacetanilide are replaced by the equivalent amount of the corresponding 3-hydroxy-4-alkylacetanilide derivative.

EXAMPLE 24

The procedure described in Example 22 is repeated except that the 4.4 parts of diethyl ethoxymethylenemalonate are replaced by 2.6 parts of dimethyl methoxymethylenemalonate. There is thus obtained methyl 7-benzyloxy-4-hydroxy-6-n-hexylquinoline-3 - carboxylate, M.P. 278–280° C.

EXAMPLE 25

The procedure described in Example 24 is repeated except that the 5.4 parts of 3-benzyloxy-4-n-hexylaniline are replaced by 2.6 parts of 3-benzyloxy-4-methylaniline, 3.4 parts of 3-benzyloxy-4-ethylaniline, 4.1 parts of 3-benzyloxy-4-n-butylaniline, 3.7 parts of 3-benzyloxy-4-isobutylaniline or 4.6 parts of 3-benzyloxy-4-n-octylaniline. There is thus obtained methyl 7-benzyloxy-4-hydroxy-6-methylquinoline-3-carboxylate, M.P. 307–309° C., methyl 7-benzyloxy-6-ethyl-4-hydroxyquinoline - 3 - carboxylate, M.P. 269–270° C., methyl 7-benzyloxy-6-n-butyl-4-hydroxyquinoline-3-carboxylate, M.P. 287–288° C., methyl 7-benzyloxy-4-hydroxy - 6 - isobutylquinoline-3-carboxylate, M.P. 288° C., methyl 7-benzyloxy-4-hydroxy-6-n-octylquinoline-3-carboxylate, M.P. 278–280° C.

The starting materials may be prepared as indicated in Example 23, or by analogous means.

EXAMPLE 26

3.7 parts of 3-benzyloxy-4-methoxyaniline and 3.0 parts of dimethyl methoxymethylenemalonate are heated at 100° C. for 3 hours and the crude dimethyl 3-benzyloxy-4-methoxyanilinomethylenemalonate so obtained is added carefully to 21 parts of stirred, boiling diphenylether. The mixture is stirred and heated under reflux for 3 minutes and then cooled rapidly. The solid product is filtered, washed with petroleum ether (B.P. 40–60° C.) and crystallised from dimethylformamide. There is thus obtained methyl 7-benzyloxy-4-hydroxy-6-methoxyquinoline-3-carboxylate, M.P. 287–288° C.

EXAMPLE 27

7.7 parts of dimethyl 3-benzyloxy-4-ethoxyanilinomethylenemalonate are added carefully to 30 parts of stirred, boiling diphenyl ether. The mixture is stirred and heated under reflux for 3 minutes and then cooled rapidly. The solid product is filtered, washed with petroleum ether (B.P. 40–60° C.) and crystallised from dimethylformamide. There is thus obtained methyl 7-benzyloxy-4-hydroxy-6-ethoxyquinoline-3-carboxylate, M.P. 281–282° C.

The dimethyl 3-benzyloxy-4 - ethoxyanilinomethylenemalonate used as starting material may be obtained as follows:

A mixture of 6.1 parts of 3-benzyloxy-4-ethoxyaniline and 4.4 parts of dimethyl methoxymethylenemalonate is heated at 100° C. for 2.5 hours and is allowed to cool overnight. The solid reaction product is washed with petroleum ether (B.P. 40–60° C.) and crystallised from methanol. There is thus obtained dimethyl 3-benzyloxy-4-ethoxyanilinomethylenemalonate, M.P. 95–96° C.

The 3-benzyloxy - 4 - ethoxyaniline may be obtained as follows:

A solution of 30 parts of sodium sulphide in 55 parts of water is added to a solution of 10.5 parts of 3-benzyloxy-4-ethoxynitrobenzene in 140 parts of ethanol, and the mixture is stirred and heated under reflux for 16 hours. Ethanol is removed by distillation, and the residue extracted with ether. The ethereal extracts are dried, filtered, and evaporated to give 3-benzyloxy-4-ethoxyaniline as an oil.

The 3-benzyloxy-4 - ethoxynitrobenzene may be obtained as follows:

A mixture of 11 parts of 2-benzyloxy-4-nitrophenol, 57 parts of ethyl chloride, 6.2 parts of anhydrous potassium carbonate, and 50 parts of dry acetone are stirred and heated under reflux for 48 hours. The hot mixture is filtered, and the filtrate is evaporated. The residue is washed with water and crystallised from ethanol. There is thus obtained 3-benzyloxy-4-ethoxynitrobenzene, M.P. 101–102° C.

