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AMENDED SPECIFICATION

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PATENT SPECIFICATION

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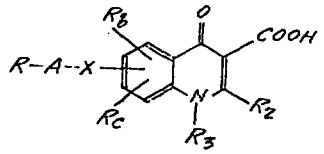
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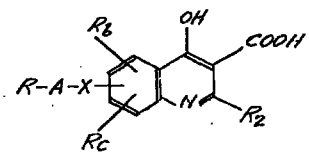
(54) 3-QUINOLINE-CARBOXYLIC ACID COMPOUNDS, PROCESS FOR THEIR MANUFACTURE AND COMPOSITIONS CONTAINING THEM

(71) We, CIBA-GEIGY AG, formerly Ciba Limited, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, 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:

Patent Specification No. 1,205,638 describes *benz*-cycloaliphatyloxy- or *benz*-cycloaliphatylthio-3-quinoline-carboxylic acids having the formula



and the corresponding 3-esters, 3-amides- 3-hydrazides and 3-nitriles, in which R stands for a cycloalkyl or cycloalkenyl radical or such radical substituted by aliphatic, aromatic or araliphatic hydrocarbon residues, or by etherified or esterified hydroxyl groups, A is a direct bond or a lower alkylene group, X is oxygen or sulfur, R_2 represents hydrogen or a lower alkyl group, and R_3 represents hydrogen, a lower alkyl, lower alkenyl, free, esterified or etherified hydroxyl-lower alkyl group, a free or esterified carboxy-lower alkyl group, an amino-lower alkyl group, an aryl-lower alkyl group or a radical having the meaning given to the group R—A—, and each of the groups R_b and R_c stands for hydrogen, a lower alkyl group, a free, etherified or esterified hydroxy or mercapto group, a trifluoromethyl group, a nitro group, an amino group, or an aryl-lower alkyl group, or the tautomers thereof having the formula



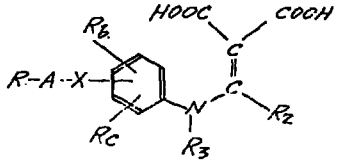
or 3-esters, 3-amides- 3-hydrazides or 3

nitriles thereof, or 4-esters of such compounds with a lower alkanoic acid as well as salts of these compounds.

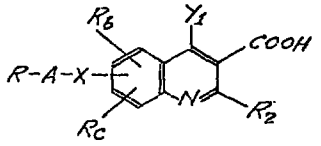
In these compounds the aromatic carbocyclic portion of the quinoline nucleus, i.e. the 1,2-phenylene group, may contain, in addition to the cycloaliphatyloxy or cycloaliphatylthio group of the formula —X—A—R, one or two, substituents, R_b and R_c that may be lower alkyl groups, free hydroxy or mercapto groups, etherified hydroxy or mercapto groups, for example, lower alkoxy, halogeno-lower alkoxy, aryloxy or aryl-lower alkoxy groups, or lower alkylmercapto halogeno-lower alkylmercapto, arylmercapto or aryl-lower alkylmercapto groups, or etherified hydroxy or mercapto groups having the formula —X—A—R, in which X, A and R have the previously given meanings, esterified hydroxy groups, for example halogen atoms, esterified mercapto groups, trifluoromethyl groups, nitro groups, amino groups, advantageously di-lower alkyl-amino groups or aryl-lower alkyl groups.

These compounds exhibit growth promoting effects, which can be demonstrated, for example by feeding a feed containing from 0.0001% to 0.1% of the above compounds to chickens during part or during the whole span of their lives. These growth promoting effects can even be shown in diseased animals, for example, in poultry infected by bacteria and protozoa, particularly by parasites causing coccidiosis, for example *Eimeria tenella, Eimeria acervulina, Eimeria adenoides, Eimeria agridis, Eimeria brunetti, Eimeria hagani, Eimeria maxima* or *Eimeria necatrix*. The coccidiostatic effects can be demonstrated, for example, by feeding the above feedstuffs to chickens 1 to 2 days prior to or then after their inoculation with sporulated oocysts of *Eimeria* strains. They are, therefore, useful as growth promoting agents, particularly in poultry, even in animals, especially in poultry which are diseased with bacteria or protozoa infections, especially with coccidiosis-producing parasite infections.

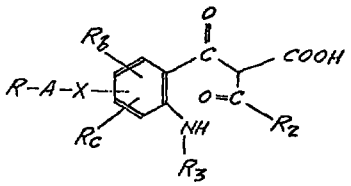
The compounds are prepared according to known methods, for example, by a) ring-closing a di-lower alkyl ester or a nitrile-lower alkyl-halfester (described and claimed in our Patent Specification No. 1,205,639) of a compound of the formula



in which one of the positions of the phenyl nucleus adjacent to the amino group is unsubstituted, or a tautomer of such compound, in which the amino group contains a hydrogen atom, by intramolecular condensation, or b) converting in a compound of the formula

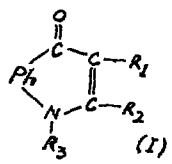


in which Y_1 is a halogen atom, or in a 3-ester, 3-amide, 3-hydrazide or 3-nitrile thereof, the group Y_1 into the hydroxyl group by hydrolysis, or c) ring-closing a compound of the formula



or a 3-ester, 3-amide, 3-hydrazide or 3-nitrile thereof, by intramolecular condensation, and, if desired, hydrolyzing a resulting ester or esterifying a resulting free acid, and/or, if desired, substituting the 1-position in a resulting compound having an unsubstituted 1-position.

It has new been found, that 4-hydroxy-3-quinoline carboxylic acids, which in addition to a cycloaliphatyloxy or cycloaliphatylmercapto group contain in the aromatic carbocyclic portion of the quinoline nucleus a higher aliphatyloxy or aliphatylmercapto group, as well as their 1-unsubstituted tautomers, or esters, amides, hydrazides or nitriles of such compounds or tautomers as well as salts thereof, particularly compounds of the formula (I)



(I)

in which Pn is a 1,2-phenylene residue substituted by a group of the formula $—X^I—A—R^I$ and a group of the formula $—X_{II}—R^{II}$, in which R^I is a cycloaliphatic radical, A represents a direct bond between X_I and R^I or a bivalent aliphatic radical, R^{II} is a higher aliphatic residue and each of X_I and X_{II} is oxygen or sulfur, R_1 represents a carboxy, an esterified carboxy, a carbamyl, a hydrazinecarbonyl or a cyano group. R_2 stands for a hydrogen atom or a lower alkyl group, and R_3 is a hydrogen atom of an optionally substituted aliphatic or cycloaliphatic hydro-

carbon radical, or a tautomer of such a compound in which R_3 represents a hydrogen atom, or a 4-O-ester of such a tautomer or a salt of such a compound of formula I, exhibit at doses of 0.0001% to 0.1% in the feed or in drinking water outstanding growth promoting effects, particularly in poultry infected by bacteria and protozoa particularly by parasites causing coccidiosis, for example *Eimeria tenella, Eimeria acervulina, Eimeria adenoides, Eimeria agridis, Eimeria brunetti, Eimeria hagani, Eimeria maxima* or *Eimeria necatrix.* Any coccidistatic effects can be demonstrated as described above.

The compounds of this invention are, therefore, useful as growth promoting agents, particularly in poultry and especially in animals, which are diseased with bacteria or protozo infections, especially with coccidiosis-producing parasites infections. They are also useful as intermediates in the manufacture of other valuable products.

In the present specification, unless otherwise specified, the term "lower" denotes an organic group, radical or compound as having up to 7, preferably up to 4, carbon atoms, whereas the term "higher" denotes an organic group, radical or compound as having from 8 to 20, preferably from 8 to 16, carbon atoms.

A cycloaliphatic residue R^I is primarily a cycloaliphatic hydrocarbon radical which may be mono-, di- or poly-substituted, for example, by an optionally substituted aliphatic, aromatic or araliphatic hydrocarbon residue, particularly by a lower alkyl group and/or by a free, etherified or esterified hydroxy group (for example a halogen atom), especially a cycloalkyl radical containing preferably 3 to 8 ring-carbon atoms, which may be substituted by one or more lower alkyl groups and/or halogen atoms, primarily a cycloalkyl radical with 3 to 6 ring-carbon atoms, which may be substituted by up to 4 lower alkyl groups. These radicals are, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl radicals, or corresponding cycloalkyl radicals mono-, di- or poly-substituted by optionally substituted aliphatic, aromatic or araliphatic hydrocarbon, for example lower alkyl, e.g. methyl or ethyl groups, as well as by free, etherified or esterified hydroxy groups, particularly halogen atoms.

An optionally substituted aliphatic hydrocarbon residue is primarily a lower alkyl, e.g. methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec.*-butyl, *tert.*-butyl, *n*-pentyl, isopentyl, *n*-hexyl, isohexyl, *n*-heptyl or isoheptyl group. An optionally substituted aromatic or araliphatic hydrocarbon residue is, for example, an R_3-phenyl residue or an R_3-phenyl-lower alkyl, e.g. R_3-benzyl, group, in which R_3 stands for hydrogen, lower alkyl (for example one of the groups mentioned above), lower alkoxy (e.g. methoxy, ethoxy, *n*-propyloxy, isopropyloxy, *n*-butyloxy or isobutyloxy), trifluoromethyl, nitro, di-lower alkylamino (e.g. dimethylamino or diethylamino), or halogeno (e.g. fluoro, chloro or bromo). An etherified hydroxy group is, for example, a lower alkoxy group, for example the groups mentioned above, as well as an aryloxy or aryl-lower alkoxy, e.g. R_3-phenyloxy or R_3-phenyl-lower alkoxy, for example R_3-benzyloxy, group, in which R_3 has the previously given meaning whereas an esterified hydroxy group is, for example, a hydroxy group esterified by an organic carboxylic acid, for example a lower alkanoyloxy, e.g. acetyloxy or propionyloxy, group, or primarily a halogen, e.g. fluorine or chlorine, atom.

Other cycloaliphatic hydrocarbon radicals R^I are cycloalkenyl radicals containing at most 2 double bonds and preferably 3 to 8 ring-carbon atoms, which may be substituted as the above cycloalkyl radicals, for example, by optionally substituted aliphatic, aromatic or araliphatic hydrocarbon residues, for example lower alkyl groups, as well as by free, etherified or esterified hydroxy groups, particularly halogen atoms, primarily cycloalkenyl groups with 5 to 6 ring-carbon atoms, which may be substituted by up to 4 lower alkyl groups. These radicals are, for example, 1-, 2- or 3-cyclopentenyl, 2,4-cyclopentadienyl, 1-, 2- or 3-cyclohexenyl or 2,5-cyclohexadienyl, as well as 2-cyclopropenyl, 1-, 2- or 3-cycloheptenyl, 2,6-cycloheptadienyl, or 2-cyclooctenyl radicals or corresponding cycloalkenyl radicals mono-, di- or poly-substituted by optionally substituted aliphatic, aromatic or araliphatic hydrocarbon residues, for example lower alkyl, e.g. methyl, groups, and/or by free, etherified or esterified hydroxy groups, particularly halogen atoms.

A bivalent aliphatic residue A is a bivalent aliphatic hydrocarbon radical, primarily a lower alkylene radical, which has preferably up to 4 carbon atoms and may be mono-, di- or polysubstituted by optionally substituted aliphatic, aromatic or araliphatic hydrocarbon residues, for example lower alkyl groups, and/or by free, etherified or esterified hydroxy groups, particularly halogen atoms. It represents primarily a methylene group, but may also stand for a 1,1- or 1,2-ethylene, 1,1-, 1,2-, 2,2- or 1,3-propylene, 2-methyl-1,3- or 1,4-butylene radical.

A higher aliphatic residue R^{II} is above all a higher aliphatic hydrocarbon residue, which may be substituted, for example, as the above cycloaliphatic hydrocarbon residue R^I, particularly a higher alkyl, as well as a higher alkenyl residue, which contains 8 to 20, particularly 8 to 16 carbon atoms. It may be straight or branched and may be linked with the oxygen or sulfur X_2 through any carbon atom. Higher alkyl residues of this type are, for example, 1- or 2-*n*-octyl, 1- or 2-*n*-nonyl,

1- or 2-*n*-decyl-, 1- or 2-*n*-undecyl-, 1- or 2-*n*-dodecyl, 1- or 2-*n*-tetradecyl, 1- or 2-*n*-hexadecyl, 1- or 2-*n*-octadecyl or 1- or 2-*n*-icosyl, as well as groups of this type substituted by lower alkyl, particularly methyl groups, for example 3,7-dimethyl-1-*n*-octyl, 3,7-dimethyl-3-*n*-octyl, 3,7,11-trimethyl-1-*n*-dodecyl or 3,7,11-trimethyl-3-*n*-dodecyl. Higher alkenyl residues are, for example, citronellyl, geranyl, neryl, linalyl, farnesyl, *n*-9-octadecenyl or phytyl residues.

In the compounds of the present invention, the cycloaliphatyloxy or cycloaliphatylmercapto group of the formula $—X_1—A—R^I$ and the higher aliphatyloxy- or aliphatylmercapto group of the formula $—X_2—R^{II}$ advantageously occupy the 6- or the 7-position of the quinoline nucleus, i.e. the 4- or the 5-position of the 1,2-phenylene residue Ph.

Apart from the cycloaliphatyloxy or cycloaliphatylmercapto group of the formula $—X_1—A—R^I$ and the higher aliphatyloxy or aliphatylmercapto group of the formula $—X_2—R^{II}$, the aromatic carbocyclic portion of the quinoline residue, i.e. the group Ph, may contain one or two additional substituents, for example lower alkyl, e.g. the previously mentioned groups, higher alkyl, e.g. the previously mentioned groups, lower alkenyl, e.g. allyl or methallyl groups, higher alkenyl, e.g. the previously mentioned groups, aryl-lower alkyl, for example R_a-phenyl-lower alkyl, e.g. benzyl or 1- or 2-phenylethyl groups, free hydroxy or mercapto groups, etherified hydroxy or mercapto groups, for example lower alkoxy, aryloxy or aryl-lower alkenyloxy, halogeno-lower alkoxy, aryloxy or aryl-lower alkoxy groups, or lower alkyl-mercapto, lower alkenyl-mercapto, halogeno-lower alkylmercapto, arylmercapto or aryl-lower alkylmercapto groups, e.g. the previously mentioned lower alkoxy groups; allyloxy or methallyloxy; 2-chloroethoxy or 3,3,3-trifluoropropyloxy; phenyloxy; benzyloxy or 1- or 2-phenylethoxy; methylmercapto or ethylmercapto; allylmercapto; 3-bromepropylmercapto; phenylmercapto, benzylmercapto or phenylethylmercapto groups, or etherified hydroxy or mercapto groups having the formulae $—X_1—A—R^I$ or $—X_2—R^{II}$, in which X_1, X_2, A, R^I and R^{II} have the previously given meanings but need not have the same meanings as the respective symbols in the formulae mentioned at the beginning of this paragraph, esterified hydroxy groups, for example halogen, e.g. fluorine, chlorine or bromine, atoms lower alkanoxyloxy, e.g. acetyloxy or propionyloxy groups, aryl-lower alkanoyloxy, for example R_a-phenyl-lower alkanoyloxy-, e.g. benzoyloxy or phenylacetyloxy, groups, esterified mercapto groups, trifluoromethyl groups, nitro groups, or amino groups, for example di-lower alkyl-amino, e.g. the previously mentioned di-lower alkyl-amino, groups, or lower alkanoylamino-, e.g. acetylamino or propionylamino, groups. In the above groups with a phenyl residue, the latter may represent, for example, an R_a-phenyl group, R_a have the previously given meaning.

The group R_1, apart from representing a free carboxyl group, is above all an esterified carboxyl group, in which the esterifying portion is preferably an optionally substituted aliphatic hydrocarbon residue, primarily a lower alkyl, e.g. methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl or isobutyl, group, as well as a higher alkyl, e.g. *n*-decyl, group, furthermore a lower or higher alkenyl group, or an optionally substituted araliphatic hydrocarbon residue, particularly an aryl-lower alkyl, for example an R_a-phenyl-lower alkyl, group, in which R_a has the previously given meaning, e.g. a benzyl or 1- or 2-phenylethyl group, which may be substituted in the phenyl nucleus as indicated, furthermore a carbamyl or hydrazinecarbonyl group, in which the nitrogen atoms may be optionally mono-, di- or polysubstituted by lower alkyl groups, as well as an aryl-lower alkyl, for example an R_a-phenyl-lower alkyl group mentioned above, or the cyano group.

The group R_2, apart from being primarily hydrogen, may also stand for lower alkyl, e.g. as defined above.

An aliphatic hydrocarbon radical represented by R_3, which primarily stands for hydrogen, is, for example, a lower alkyl group, as well as lower alkenyl, as defined above, whereas a cycloaliphatic radical R_3 may be one of the above defined cycloalkyl or cycloalkenyl groups represented by R^I. A substituted aliphatic hydrocarbon radical is, for example, a lower alkyl radical (as represented, for example, by the above lower alkylene group A) substituted, for example, by hydroxy groups, etherified hydroxy, for example lower alkoxy groups, esterified hydroxy groups, for example halogen atoms, free or esterified carboxyl groups, for example carbo-lower alkoxy, e.g. carbomethoxy or carbethoxy groups, amino groups, for example free amino groups, mono-lower alkylamino or di-lower alkylamino groups, e.g. methylamino, ethylamino, *n*-propylamino, dimethylamino or diethylamino, lower alkyleneamino, as well as mono-aza-, mono-oxa- or mono-thia-lower alkyleneamino groups, in which ring heteroatoms are separated from another by at least two carbon atoms, for example ethyleneamino, pyrrolidino, piperidino, piperazino, 4-methylpiperazino, 4-ethylpiperazino, morpholino or thiamorpholino groups, or cycloalkyl or cycloalkenyl groups, which may be optionally substituted, e.g. by lower alkyl groups and/or halogen atoms, for example those having the meaning given above for the corresponding group R^I, or aryl, for example phenyl, for example, R_a-phenyl, groups.

As indicated above, the present invention

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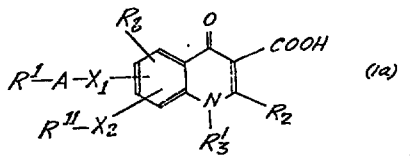
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also comprises the tautomers of the compounds of the above formula I in which R_3 is hydrogen, as well as 4-O-esters of such tautomers, in which the esterifying portion is preferably the acyl radical of an organic, particularly an aliphatic, as well as aromatic, carboxylic acid, primarily of a lower alkanoic, e.g. acetic, propionic or pivalic acid.

More especially, the present invention concerns compounds of the formula

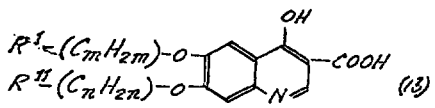


(Ia)

particularly the corresponding esters, as well as the corresponding amides, hydrazides and nitriles of such acids, in which R^I, A, X_1, X_2 and R_2 have the previously given meanings, R^I being primarily a cycloalkyl or cycloalkenyl radical, which may be optionally substituted, for example, as indicated above, primarily by lower alkyl groups and/or halogen atoms, R^{II} stands for a higher alkyl or a higher alkenyl group, R_3' is hydrogen, a lower alkyl or lower alkenyl group, a free, esterified or etherified hydroxy-lower alkyl group, a free or esterified carboxy-lower alkyl group, an amino-lower alkyl group, an aryl-lower alkyl group or a radical having the meaning given to the group R^I—A—, and R_5 stands for hydrogen, a lower alkyl or aryl-lower alkyl group, a free, etherified or esterified hydroxy or mercapto group, a trifluoromethyl group, a nitro group or an optionally substituted amino group, and the tautomers of such compounds in which R_3' stands for hydrogen, and 4-O-esters of such tautomers, as well as salts of such compounds.