The whole of the above process is repeated except that the 4.4 parts of dimethyl methoxymethylenemalonate are replaced by 5.4 parts of diethyl ethoxymethylenemalonate. There is thus obtained ethyl 7-benzyloxy-6-ethoxy-4-hydroxyquinoline - 3 - carboxylate, M.P. 289–290° C.

EXAMPLE 28

20 parts of diethyl 3-benzyloxy-4-n-propoxyanilinomethylenemalonate are added carefully to 80 parts of stirred, boiling diphenyl ether. The mixture is stirred and heated under reflux for 11 minutes and then cooled rapidly. The solid product is filtered, washed with petroleum ether (B.P. 40–60° C.), and crystallised from dimethylformamide. There is thus obtained ethyl 7-benzyloxy-4-hydroxy - 6 - n - propoxyquinoline-3-carboxylate, M.P. 278–279° C. with decomposition.

The diethyl 3-benzyloxy-4-n-propoxyanilinomethylenemalonate may be obtained as follows:

A mixture of 14 parts of 3-benzyloxy-4-n-propoxyaniline and 11.8 parts of diethyl ethoxymethylenemalonate is heated at 100° C. for 2 hours and then cooled. There is thus obtained diethyl 3 - benzyloxy-4-n-propoxyanilinomethylenemalonate as an oil.

The 3 - benzyloxy - 4 - n - propoxyaniline may be obtained by repeating the procedure described in Example 27 for the preparation of 3-benzyloxy-4-ethoxyaniline except that the 10.5 parts of 3-benzyloxy-4-ethoxynitrobenzene are replaced by 11.1 parts of 3-benzyloxy-4-n-propoxynitrobenzene. There is thus obtained 3-benzyloxy-4-n-propoxyaniline as an oil.

The 3-benzyloxy-4 - n - propoxynitrobenzene may be obtained by repeating the procedure described in Example 27 for the preparation of 3-benzyloxy-4-ethoxynitrobenzene except that the 57 parts of ethyl chloride are replaced by 52 parts of n-propyl iodide. There is thus obtained 3-benzyloxy-4-n-propoxynitrobenzene, M.P. 73–74° C.

EXAMPLE 29

The procedure described in Example 28 is repeated except that the 20 parts of diethyl 3-benzyloxy-4-n-propoxyanilinomethylenemalonate are replaced by 20 parts of dimethyl 3-benzyloxy-4-n-propoxyanilinomethylenemalonate. There is thus obtained methyl 7-benzyloxy-4-hydroxy-6-n-propoxyquinoline-3-carboxylate, M.P. 266–267° C.

The dimethyl 3-benzyloxy-4-n-propoxyanilinomethylenemalonate may be obtained as follows:

A mixture of 9.3 parts of 3-benzyloxy-4-n-propoxyaniline and 63 parts of dimethyl methoxymethylenemalonate is heated at 100° C. for 2 hours. There is thus obtained 3-benzyloxy - 4 - n - propoxyanilinomethylenemalonate as an oil.

EXAMPLE 30

14.5 parts of ethyl 7-benzyloxy-4-hydroxyquinoline-3-carboxylate are dissolved in 2200 parts of dry dimethylformamide. 20 parts of N-chlorosuccinimide are added, and the mixture is heated at 100° C. for 10 hours and then allowed to cool. The solid product which crystallised out is filtered off, and recrystallised from dimethylformamide. There is thus obtained ethyl 7-benzyloxy-4-hydroxy-6 - chloroquinoline-3 - carboxylate, M.P. 295–297° C.

EXAMPLE 31

15 parts of ethyl 7-benzyloxy-4-hydroxyquinoline-3-carboxylate are dissolved in 2400 parts of dry dimethylformamide. 40.5 parts of N-chlorosuccinimide are added, and the mixture is heated at 100° C. for 6½ hours. The dimethylformamide is removed by distillation, and the residue extracted with 400 parts of boiling ethanol and filtered rapidly. The separated solid is crystallised from dimethylformamide. There is thus obtained ethyl 7-benzyloxy-4-hydroxy - 6,8 - dichloroquinoline - 3 - carboxylate, M.P. 285–287° C.