Particularly useful properties of the above type are shown by the compounds of the formula Ia, in which R^I is a 3- to 8-membered $(R_4)_n$-cycloalkyl radical, A represents a direct bond or a lower alkylene radical, each of X_1 and X_2 stands for an oxygen atom, R^{II} is a higher alkyl group, R_5 is a hydrogen atom, a lower or higher alkyl group, a R_6-phenyl-lower alkyl group, a lower or higher alkoxy group, a halogeno-lower alkoxy group with 2—7 carbon and at most 3 halogen atoms, an R_6-phenyl-lower alkoxy group, an R_6-phenyloxy group, a group of the formula R^I—A—X_1—, R^I, A and X_1 having the meanings given immediately above, a halogen atom, a trifluoromethyl, nitro or di-lower alkylamino group, R_2 represents a hydrogen atom or a lower alkyl group, and R_3' stands for a hydrogen atom or a lower alkyl group, or a hydroxy-lower alkyl or di-lower alkylamino-lower alkyl group, in which the hetero atoms are separated from the ring-nitrogen atom by at least 2 carbon atoms, and wherein R_4 has the previously given meaning, R_5 is a hydrogen atom, a lower alkyl group or a halogen atom, and n represents 1 or 2, and above all their tautomers in which R_3' represents hydrogen, and the 4-O-esters of such tautomers with lower alkanoic acids, and primarily the lower alkyl, as well as higher alkyl esters of such acids of formula Ia, as well as salts, for example ammonium, alkali metal, alkaline earth metal or acid addition salts thereof. Advantageously, R_5 represents hydrogen and each of the groups of the formulae R^I—A—X_1— and R^{II}—X_2— occupies the 6- or the 7-position.

Useful properties of the above type are primarily exhibited by the compounds of the formula



(Ib)

in which one of the groups R^I and R^{II}, particularly R^{II}, is hydrogen and the other is a cycloalkyl group having 3 to 6 ring carbon atoms and being optionally substituted by lower alkyl, and in which the one residue of the formulae $—(C_mH_{2m})—$ and $—(C_nH_{2n})—$, which carries the cycloalkyl group, particularly the group of the formula $—(C_mH_{2m})—$, contains 1—4 carbon atoms and the other 8—16 carbon atoms, or the 4-O-lower alkanoyl compounds thereof, and above all the lower alkyl esters of such acids, as well as salts, for example ammonium, alkali metal, alkaline earth metal and acid addition salts of such compounds, particularly their non-toxic salts of the above type.

Preferred are compounds of the formula (Ib), in which one of the groups R^I and R^{II}, especially R^{II}, is hydrogen and the other is the cyclopropyl group, and in which the one group of the formulae $—(C_mH_{2m})—$ and $—(C_nH_{2n})—$, which carries the cyclopropyl group, particularly the group of the formula $—(C_mH_{2m})—$, contains 1 carbon atom and the other 8—16 carbon atoms, as well as the 4-O-lower alkanoyl, particularly the 4-O-acetyl, derivatives thereof, and above all the lower alkyl esters of these acids of formula Ib as well as the ammonium, alkali metal, alkaline earth metal salts or acid addition salts, particularly the non-toxic salts, of such compounds of formula Ib.

Of special value are the lower alkyl, especially methyl or ethyl, esters of 6-cyclopropylmethoxy-7-(*n*-octyloxy-, *n*-decyloxy-, *n*-dodecyloxy or *n*-tetradecyloxy)-4-hydroxy-3-quinoline carboxylic acid, as well as the lower alkyl, e.g. methyl or ethyl, esters of the 7-cyclopropylmethoxy - 6 - *n* - decyloxy - 4-hydroxy-3-quinoline carboxylic acid, or the

4-O-acetyl compounds thereof, which, when given together with a balanced feed at doses of 0.0001% to 0.01%, by weight particularly of 0.001% to 0.008% by weight to healthy or primarily to infected (for example, with one of the above *Eimeria* strains) chickens, causes pronounced weight gains and an increase of the feed conversion index.

The compounds of the present invention are prepared according to known methods, for example, by a) ring-closing an α-(1-phenyl-amino-1,1-alkylidene)-malonic acid diester, in which the phenyl residue contains a cycloaliphatyloxy or cycloaliphatylmercapto group and a higher aliphatyloxy or aliphatylmercapto group, and in which one of the positions of the phenyl nucleus adjacent to the amino group is unsubstituted, or a tautomer of such compound, in which the amino group is unsubstituted, or b) converting in a 4-Y_1-3-quinoline carboxylic acid, in which the aromatic carbocyclic portion of the quinoline nucleus is substituted by a cycloaliphatyloxy or a cycloaliphatylmercapto group and a higher aliphatyloxy or aliphatylmercapto group, and in which Y_1 is a reactive esterified hydroxy group, or in a 1-substituted tautomer thereof, in which Y_1 is an optionally substituted imino, oximino, hydrazono, semicarbazono or ketal group, or in an ester, an amide, a hydrazile or a nitrile thereof, the group Y_1 into the hydroxyl or oxo group by hydrolysis, or c) ring-closing an O-aminobenzoyl-acetic acid, in which the phenyl residue contains a cycloaliphatyloxy or cycloaliphatylmercapto group and a higher aliphatyloxy or aliphatylmercapto group, and in which the amino group or the α-position of the acetic acid moiety is substituted by a lower alkanoyl group, or an ester, an amide, a hydrazide or a nitrile thereof, by intramolecular condensation, and, if desired, hydrolizing or transesterifying a resulting ester or reacting it with ammonia, an amine or a hydrazine, or esterifying or amidating a resulting free acid, and/or substituting a resulting 1-unsubstituted compound in 1-position or removing a 1-substituent in 1-position of a resulting 1-substituted compound, and/or esterifying a 4-hydroxy group in a resulting compound, and/or, if desired, converting a resulting free compound into a salt and/or a resulting salt into the free compound or into another salt and/or, if desired, separating a resulting mixture of isomers into the single isomers.

A diester starting material used under a) is primarily a lower alkyl, as well as a higher alkyl, or an aryl-lower alkyl ester, e.g. the methyl, ethyl, *n*-propyl, butyl, decyl or benzyl ester. The ring-closure in variation (a) is preferably carried out according to the Gould-Jacobs method, advantageously at an elevated temperature, for example, between 240°C and 280°C; usually, no condensing agent is required.

A residue Y_1 and Y_2 in a starting material of the process modification (b), capable of being converted into a hydroxy group is primarily a reactive esterified hydroxy group, for example, a hydroxy group esterified by a strong acid, particularly a hydrohalic acid, as well as a strong organic sulfonic acid, e.g. hydrochloric, hydrobromic, hydriodic, methane sulfonic, ethane sulfonic or p-toluene sulfonic acid. A residue Y_1 and Y_2 capable of being converted into an oxo group is an optionally substituted imino, oximino, hydrazono or semicarbazono group, or a ketal group, the latter preferably with a lower alkanediol or a corresponding thioglycol.

The above groups Y_1 and Y_2 are converted into the hydroxy and oxo group, respectively, by hydrolysis according to known methods. Suitable hydrolyzing agents are water acids, for example aqueous mineral or carboxylic acids, e.g. hydrochloric or acetic acid, or bases, e.g. alkali metal hydroxides. These reagents may be used, if desired, in the presence of solvents, for example lower alkanols.

The ring-closure of process variation (c) is carried out according to the Camps method, advantageously in the presence of a condensing agent capable of eliminating water, the usual acidic or basic dehydrating agents, e.g. zinc halides, phosphorus oxyhalides or alkali metal amides or alkoxides being used.

The above-mentioned reactions are carried out under standard conditions, for example, in the presence or absence of solvents or diluents, preferably those inert towards the reaction components and in the presence or absence of catalysts and/or condensing agents, if necessary, while cooling or heating, under increased pressure, and/or in the atmosphere of an inert gas.

Resulting compounds of the invention may be converted into each other according to known methods. Thus, compounds containing free hydroxy or mercapto groups in the aromatic carbocyclic ring, may be etherified, for example, according to reaction modification c); by treatment with a halogeno-lower alkene, a halogeno-lower alkoxy or halogeno-lower alkyl-mercapto group may be introduced. Resulting esters, for example lower alkyl or phenyl-lower alkyl esters, as well as esters of 4-hydroxy compounds, e.g. those with lower alkanoic acids, may be hydrolyzed, for example, by treatment with acidic or alkaline hydrolysis reagents, for example aqueous alkali metal hydroxides, or transesterified, if necessary in the presence of acidic or basic transesterifying reagents, for example alkali metal-lower alkoxides. Lower alkyl or aryl-lower alkyl esters may be converted into amides or hydrazides by reaction with ammonia, amines, preferably lower alkyl-amines,

is re- material able of is pri- group, d by a acid, as id, e.g. driodic, toluene able of an op- drazono up, the iol or a nverted ectively, ethods. r acids, carboxylic cid, or ese re- presence s. n (c) is method, ondens- ter, the nts, e.g. r alkali carried xample, ents or rds the ence or idensing heating, the at- on may ding to ntaining the aro- fied, for ification alkene, no-lower ed. Re- lkyl or sters of h lower for ex- alkaline aqueous ified, if or basic e alkali or aryl- ed into ith am- -amines,

or hydrazines, for example lower alkylhydrazines. Resulting free acids may be esterified or amidated, if desired, by way of acid halides or anhydrides, which may be obtained, for example, by reaction with thionyl halides and ketenes, respectively.

Resulting compounds, unsubstituted in 1-position, may be substituted in that position, of corresponding alcohols and strong acids, e.g. hydrohalic, sulfuric or strong organic sulfonic acids, advantageously in an alkaline medium, as well as with corresponding epoxides. Resulting compounds with a suitable substituent, e.g. a benzyl group, in 1-position may be converted into the corresponding 1-unsubstituted compounds, for example, by hydrogenolysis, e.g. by treatment with catalytically activated or nascent hydrogen.

A hydroxy group in 4-position of a resulting compound may be esterified, for example, by treatment with a reactive acid derivative, for example a lower alkanoic acid anhydride, also an inner anhydride, i.e. the corresponding ketene.

The compounds of the invention are obtained in the free form or in the form of their salts, depending on the conditions under which they are prepared; the salts are also included in the present invention. Resulting salts can be converted in a known manner, into the free acids and bases, respectively, for example, by treatment with acids, alkaline reagents or ion exchangers. Resulting free bases can be converted into acid addition salts e.g. by reaction with inorganic or organic acids, especially those suitable for the formation of non-toxic salts. Such acids are inorganic acids, for example, mineral acids, e.g. hydrochloric, hydrobromic, sulfuric, phosphoric, nitric or perchloric acid, or organic carboxylic or sulfonic acids, for example, aliphatic or aromatic carboxylic or sulfonic acids, e.g. formic acetic, propionic, succinic, glycollic, lactic, malic, tartaric, citric, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, embonic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogenobenzenesulfonic, toluenesulfonic, naphthalenesulfonic, N-cyclohexylsulfamic, and sulfanilic acid, as well as ascorbic acid. Resulting free acids may be converted into ammonium or metal salts, preferably those with ammonia or aliphatic amines, e.g. lower alkylamines, or with alkali metals or alkaline earth metals, e.g. sodium, potassium, magnesium or calcium.

These or other salts, for example, the picrates, can also be used for identification, as well as purification of resulting free compounds; thus, the latter may be converted, for example, in the reaction mixture into salts, resulting salts are separated and the free compounds may be liberated from the isolated salts.

In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a free compound or a salt is referred to in this context, a corresponding salt or free compound is also intended, provided such is possible or appropriate under the circumstances.

Resulting mixtures of isomers may be separated according to known separation methods, racemates, for example, by conversion into mixtures of diastereoisomeric salts, separation of the mixture and liberation of the free compounds.

Preferably these starting materials are used in the process of the invention which lead to the formation of preferred compounds mentioned before.

The starting materials may be prepared according to known methods. For example, those used in reaction a), may be prepared for example, according to the procedure described in British Patent Application No. 2653/70 Serial No. 1,270,413.

Starting materials used in reaction b) are prepared, for example, analogous to reaction a), however, the starting material, i.e. the malonic acid derivative, is condensed in the presence, for example, of a halogenating, sulfurizing or ketalizing agent, for example a phosphorus oxyhalide, e.g. phosphorus oxychloride, or a phosphorus sulfide, or a lower alkylene glycol or -thioglycol, e.g. ethylene glycol or thioglycol, in the presence of an acid, e.g. p-toluenesulfonic acid. Diazo groups in such starting materials may be formed from the corresponding amino groups by treatment, for example, with nitrous acid, or a salt thereof in an acidic medium.

The starting material mentioned under c) may for example, either be prepared by acylation of the corresponding primary or secondary anilines or by reaction of corresponding anthranilic acid esters or halides with alkali metal salts of alkanoyl-acetic acid derivatives, e.g. sodium ethyl acetoacetate.

The compounds of the invention can be used, for example, in the form of veterinary compositions, animal feedstuffs or additives suitable for feedstuffs or drinking water, which are a further object of the present invention. Veterinary compositions contain said compounds in conjunction or admixture with inorganic or organic, solid or liquid excipients, particularly those suitable for enteral administration. These are substances which do not react with the compounds of the invention, for example, water, gelatine, sugars, e.g. lactose, glucose or sucrose, starches, e.g. corn starch, wheat starch, rice starch or arrowroot, stearic acid or salts thereof, e.g. magnesium stearate or calcium stearate, talc, alcohols, e.g. stearyl or benzyl alcohol, propylene glycol or poly-

alkylene glycols, alginic acid or any other known pharmaceutical excipients. The compositions may be, for example, in the form of tablets or pills, e.g. micropills, or in liquid form as solutions, suspensions or emulsions. They may be sterilized and/or contain auxiliary substances, for example preserving, stabilizing, wetting or emulsifying agents, solubilizers, salts for regulating the osmotic pressure or buffers. They are prepared by conventional methods, and contain from 0.1% to 75% (by weight), more particularly, from 1% to 50% (by weight) of the active ingredient; they may, in addition and if desired, contain other physiologically active substances.

Feedstuffs, which are particularly useful in raising poultry, particularly animals with parasitic infections, for example coccidiosis, and additives to feedstuffs or to the drinking water contain compounds of the invention together with conventional extenders, diluents and/or nutrients, for example sucrose, glucose, molasses, fermentation residues, corn meal, ground and rolled oats, wheat shorts and middlings, meat scraps, oil cake, soybean and fish meal, alfalfa, clover or grass clippings, mineral supplements, for example bone meal, calcium carbonate or iodized salt, vitamins, for example vitamins A, B, C or D, and other suitable substances, for example preservants, e.g. benzoic acid.

Feedstuffs, as well as drinking water contain the active ingredients in an amount ranging from 0.0001% to 0.1% (by weight), preferably from 0.001% to 0.02% (by weight); additives may consist of pure substances, when used, for example, for the drinking water, but usually contain from 1% to 75% (by weight), preferably 1% to 50% (by weight), thereof. The total amount of the compounds of the invention administered by way of veterinary compositions or drinking water corresponds to that given with the feedstuffs shown above.

Veterinary compositions, feedstuffs and additives may contain other physiologically active agents, for example, sulfonamides, especially N_1 - (6 - chloro - 2 - pyrazinyl)-sulfanilamide or N_1 - (2 - quinoxalinyl) - sulfanilamide, but also N_1 - (2,6 - dimethoxy-4 - pyrimidinyl) - sulfanilamide, N_1 - (5-ethyl - 1,3,4 - thiadiazol - 2 - yl) - sulfanilamide, N_1 - (5 - methyl - 3 - isoxazolyl)-sulfanilamide, N_1 - (6 - methoxy - 3 - pyridazinyl) - sulfanilamide or the N_1 - acetyl derivative thereof, N_1 - (4 - methyl - 2-pyrimidinyl) - sulfanilamide, N_1 - (2,6-dimethyl - 4 - pyrimidinyl) - sulfanilamide, N_1 - (5 - methyl - 1,3,4 - thiadiazol - 2 - yl) - sulfanilamide, N_1 - (6-chloro - 3 - pyridazinyl) - sulfanilamide or the sodium salt thereof, N_1 - (2 - phenyl - 3-pyrazolyl) - sulfanilamide, or N_1 - (2 - phenyl-5 - methyl - 3 - pyrazolyl) - sulfanilamide. Sulfonamides of the above type can be used in approximately 1/5 to 1/2 of the amount effective as an antibacterial. In addition, veterinary compositions, feedstuffs and additives of the invention may contain arsenium derivatives, for example 4 - hydroxy - 3-nitro - benzenearsonic acid or 4 - amino-benzenearsonic acid, antibiotics, for example penicillin, e.g. procaine penicillin, streptomycin, tetracyclines, e.g. aureomycin, terramycin or tetracycline, bacitracines, e.g. zinc or manganese bacitracin or bacitracin methylene disalicylate, antiparasitic agents, e.g. methyl 4 -acetamino - 2 - ethoxy - benzoate, 2 - amino - 5 - nitrothiazole, 1 - (5 - nitro-2 - thiazolyl) - 2 - oxo - tetrahydroimidazole, 6,7 - dialkoxy - 4 - hydroxy - 3 - quinoline-carboxylic acids, particularly their lower alkyl esters, and/or quaternary 5 - ammonium-methyl - 4 - amino - pyrimidine salts, for example the 2 - cyclopropyl- or 2-cyclopropyl-methyl - 4 - amino - 5 - (2,4 - dimethyl-pyridinium) - methyl - pyrimidine chloride-hydrochloride, as well as the 2 - methyl- or 2 - n - propyl - 4 - amino - 5 - (2 - methyl- or 2,4 - dimethylpyridinium) - methyl-pyrimidine chloride hydrochloride, and/or tranquilizing agents, for example reserpine, methyl 18 - epi - O - methyl - reserpate, or meprobamate.

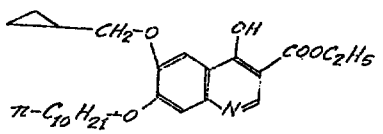
A preferred feed additive contains, for example, 15% (by weight) of one of the compounds of the present invention, for example, the 6 - cyclopropylmethoxy - 7 - n - decyloxy-4 - hydroxy - 3 - quinoline - carboxylic acid ethyl ester, advantageously in micronized form, alone or, if desired, in admixture with some of the following growth promoters, the feed additive being mixed with the feed formula so as to obtain a balanced feed containing between 0.0001% to 0.01% (by weight), preferably 0.001% to 0.008% (by weight) of the active ingredient of this invention and, if desired, (a) 0.0025% to 0.005% (by weight) of 3 - nitro - 4 - hydroxy - benzene - arsonic acid, (b) 0.005% to 0.01% (by weight) of 4-amino - benzene arsonic acid, (c) 2 to 50g/ton of procaine penicillin, (d) 4 to 50g/ton of zinc bacitracin or bacitracin methylene disalicylate, (e) 0.0025% to 0.005% (by weight) of 3-nitro - 4 - hydroxy - benzenearsonic acid and 0.00004% to 0.006% (by weight) of bacitracin, or (f) 0.00006% to 0.0009% (by weight) of procaine penicillin and 0.003% to 0.005% (by weight) bacitracin or zinc bacitracin.

The following Examples illustrate the invention; temperatures are given in degrees Centigrade.

Example 1.