EXAMPLE 32

14.6 parts of 3-n-tetradecyloxyaniline and 6.6 parts of dimethyl methoxymethylenemalonate are heated at 100° C. for 2 hours and the crude dimethyl 3-n-tetradecyloxyanilinomethylenemalonate so obtained is added to 100 parts of boiling diphenyl ether. The mixture is heated under reflux for 30 minutes and then cooled. The solid product is filtered off, washed with carbon tetrachloride, and crystallised from dimethylformamide. There is thus obtained methyl 7-n-tetradecyloxy - 4 - hydroxyquinoline-3-carboxylate, M.P. 244–246° C.

EXAMPLE 33

The process of Example 32 is repeated except that the 6.6 parts of dimethyl methoxymethylenemalonate are replaced by 10 parts of diethyl ethoxymethylenemalonate. There is thus obtained ethyl 7-n-tetradecyloxy-4-hydroxyquinoline-3-carboxylate, M.P. 243–245° C.

EXAMPLE 34

The procedure described in Example 26 is repeated except that the 3.7 parts of 3-benzyloxy-4-methoxyaniline are replaced by 4.4 parts of 3-benzyloxy-4-isopropoxyaniline. There is thus obtained methyl 7-benzyloxy-4-hydroxy-6-isopropoxyquinoline-3-carboxylate, M.P. 262–263° C.

The 3-benzyloxy-4-isopropoxyaniline used as starting material may be obtained as follows:

The procedure described in Example 28 for the preparation of 3-benzyloxy-4-n-propoxyaniline is repeated except that the 11.1 parts of 3-benzyloxy-4-n-propoxynitrobenzene are replaced by 11.1 parts of 3-benxyloxy-4-isopropoxynitrobenzene (M.P. 65–66° C.). There is thus obtained 3-benzyloxy-4-isopropoxyaniline as an oil.

EXAMPLE 35

11 parts of 3-(4-nitrobenzyloxy) aniline and 8.2 parts of dimethyl methoxymethylenemalonate are intimately mixed and heated at 100° C. for 2 hours. The product is cooled and crystallised from dimethylformamide to give dimethyl 3 - (4 - nitrobenzyloxy)anilinomethylenemalonate, M.P.

144° C. 6 parts of the latter compound are added to 107 parts of boiling diphenyl ether, and the mixture is heated under reflux for 15 minutes, cooled and filtered. The residue is washed with petroleum ether (B.P. 60–80° C.), and crystallised from dimethylformamide. There is thus obtained methyl 4-hydroxy-7-(4-nitrobenzyloxy)-quinoline-3-carboxylate, M.P. 300° C.

The 3-(4-nitrobenzyloxy)aniline used as starting material may be obtained as follows:

A mixture of 17.2 parts of 4-nitrobenzyl chloride, 15.1 parts of 3-hydroxyacetanilide, 15.2 parts of potassium carbonate and 110 parts of acetone is heated under reflux for 18 hours. The mixture is filtered and the filtrate is evaporated under reduced pressure. The residue is crystallised from ethanol to give 3-(4-nitrobenzyloxy)acetanilide, M.P. 158° C. 2 parts of the latter compound are refluxed for 1½ hours in a mixture of 8 parts of concentrated hydrochloric acid and 8 parts of water. The cooled solution is made alkaline with concentrated ammonia and then filtered. The residue is crystallised from ethanol to give 3-(4-nitrobenzyloxy)aniline, M.P. 114° C.

EXAMPLE 36

9 parts of N-chlorosuccinimide are added to a solution of 3.3 parts of methyl 7-(2,4-dichlorobenzyloxy)-4-hydroxy-6-n-propylquinoline-3-carboxylate in 1500 parts of dry dimethylformamide, and the mixture is heated at 100° C. for 12 hours. The mixture is cooled and evaporated, and the residue is crystallised from ethanol. There is thus obtained methyl 8-chloro-7-(2,4-dichlorobenzyloxy)-6-n-propylquinoline-3-carboxylate, M.P. 309–311° C.

EXAMPLE 37

10 parts of ethyl 7-benzyloxy-4-hydroxy-quinoline-3-carboxylate and 90 parts of whole ground corn are thoroughly mixed in a blending machine. There is thus obtained a concentrated food pre-mix which may be mixed in suitable proportions with an animal foodstuff, and the medicated foodstuff so obtained can be fed to poultry for the prophylactic control of coccidiosis.

The above process is repeated except that the whole ground corn is replaced by corn distillers dry grain, wheat shorts, corn cob meal, fuller's earth, calcium carbonate, attapulgus clay or ground oyster shells. There are likewise obtained concentrated food pre-mixes which can be added in suitable proportions to animal foodstuffs thereby providing medicated foodstuffs which can be fed to poultry for the prophylactic control of coccidiosis.