A mixture of 8 g of diethyl N - (4 - cyclopropylmethoxy - 3 - *n* - decyloxy - phenyl)-aminomethylene - malonate and 48 ml of diphenyl ether is refluxed for 20 minutes under

a stream of nitrogen. After cooling, the mixture is diluted with pentane; the resulting precipitate is filtered off and recrystallized from dimethylformamide, to yield the 6-cyclopropylmethoxy - 7 - *n* - decyloxy - 4-hydroxy - 3 - quinoline - carboxylic acid ethyl ester of the formula

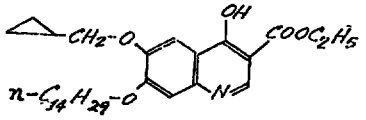


m.p. 253—254°.

In an analogous manner, the dimethyl N-(4 - cycloproplymethoxy - 3 - *n* - decyloxyphenyl) - aminemethylen - malonate is used as the starting material and yields the 6-cyclopropylmethoxy - 7 - *n* - decyloxy - 4-hydroxy - 3 - quinoline carboxylic acid methylester, m.p. 254—255°.

Example 2.

A total of 18 g of diethyl N - (4 - cyclopropylmethoxy - 3 - *n* - tetradecyloxyphenyl) - aminomethylene - malonate is added to 110 ml of the refluxing eutectic mixture of diphenyl ether and biphenyl; refluxing is maintained for 8 minutes. The mixture is cooled quickly and diluted with hexane; the resulting precipitate is filtered off and washed with hexane, to yield the 6 - cyclopropylmethoxy - 7 - *n* - tetradecyloxy - 4 - hydroxy-3 - quinolinecarboxylic acid ethyl ester of the formula



m.p. 237—238°.

Example 3.

A mixture of 1 g of 6 - cyclopropylmethoxy - 7 - n - decyloxy - 4 - hydroxy - 3-quinoline - carboxylic acid ethyl ester and 20 ml of methanol is heated in an autoclave for 10 minutes at a temperature of about 200—250° and allowed to cool to room temperature; then evaporated under reduced pressure. The residue is recrystallized from dimethylformamide, to yield the 6 - cyclopropylmethoxy - 7 - n - decyloxy - 4 - hydroxy-3 - quinoline - carboxylic acid methyl ester, m.p. 254—256°; it is identical with the product obtained according to the procedure described in Example 1.

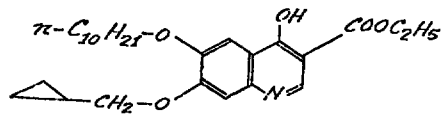
Example 4.

A mixture of 4 g of diethyl N - (4 - cyclopropylmethoxy - 3 - n - decyloxy - phenyl)-phorus oxychloride is heated on the steam bath for 4 hours. It is then cooled and treated with ice and chloroform. The mixture, containing the 4 - chloro - 6 - cyclopropylmethoxy - 7 - n - decyloxy - 3 - quinoline carboxylic acid ethyl ester, is made slightly alkaline with a 2N aqueous sodium hydroxide solution. The resulting solid material is filtered off, washed with benzene and aqueous ethanol and recrystallized from dimethylformamide, to yield the 6 - cyclopropylmethoxy - 7 - *n* - decyloxy - 4 - hydroxy - 3-quinoline - carboxylic acid ethyl ester, m.p. 251 to 253°; it is identical with the product obtained according to the procedure described in Example 1.

The 4 - chloro - 6 - cyclopropylmethyl - 7-*n* - decyloxy - 3 - quinoline carboxylic acid ethyl ester, formed as intermediate, may also be hydrolyzed with diluted aqueous acetic acid after the phosphorus oxychloride has been evaporated under reduced pressure.

Example 5.

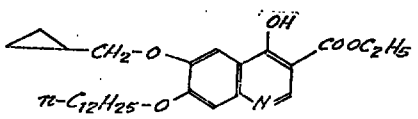
A mixture of 13 g of diethyl N - (3 - cyclopropylmethoxy - 4 - n - decyloxy - phenyl)-aminomethylene - malonate and 80 ml of diphenyl ether is refluxed for 20 minutes, and, after cooling, diluted with pentane. The precipitate is filtered off, and washed with ethanol, acetone and ether to yield the 7-cyclopropylmethoxy - 6 - n - decyloxy - 4-hydroxy - 3 - quinoline - carboxylic acid ethyl ester of the formula



m.p. 234—235°.

Example 6.

A total of 12.8 g of diethyl N - (4 - cyclopropylmethoxy - 3 - *n* - dodecyloxy - phenyl)-aminomethylene - malonate is added to 75 ml of refluxing diphenyl ether; the mixture is refluxed for 30 minutes, then cooled, diluted with pentane and filtered. The filter residue is washed with pentane to yield the 6 - cyclopropylmethoxy - 7 - *n* - dodecyloxy - 4-hydroxy - 3 - quinoline - carboxylic acid ethyl ester of the formula

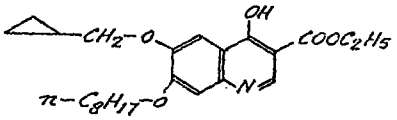


m.p. 210—213°.

Example 7.

A mixture of 10 g of diethyl N - (4 - cyclo-

propylmethoxy - 3 - n - octyloxy) - aminomethylene - malonate and 65 ml of diphenyl ether is refluxed for 20 minutes under a stream of nitrogen. After cooling, the mixture is diluted with pentane; the resulting precipitate is filtered off and recrystallized from dimethylformamide to yield the 6 - cyclopropylmethoxy - 4 - hydroxy - 7 - n - octyloxy - 3-quinoline - carboxylic acid ethyl ester of the formula

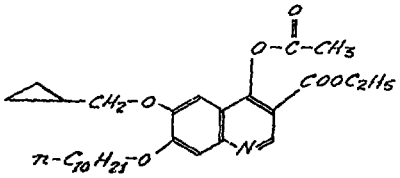


m.p. 256—258°.

Using dimethyl N - (4 - cyclopropylmethoxy - 3 - n - octyloxy - phenyl) - aminomethylene - malonate as the starting material in the above procedure, one obtains the 6-cyclopropylmethoxy - 4 - hydroxy - 7 - n-octyloxy - 3 - quinoline carboxylic acid methyl ester, m.p. 258—259.5°.

Example 8.

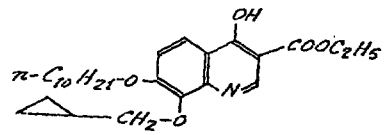
A mixture of 0.6 g of 6 - cyclopropylmethoxy - 7 - *n* - decyloxy - 4 - hydroxy - 3-quinoline - carboxylic acid ethyl ester, 1.5 g of anhydrous sodium acetate and 15 ml of acetic acid anhydride is refluxed for three hours while stirring, then evaporated under reduced pressure. The residue is triturated with methylene chloride, the solution is evaporated and the residue is recrystallized from a mixture of ether and pentane to yield the 4 - acetyloxy - 6 - cyclopropylmethoxy-7 - n - decyloxy - 3 - quinoline - carboxylic acid ethyl ester of the formula



m.p. 101.5—102°.

Example 9.

A total of 40 g of diethyl N - (2 - cyclopropylmethoxy - 3 - *n* - decyloxy - phenyl)-aminomethylene - malonate is added to 400 ml of the boiling eutectic mixture of diphenyl ether and biphenyl. The mixture is refluxed for 10 minutes, then cooled rapidly, diluted with 800 ml of heptane and allowed to stand at room temperature for two days. The resulting precipitate is filtered off, washed with 200 ml of heptane and recrystallized from aqueous methanol, to yield the monohydrate of the 8 - cyclopropylmethoxy - 7 - *n* - decyloxy - 4 - hydroxy - 3 - quinoline - carboxylic acid ethyl ester of the formula



m.p. 99—102°.

A mixture of 12 g of the monohydrate and 100 ml of toluene is refluxed until no further water is collected in the water trap, then evaporated. The residue is triturated with ether to yield the anhydrous compound, m.p. 75—78°.

Example 10.

A mixture of 4 g of ethyl (5 - cyclopropylmethoxy - 4 - n - decyloxy - 2 - formylaminobenzoyl) - acetate, 50 ml of anhydrous ethanol and 0.6 g of sodium methoxide is stirred for 2 hours at room temperature and refluxed for 3 hours, then evaporated under reduced pressure. The residue is taken up in water, the aqueous mixture is quickly neutralized with 2N hydrochloric acid and the resulting precipitate is filtered off, washed with water and recrystallized from dimethylformamide, to yield the 6 - cyclopropylmethoxy - 7 - n-decyloxy - 4 - hydroxy - 3 - quinoline - carboxylic acid ethyl ester, m.p. 251—253°, which is identical with the compound obtained according to the procedure described in Example 1.

The starting material is prepared as follows: While stirring, a mixture of 16.4 g of pyrocatechol mono-cyclopropylmethyl ether and 75 ml of 50% by weight aqueous sodium hydroxide is treated with 24 g of chloroform at 68—70°; stirring is continued for 6 hours at that temperature. The mixture is filtered hot, the filtrate is cooled, acidified with concentrated hydrochloric acid and extracted with methylene chloride. The organic extract is combined with the filter residue, washed with water, dried, filtered and evaporated. The residue is distilled; the fraction boiling between 140—152°/0.3 mm Hg yields the 3-cyclopropylmethoxy - 4 - hydroxy - benzaldehyde.

A mixture of 9.6 g of 3 - cyclopropylmethoxy - 4 - hydroxy - benzaldehyde and 20 ml of dimethylformamide is added while stirring to a suspension of 2.2 g of 56% by weight sodium hydride in 25 ml of dimethylformamide; stirring is continued for 2 hours at room temperature. Then 11.5 g of n - decyl bromide are added dropwise while stirring and the mixture is stirred for 12 hours at 110°, then cooled and poured into water. The aqueous mixture is washed with pentane and extracted with methylene chloride. The organic extract is dried, filtered, evaporated and

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the residue is distilled; the fraction boiling at 195—210°/0.02 mm Hg yields the 3-cyclopropylmethoxy - 4 - *n* - decyloxy-benzaldehyde.

A mixture of 10 g of 3 - cyclopropylmethoxy - 4 - n - decyloxy - benzaldehyde and 50 ml of aqueous nitric acid (specific weight; 1.16) is vigorously stirred at 60° for 5 hours and then poured into cold water. The aqueous mixture is extracted with methylene chloride, and the organic extract is washed with water, dried and evaporated to yield the 5 - cyclopropylmethoxy - 4 - *n* - decyloxy - 2-nitro - benzaldehyde.

A mixture of 11 g of 5 - cyclopropylmethoxy - 4 - n - decyloxy - 2 - nitro - benzaldehyde, 100 ml of water and 25 g of silver nitrate is stirred and refluxed while adding dropwise 50 ml of 10% aqueous sodium hydroxide. The mixture is then filtered hot, the filtrate is cooled and acidified with hydrochloric acid, and the resulting precipitate is filtered off to yield the 5 - cyclopropylmethoxy - 4 - n - decyloxy - 2 - nitro - benzoic acid.

A total of 9 g of 5 - cyclopropyl - methoxy-4 - n - decyloxy - 2 - nitro - benzoic acid is taken up in the minimum amount of ethanol and the solution is treated with a solution of diazomethane in ether until the yellow color persists. A few drops of acetic acid and 0.3 g of platinum oxide are then added; the mixture is hydrogenated under atmospheric pressure until the hydrogen uptake ceases, heated and then filtered hot. The filtrate is treated with 2 g of ethyl formate, the mixture is refluxed for 4 hours and evaporated under reduced pressure, to yield the methyl 5 - cyclopropylmethoxy - 4 - n-decyloxy - 2 - formylamino - benzoate.

A mixture of 9.75 g of methyl 5 - cyclopropylmethoxy - 4 - *n* - decyloxy - 2-formylamino - benzoate, 4.5 g of ethyl acetate, 15 ml of dimethylformamide and 1.5 g of sodium methoxide is heated to 70° for 5 hours while stirring, and is then cooled, diluted with water, acidified with hydrochloric acid and extracted with methylene chloride. The organic extract is washed with water, dried, filtered and evaporated to yield the ethyl (5-cyclopropylmethoxy - 4 - n - decyloxy - 2-formylaminobenzoyl) - acetate, which is used without further purification.

Example 11.

A feed additive, containing 15% by weight of the active ingredient, is prepared as follows:

6 - cyclopropylmethoxy - 7 - *n*-decyloxy - 4 - hydroxy - 3-quinoline carboxylic acid ethyl ester	500 g
stearyl alcohol	250 g
glycerol monostearate	250 g
soybean meal	2,330 g

The stearyl alcohol and the glycerol monostearate are melted and the 6 - cyclopropylmethoxy - 7 - *n* - decyloxy - 4 - hydroxy - 3-quinoline carboxylic acid ethyl ester is suspended in the melt, using a turbo stirrer. The mixture is allowed to congeal on a cooled flaking drum and the flakes are passed through a screen having 0.6 mm openings. They are mixed with soybean meal in a V-shaped mixer and the whole is screened through 0.6 mm openings.

The resulting additive is added to regular poultry feed in an amount which is necessary to obtain a concentration of the active ingredient of between about 0.0001% to about 0.0075% by weight.

Example 12.

A poultry feed containing 0.001% by weight of the active ingredient is prepared as follows:

6 - cyclopropylmethoxy - 7 - *n*-decyloxy - 4 - hydroxy - 3 - quinolinecarboxylic acid ethyl ester	10 g
Standard Feed Formula (for 912585 g)	
Corn meal	508500 g
Soybean meal (44% by weight protein)	297300 g
Alfalfa meal	13500 g
Dicalcium phosphate	18000 g
Limestone meal	4500 g
Sodium chloride	2250 g
Fish meal (60% by weight protein)	18000 g
Stabilized fat	27000 g
Dried whey	18000 g
Manganese sulfate	225 g
Zinc oxide	135 g
d,l - methionine	675 g
Vitamin premix	4500 g

(4536 g of the vitamin composition contain: 16,000,000 I.U. of Vit. A; 1,000,000 I.U. of Vit. D_3; 5,000 I.U. of Vit. E acetate; 6 g of Vit. K_3; 0.006 g of Vit. B_{12}; 3 g of riboflavin; 30 g of niacin; 5 g of calcium pantothenate and 100 g of ethoxyquin, made up to 4536 g with corn meal).

The 6 - cyclopropylmethoxy - 7 - n -decyloxy - 4 - hydroxy - 3 - quinolinecarboxylic acid ethyl ester is first premixed with about 1000 g of the finely ground feed mixture; the premix is increased to about 25000 g with the feed and then thoroughly mixed with the main batch in a horizontal mixer.

Example 13.

A poultry feed containing 0.001% and 0.006% by weight, respectively, of the two active ingredients is prepared as follows:

Premix:

I. 6 - cyclopropylmethoxy - 7- *n* - decyloxy - 4 - hydroxy- 3 - quinolinecarboxylic acid ethyl ester	10 g
II. 4 - amino - 2 - cyclopropyl- methyl - 5 - (2,4 - dimethyl- pyridinium) - methyl - pyrimidine chloride hydrochloride	60 g
III. Confectioners Sugar	50 g
IV. Soybean Feed, solvent extracted	305 g

The premix is prepared by triturating I and II with III and the mixture is then screened through a 30 mesh screen, U.S. standard sieve size. The screened material is then blended with IV in a mixer, the thoroughly mixed ingredients are added to 999575 g of the feed formula as described in Example 12 and the whole is homogenized in a horizontal mixer.

Example 14.

A poultry feed containing 0.001% by weight of each of the active ingredients is prepared as follows:

Premix:

I. 6 - cyclopropylmethoxy - 7- *n* - decyloxy - 4 - hydroxy- 3 - quinolinecarboxylic acid ethyl ester	10 g
II. 4 - amino - 2 - cyclopropyl- 5 - (2,4 - dimethyl - pyridinium) - methyl - pyrimidine chloride hydrochloride	10 g
III. Soybean Oil	18 g
IV. Corn Gluten Feed	312 g

About one third of the amount of IV is combined with I and II, mixed and then screened through a 30 mesh screen, U.S. standard sieve. The remainder of IV is then placed into a mixer, III is added and the material mixed to form a uniform dispersion, to which the screened material is added. After mixing until uniformity is obtained, the mixture is then added to 999650 g of the feed formula shown in Example 12 and the whole is homogenized in a horizontal mixer.

Example 15.

A poultry feed is prepared as follows:

Premix:

I. 6 - cyclopropylmethoxy - 7 - *n* - decyloxy - 4 - hydroxy- 3 - quinolinecarboxylic acid ethyl ester	25 g
II. N_1 - (2 - quinoxalinyl) - sulfanilamide	125 g
III. Confectioners Sugar	175 g
IV. Soybean Feed, solvent extracted	675 g

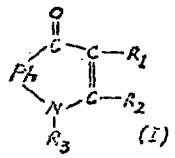
The premix is prepared by triturating I and II with III and the mixture is then screened through screen (sieve opening: 0.59 mm); the screened material is then blended with IV in a mixer and the thoroughly mixed ingredients are added to 9999000 g of the feed formula shown in Example 12; the whole is homogenized in a horizontal mixer.

The above examples 11—15 may otherwise be modified so as to obtain a poultry feed containing from about 0.0001% to about 0.01 % by weight of the active component shown in any one of the Examples 1 to 10 alone or in admixture with another active agent, for example, a sulfonamide, which may be present in an amount of between about 0.001% and about 0.01% by weight. In preparing the premix (or feedstuff additives, respectively) in the above-identified examples one may, of course, substitute an equivalent amount of other carriers and nutrients, respectively, such as cotton seed meal, linseed meal or oatmeal.

WHAT WE CLAIM IS:—

1. A 4 - hydroxy - 3 - quinoline carbocylic acid, which contains in the aromatic carbocyclic portion of the quinoline nucleus a cycloaliphatyloxy or cycloaliphatylmercapto group and a higher aliphatyloxy or aliphatylmercapto group, or a 1 - unsubstituted tautomer thereof, or an ester, amide, hydrazide or nitrile of such a compound or tautomer or a salt thereof.

2. A compound of the formula



(I)

in which Ph is a 1,2 - phenylene residue substituted by a group of the formula $-X_1-A-R^I$ and a group of the formula $-X_2-R^{II}$, in which R^I is a cycloaliphatic radical, A represents a direct bond between X_1 and R^I or a bivalent aliphatic radical, R^{II} is a higher aliphatic residue and each of X_1 and X_2 is oxygen or sulfur, R_1 represents a carboxy, an esterified carboxy, a carbamyl, a hydrazinecarbonyl or a cyano group, R_2 stands for a hydrogen atom or a lower alkyl group, and R_3 is a hydrogen atom or an optionally substituted aliphatic or cycloaliphatic hydrocarbon radical, or a tautomer of such a compound in which R_3 represents a hydrogen atom, or a 4-O-ester of such a tautomer or a salt of such a compound of formula I.

Premix:

I. 6 - cyclopropylmethoxy - 7- *n* - decyloxy - 4 - hydroxy- 3 - quinolinecarboxylic acid ethyl ester	10 g
II. 4 - amino - 2 - cyclopropylmethyl - 5 - (2,4 - dimethylpyridinium) - methyl - pyrimidine chloride hydrochloride	60 g
III. Confectioners Sugar	50 g
IV. Soybean Feed, solvent extracted	305 g

The premix is prepared by triturating I and II with III and the mixture is then screened through a 30 mesh screen, U.S. standard sieve size. The screened material is then blended with IV in a mixer, the thoroughly mixed ingredients are added to 999575 g of the feed formula as described in Example 12 and the whole is homogenized in a horizontal mixer.