EXAMPLE 38

1 part of a concentrated food pre-mix, obtained as described in Example 37, is uniformly dispersed in 2000 parts of a commercial poultry starting mash. There is thus obtained a medicated foodstuff suitable for feeding to poultry for the prophylactic control of coccidiosis.

EXAMPLE 39

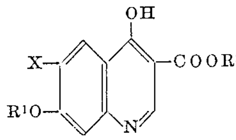
The procedures described in Example 37 are repeated except that the 10 parts of ethyl 7-benzyloxy-4-hydroxy-quinoline-3-carboxylate are replaced by 1 part of methyl 7 benzyloxy-4-hydroxy-6-n-propylquinoline-3-carboxylate. There are thus obtained concentrated food pre-mixes which can be added in suitable proportions to animal foodstuffs thereby providing medicated foodstuffs which can be fed to poultry for the prophylactic control of coccidiosis.

EXAMPLE 40

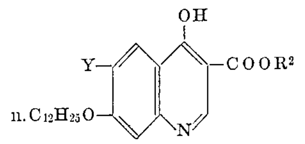
1 part of a concentrated food pre-mix, obtained as described in Example 39, is uniformly dispersed in 2000 parts of a commercial poultry starting mash. There is thus obtained a medicated foodstuff suitable for feeding to poultry for the prophylactic control of coccidiosis.

What we claim is:

1. A veterinary composition comprising, as the essential active component, an effective amount of a quinoline-3-carboxylic ester selecter from the group consisting of compounds of the formula:



wherein R¹ is selected from the group consisting of benzyl and chlorobenzyl, R² is alkyl of 1–4 carbon atoms, and X is selected from the group consisting of hydrogen, alkyl of 1–6 carbon atoms, alkenyl of up to 4 carbon atoms and alkoxy of 1–4 carbon atoms, and compounds of the formula:



wherein R² has the meaning stated above and Y is selected from the group consisting of hydrogen and alkyl of 1–4 carbon atoms, in admixture with a major amount of a non-toxic veterinary carrier therefor.

2. A composition as claimed in claim **1** wherein the quinoline-3-carboxylic ester is methyl 7-benzyloxy-6-n-butyl-4-hydroxyquinoline-3-carboxylate.

3. A composition according to claim **1** which is in the form of a concentrated food pre-mix.

4. A composition according to claim **1** which is in the form of a medicated foodstuff.

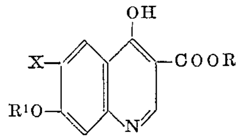
5. A pre-mix as claimed in claim **3** wherein the quinoline-3-carboxylic ester is present to the extent of between 0.1% and 25% by weight.

6. A pre-mix as claimed in claim **5** wherein the quinoline-3-carboxylic ester is present to the extent of between 0.2% and 2% by weight.

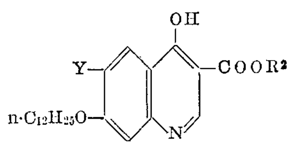
7. A medicated foodstuff as claimed in claim **4** wherein the quinoline-3-carboxylic ester is present to the extent of between 0.00005% and 0.1% by weight.

8. A medicated foodstuff as claimed in claim **7** wherein the quinoline-3-carboxylic ester is present to the extent of between 0.0001% and 0.001% by weight.

9. A method for the prophylactic treatment of coccidiosis in poultry or other domestic animals which comprises administering thereto an effective amount of a quinoline-3-carboxylic ester of the formula:



wherein R¹ is selected from the group consisting of benzyl and chlorobenyl, R² is alkyl of 1–4 carbon atoms, and X is selected from the group consisting of hydrogen, alkyl of 1–6 carbon atoms, alkenyl of up to 4 carbon atoms and alkoxy of 1–4 carbon atoms, and compounds of the formula:



wherein R² has the meaning stated above and Y is selected from the group consisting of hydrogen and alkyl of 1–4 carbon atoms.

10. A method as claimed in claim **9** wherein the quinoline-3-carboxylic ester is methyl 7-benzyloxy-6-n-butyl-4-hydroxyquinoline-3-carboxylate.

11. A method according to claim **9** wherein the quinoline-3-carboxylic ester is administered in the form of a medicated foodstuff.

12. A method as claimed in claim **11** wherein the medicated foodstuff contains between 0.00005% and 0.1% by weight of the quinoline-3-carboxylic ester.

13. A method as claimed in claim **12** wherein the medicated foodstuff contains between 0.00001% and 0.001% by weight of the quinoline-3-carboxylic ester.

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