Example 14.

A poultry feed containing 0.001% by weight of each of the active ingredients is prepared as follows:

Premix:

I. 6 - cyclopropylmethoxy - 7- *n* - decyloxy - 4 - hydroxy- 3 - quinolinecarboxylic acid ethyl ester	10 g
II. 4 - amino - 2 - cyclopropyl- 5 - (2,4 - dimethyl - pyridinium) - methyl - pyrimidine chloride hydrochloride	10 g
III. Soybean Oil	18 g
IV. Corn Gluten Feed	312 g

About one third of the amount of IV is combined with I and II, mixed and then screened through a 30 mesh screen, U.S. standard sieve. The remainder of IV is then placed into a mixer, III is added and the material mixed to form a uniform dispersion, to which the screened material is added. After mixing until uniformity is obtained, the mixture is then added to 999650 g of the feed formula shown in Example 12 and the whole is homogenized in a horizontal mixer.

Example 15.

A poultry feed is prepared as follows:

Premix:

I. 6 - cyclopropylmethoxy - 7 - *n* - decyloxy - 4 - hydroxy- 3 - quinolinecarboxylic acid ethyl ester	25 g
II. N_1 - (2 - quinoxalinyl) - sulfanilamide	125 g
III. Confectioners Sugar	175 g
IV. Soybean Feed, solvent extracted	675 g

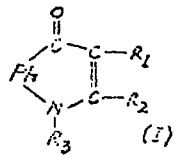
The premix is prepared by triturating I and II with III and the mixture is then screened through screen (sieve opening: 0.59 mm); the screened material is then blended with IV in a mixer and the thoroughly mixed ingredients are added to 9999000 g of the feed formula shown in Example 12; the whole is homogenized in a horizontal mixer.

The above examples 11—15 may otherwise be modified so as to obtain a poultry feed containing from about 0.0001% to about 0.01 % by weight of the active component shown in any one of the Examples 1 to 10 alone or in admixture with another active agent, for example, a sulfonamide, which may be present in an amount of between about 0.001% and about 0.01% by weight. In preparing the premix (or feedstuff additives, respectively) in the above-identified examples one may, of course, substitute an equivalent amount of other carriers and nutrients, respectively, such as cotton seed meal, linseed meal or oatmeal.

WHAT WE CLAIM IS:—

1. A 4 - hydroxy - 3 - quinoline carbocylic acid, which contains in the aromatic carbocyclic portion of the quinoline nucleus a cycloaliphatyloxy or cycloaliphatylmercapto group and a higher aliphatyloxy or aliphatylmercapto group, or a 1 - unsubstituted tautomer thereof, or an ester, amide, hydrazide or nitrile of such a compound or tautomer or a salt thereof.

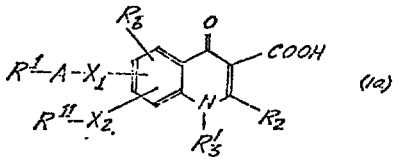
2. A compound of the formula



(I)

in which Ph is a 1,2 - phenylene residue substituted by a group of the formula $-X_1-A-R^I$ and a group of the formula $-X_2-R^{II}$, in which R^I is a cycloaliphatic radical, A represents a direct bond between X_1 and R^I or a bivalent aliphatic radical, R^{II} is a higher aliphatic residue and each of X_1 and X_2 is oxygen or sulfur, R_1 represents a carboxy, an esterified carboxy, a carbamyl, a hydrazinecarbonyl or a cyano group, R_2 stands for a hydrogen atom or a lower alkyl group, and R_3 is a hydrogen atom or an optionally substituted aliphatic or cycloaliphatic hydrocarbon radical, or a tautomer of such a compound in which R_3 represents a hydrogen atom, or a 4-O-ester of such a tautomer or a salt of such a compound of formula I.

3. A compound of the formula



(Ia)

in which R^I is a cycloalkyl or cycloalkenyl residue, which may be optionally substituted by one or more optionally substituted aliphatic, aromatic or araliphatic hydrocarbon residues and/or one or more free, etherified or esterified hydroxyl groups, A represents a direct bond between R^I and X_1 or a bivalent aliphatic residue, each of X_1 and X_2 represents an oxygen or sulfur atom, R^{II} stands for a higher alkyl or a higher alkenyl group, R_2 is a hydrogen atom or a lower alkyl radical, R_3' is a hydrogen atom, a lower alkyl or lower alkenyl group a lower alkyl group substituted by a free, etherified or esterified hydroxy group, a free or esterified carboxyl group, or by an amino or an aryl group, or R_3' is a group of the formula R^I—A—, R^I and A having the previously given meaning, and R_b represents a hydrogen atom, a lower alkyl group, an aryl-lower alkyl group, a free, etherified or esterified hydroxy or mercapto group, a trifluoromethyl group, a nitro group or an optionally substituted amino group, or a tautomer of such a compound in which R_3' stands for hydrogen, or a 4-O-ester of such a tautomer, or an ester, amide, hydrazide or nitrile of such a compound of formula Ia.

4. A compound of the formula Ia given in claim 3, in which R^I stands for a 3- to 8-membered $(R_b)_n$-cycloalkyl residue, A is a direct bond between R^I and X_1 or a lower alkylene residue, each of X_1 and X_2 stands for an oxygen atom, R^{II} is a higher alkyl group, R_b is a hydrogen atom, a lower alkyl residue an R_a-phenyl-lower alkyl residue, a lower alkoxy group, a halogene-lower alkoxy group with 2—7 carbon atoms and at most 3 halogen atoms, an R_a-phenyl-lower alkoxy group, an R_a-phenyleoxy group, a group of the formula R^I—A—X_1— in which R^I, A and X_1 have the above given meaning, a halogen atom, a trifluoromethyl group, a nitro group or a di-lower alkylamino group, R_2 is a hydrogen atom or a lower alkyl group and R_3' is a hydrogen atom, a lower alkyl group, or a hydroxy-lower alkyl or di-lower alkyl-amino-lower alkyl group, in which the hetero atoms are separated from the ring nitrogen atom by at least 2 carbon atoms, and in which R_a is a hydrogen atom, a lower alkyl, a lower alkoxy, a trifluoromethyl, a nitro, or a di-lower alkylamino group or a halogen atom, R_b is a hydrogen atom, a lower alkyl group or a halogen atom, and n is 1 or 2, a tautomer of such a compound in which R_3' represents hydrogen, a lower alkyl ester or salt of such a compound.

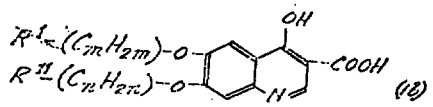
5. A compound of the formula Ia given in claim 3, in which each of R^I, A, X_1, X_2, R^{II}, R_b, R_2 and R_3' have the meanings given in claim 4, R_b also representing a higher alkyl or a higher alkoxy group, a tautomer of such a compound in which R_3' represents hydrogen, or a lower alkyl or higher alkyl ester or salt of such a compound.

6. A compound of the formula Ia given in claim 3, in which each of R^I, A, X_1, X_2, R^{II}, R_b, R_2 and R_3' have the meaning given in claim 4, R_b also representing a higher alkyl or a higher alkoxy group, a tautomer of such a compound which R_3' represents hydrogen, a 4-O-ester of such a tautomer with a lower alkanoic acid, or a lower alkyl or higher alkyl ester or a salt of such compound.

7. A compound of the formula Ia given in claim 3, in which each of R^I, A, X_1, X_2, R^{II}, R_2 and R_3' have the meanings given in claim 4, R_b is hydrogen and the groups of the formulae R^I—A—X_1— and R^{II}—X_2— occupy the 6- and 7-positions in either order, or a tautomer of such a compound in hich R_3' represents hydrogen, or a lower alkyl or higher alkyl ester or salt of such a compound.

8. A compound of the formula Ia given in claim 3, in which each of R^I, A, X_1, X_2, R^{II}, R_2 and R_3' have the meanings given in claim 4, R_b is hydrogen, and the groups of the formulae R^I—A—X_1— and R^{II}—X_2 occupy the 6- and 7-positions in either order, or a tautomer of such a compound in which R_3' is hydrogen, or a 4-O-ester of such a tautomer with a lower alkanoic acid, or a lower alkyl or higher alkyl ester or salt of such a compound.

9. A compound of the formula



(Ib)

in which compounds one of the groups R^I and R^{II} is hydrogen and the other is a cycloalkyl group having 3 to 6 ring carbon atoms and being optionally substituted by lower alkyl, and in which the one residue of the formulae $-(C_mH_{2m})-$ and $-(C_nH_{2n})-$, which carries the cycloalkyl group contains 1—4 carbon atoms and the other 8—16 carbon atoms, or a lower alkyl ester of such a compound or an ammonium, alkali metal, alkaline earth metal or acid addition salt of such a compound.

10. A compound of the formula Ib given in claim 9, in which one of the groups R^I and R^{II} is hydrogen and the other is a cycloalkyl group having 3 to 6 ring carbon atoms and being optionally substituted by lower alkyl, and in which the one residue of the formulae $-(C_mH_{2m})-$ and $-(C_nH_{2n})-$, which carries the cycloalkyl group contains 1—4 carbon atoms and the other 8—16 carbon atoms, or

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a 4-O-lower alkanoyl derivative thereof, or a lower alkyl ester of such a compound, or an ammonium alkali metal, alkaline earth metal or acid addition salt of such a compound.

11. A compound of the formula Ib given in claim 9, in which one of the groups R^I and R^{II} is hydrogen and the other is the cyclopropyl group, and in which the one group of the formula $-(C_mH_{2m})-$ and $-(C_nH_{2n})-$ which carries the cyclopropyl group contains 1 carbon atom and the atom and the other 8—16 carbon atoms, or a lower alkyl ester of such a compound or an ammonium, alkali metal, alkaline earth metal or acid addition salt thereof.

12. A compound of the formula Ib given in claim 9, in which one of the groups R^I and R^{II} is hydrogen and the other is the cyclopropyl group, and in which the one group of the formulae $-(C_mH_{2m})-$ and $-(C_nH_{2n})-$ which carries the cyclopropyl group contains 1 carbon atom and the other 8—16 carbon atoms, or a 4-O-lower alkanoyl derivative thereof, or a lower alkyl ester of such a compound, or an ammonium, alkali metal, alkaline earth metal salts or acid addition salt thereof.

13. 6 - Cyclopropylmethoxy - 7 - *n* - decyloxy - 4 - hydroxy - 3 - quinoline - carboxylic acid ethyl ester.

14. 6 - Cyclopropylmethoxy - 7 - *n* - decyloxy - 4 - hydroxy - 3 - quinoline - carboxylic acid methyl ester.

15. 6 - Cyclopropylmethoxy - 6 - *n* - decyloxy - 4 - hydroxy - 3 - quinoline - carboxylic acid ethyl ester.

16. 7 - Cyclopropylmethoxy - 6 - *n* - decyloxy - 4 - hydroxy - 3 - quinoline - carboxylic acid ethyl ester.

17. 6 - Cyclopropylmethoxy - 7 - *n* - dodecyloxy - 4 - hydroxy - 3 - quinoline - carboxylic acid ethyl ester.

18. 6 - Cyclopropylmethoxy - 7 - *n* - octyloxy - 3 - 4 - hydroxy - quinoline - carboxylic acid ethyl ester.

19. 6 - Cyclopropylmethoxy - 7 - *n* - octyloxy - 3 - 4 - hydroxy - 3 - quinoline carboxylic acid methyl ester.

20. 4 - Acetyloxy - 6 - cyclopropylmethoxy-7 - *n* - decyloxy - 3 - quinoline - carboxylic acid ethyl ester.

21. 8 - Cyclopropylmethoxy - 7 - *n* - decyloxy - 4 - hydroxy - 3 - quinoline - carboxylic acid ethyl ester.

22. A salt of a compound claimed in any one of claims 13, 14, 16 and 17.

23. A non-toxic salt of a compound claimed in any one of claims 13, 14, 16 and 17.

24. A salt of a compound claimed in claim 15 or claim 21.

25. A non-toxic salt of a compound claimed in claim 15 or claim 21.

26. A salt of a compound claimed in any one of claims 18 to 20.

27. A non-toxic salt of a compound claimed in any one of claims 18 to 20.

28. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising a compound as claimed in claim 1, or a non-toxic salt thereof.

29. Animal feedstuffs or drinking water additives comprising a compound as claimed in claim 2 or a non-toxic salt thereof.

30. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising a compound as claimed in claim 3 or a non-toxic salt thereof.

31. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising a compound as claimed in claim 4 or a non-toxic salt of such compound.

32. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising a compound as claimed in claim 5 or a non-toxic salt of such compound.

33. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising a compound as claimed in claim 6 or a non-toxic salt of such compound.

34. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising a compound as claimed in claim 7 or a non-toxic salt of such compound.

35. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising a compound as claimed in claim 8 or a non-toxic salt of such compound.

36. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising a compound as claimed in claim 9.

37. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising a compound as claimed in claim 10.

38. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising a compound as claimed in claim 11.

39. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising a compound as claimed in claim 12.

40. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising the compound as claimed in claim 13 or a non-toxic salt thereof.

41. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising the compound as claimed in claim 14 or a non-toxic salt thereof.

42. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising the compound as claimed in claim 15 or a non-toxic salt thereof.

43. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising the compound as claimed in claim 16 or a non-toxic salt thereof.

44. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising the compound as claimed in claim 17 or a non-toxic salt thereof.

45. Animal feedstuffs or drinking water or animal feed or drinking water additives com-

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prising the compound as claimed in claim 18 or a non-toxic salt thereof.

46. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising the compound as claimed in claim 19 or a non-toxic salt thereof.

47. Animal feedstuffs or drinking water or animal feed or drinking water additives comprising a compound as claimed in claim 20 or a non-toxic salt thereof.

48. Animal feedstuffs or drinking water as claimed in any one of claims 28 to 47 comprising from 0.0001% to 0.1% (by weight) of the compound.

49. Animal feedstuffs or drinking water as claimed in any one of claims 28 to 47 comprising from 0.0001% to 0.1% (by weight) of the compound.

50. Animal feedstuffs or additives as claimed in any one of claims 28 to 49 comprising in addition a sulfonamide.

51. Animal feedstuffs or additives as claimed in claim 50, comprising the sulfonamide in approximately 1/5 to 1/2 of the amount effective as an antibacterial.

52. Animal feedstuffs or additives as claimed in any one of claims 28 to 51 comprising in addition an arsenium compound.

53. Animal feedstuffs or additives as claimed in any one of claims 28 to 51 comprising in addition an antibiotic.

54. Animal feedstuffs or additives as claimed in any one of claims 28 to 51 and 53 comprising in addition an antiparasitic compound.

55. Animal feedstuffs or additives as claimed in any one of claims 28 to 51, 53 and 54, comprising in addition a tranquillizing agent.

56. A process for the manufacture of a 4-hydroxy - 3 - quinoline carboxylic acid, which contains in the aromatic carbocyclic portion of the quinoline nucleus a cycloaliphatyloxy or cycloaliphatylmercapto group and a higher aliphatyloxy or aliphatylmercapto group, or a 1-substituted tautomer thereof, or an ester, amide, hydrazide or nitrile of such a compound, or a salt thereof, which comprises a) ring-closing an α - (1 - phenylamino - 1,1-alkylidene) - malonic acid diester, in which the phenyl residue contains a cycloaliphatyloxy or cycloaliphatylmercapto group and a higher aliphatyloxy or aliphatylmercapto group, and in which one of the positions of the phenyl residue adjacent to the amino group is unsubstituted, or a tautomer thereof in which the amino group is unsubstituted, by intramolecular condensation, or b) converting in a 4 - Y_1 - 3 - quinoline carboxylic acid, in which the aromatic carbocyclic portion of the quinoline nucleus is substituted by a cycloaliphatyloxy or a cycloaliphatylmercapto group and a higher aliphatyloxy or aliphatylmercapto group, and in which Y_1 is a reactive esterified hydroxy group, or in a 1-substituted tautomer thereof in which Y_1 is an optionally substituted imino, oximino, hydrazono, semicarbazono or ketal group, or in an ester, an amide, a hydrazide or a nitrile thereof, the group Y_1 into the hydroxy or oxo group, by hydrolysis, or c) ring-closing an o - aminobenzoyl - acetic acid, in which the phenyl residue contains a cycloaliphatyloxy or cycloaliphatylmercapto group and a higher aliphatyloxy or aliphatylmercapto group, and in which the amino group or the α-position of the acetic acid moiety carries a lower alkanoyl group, or an ester, amide, hydrazide or nitrile of such acid by intramolecular condensation; and, if desired, hydrolizing or transesterifying a resulting ester or reacting it with ammonia, an amine or a hydrazine, and/or esterifying or amidating a resulting free acid, and/or substituting a resulting 1-unsubstituted compound in 1-position or removing a substituent in 1-position of a resulting 1-substituted compound and/or esterifying a 4-hydroxy group in a resulting compound, and/or, if desired, converting a resulting free compound into a salt and/or a resulting salt into the free compound or into another salt, and/or, if desired, separating a resulting mixture of isomers into the single isomers.

57. A process as claimed in claim 56, wherein, in variation (a), a lower or higher alkyl or an aryl-lower alkyl ester is used as the diester.

58. A process as claimed in claim 56 or claim 57, wherein the ring-closure (a) is carried out at an elevated temperature.

59. A process as claimed in claim 56, wherein, in variation (b), a reactive esterified hydroxyl group is a hydroxyl group esterified by a hydrohalic acid.

60. A process as claimed in claim 56, wherein, in variation (b), hydrolysis is carried out with an acidic agent.

61. A process as claimed in claim 60, wherein an aqueous mineral or carboxylic acid is used.

62. A process as claimed in claim 56, wherein ring-closure (c) is carried out in the presence of a dehydrating agent.

63. A process as claimed in claim 56, wherein in a resulting compound a 4-hydroxy group is esterified by treatment with a reactive derivative of a lower alkanoic acid.

64. A process as claimed in claim 56 and conducted substantially as described in any one of Examples 1, and 3 to 6.

65. A process as claimed in claim 56 and conducted substantially as described in either of Examples 2 and 9.

66. A process as claimed in claim 56 and conducted substantially as described in either of Examples 7 and 8.

67. A compound as claimed in claim 1 whenever prepared by a process claimed in

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any one of claims 56 to 62.

68. A compound as claimed in claim 1 whenever prepared by a process claimed in any one of claims 56 to 63.

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ERRATA

AMENDED SPECIFICATION No. 1,270,412

Page 2, line 89, *for* —X^1 *read* —X_1
Page 2, line 90, *for* —X_2 *read* —X_2
Page 4, line 36, *after* alkoxy, *delete* aryloxy or aryl-
Page 6, line 31, *for* hydrazile *read* hydrazide
Page 6, line 33, *for* O-amino- *read* o-amino-
Page 7, line 2, *delete* whole line
Page 7, line 9, *after* position, (second occurrence) *insert* for example, by treatment with reactive esters
Page 9, line 49, *after* phenyl)- *insert* aminomethylene-malonate and 2g of phos-
Page 14, line 11, *after* atom (first occurrence) *delete* and the atom
Page 14, line 33, *for* 6-n-de- *read* 7-*n*-tetrade-
Page 14, line 43, *after* loxy- *delete* 3 *after* hydroxy- *insert* 3-
Page 14, line 46, *after* loxy- *delete* 3
Page 14, line 70, *after water insert* or animal feed or drinking water
Page 15, line 17, *for* 0.0001% to 0.1% *read* 0.001% to 0.02%

THE PATENT OFFICE
10th February, 1975