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3,830,817

1 - AZIRIDINYLCARBONYL - QUINOLINE-CARBOXYLIC ACID DERIVATIVES

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No Drawing. Continuation-in-part of abandoned application Ser. No. 73,669, Sept. 18, 1970. This application Nov. 13, 1972, Ser. No. 306,262

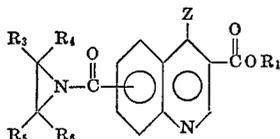
Int. Cl. C07d 33/48

U.S. Cl. 260-287 R

8 Claims

ABSTRACT OF THE DISCLOSURE

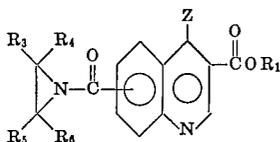
Quinoline derivatives are provided having the structure



These derivatives are useful as coccidiostats and nematocides.

This application is a continuation-in-part of United States patent application Ser. No. 73,669, filed Sept. 18, 1970 and now abandoned.

The present invention relates to quinoline derivatives having the structure



wherein Z is hydroxy or halogen; R₁ is hydrogen or lower alkyl; R₃, R₄, R₅ and R₆ can be the same or different and represent hydrogen, lower alkyl and monocyclic aryl; however, not more than two of R₃, R₄, R₅, and R₆ can be aryl and neither of the carbon atoms in the aziridinyl ring may contain two branched chain lower alkyl groups; and to pharmaceutically acceptable salts thereof.

In formula I, the aziridinylcarbonyl group can be in the 6 or 7 position.

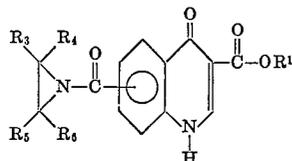
The term "lower alkyl" as employed herein includes both straight and branched chain radicals of up to and including eight carbon atoms, for instance, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl and the like. The lower alkyl group can include substituents such as aryl.

The halogen can be Br, Cl, I or F, with Br and Cl being preferred.

The term "monocyclic aryl" as employed herein includes monocyclic carbocyclic aryl radicals, for instance, phenyl and substituted phenyl radicals, including lower alkyl phenyl, such as tolyl, ethylphenyl, butylphenyl and the like, di(lower alkyl)phenyl (e.g., dimethylphenyl, 3,5-diethylphenyl and the like), halophenyl (e.g., chlorophenyl, bromophenyl, and 2,4,6-trichlorophenyl) and nitrophenyl. Phenyl is the preferred monocyclic aryl group.

It should be noted that the compounds of the invention wherein Z is OH may exist as the keto tautomer

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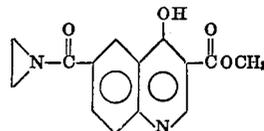


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Preferred are compounds wherein R₃ to R₆ are hydrogen or lower alkyl of 1 to 4 carbon atoms and R₁ is lower alkyl. Particularly preferred are compounds wherein R₃ to R₆ is hydrogen.

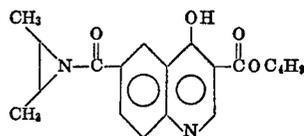
5 Examples of compounds falling within the present invention include, but are not limited to, the following:

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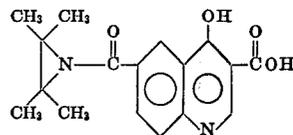
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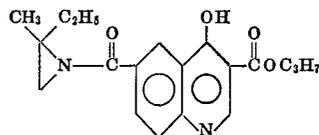
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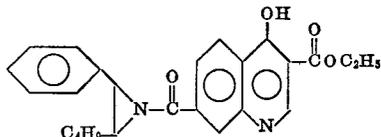
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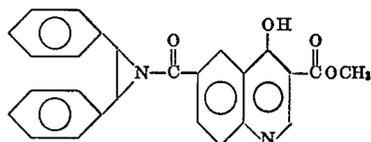
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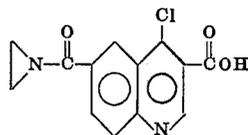
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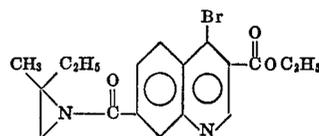
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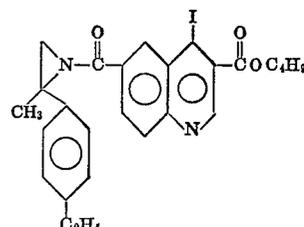
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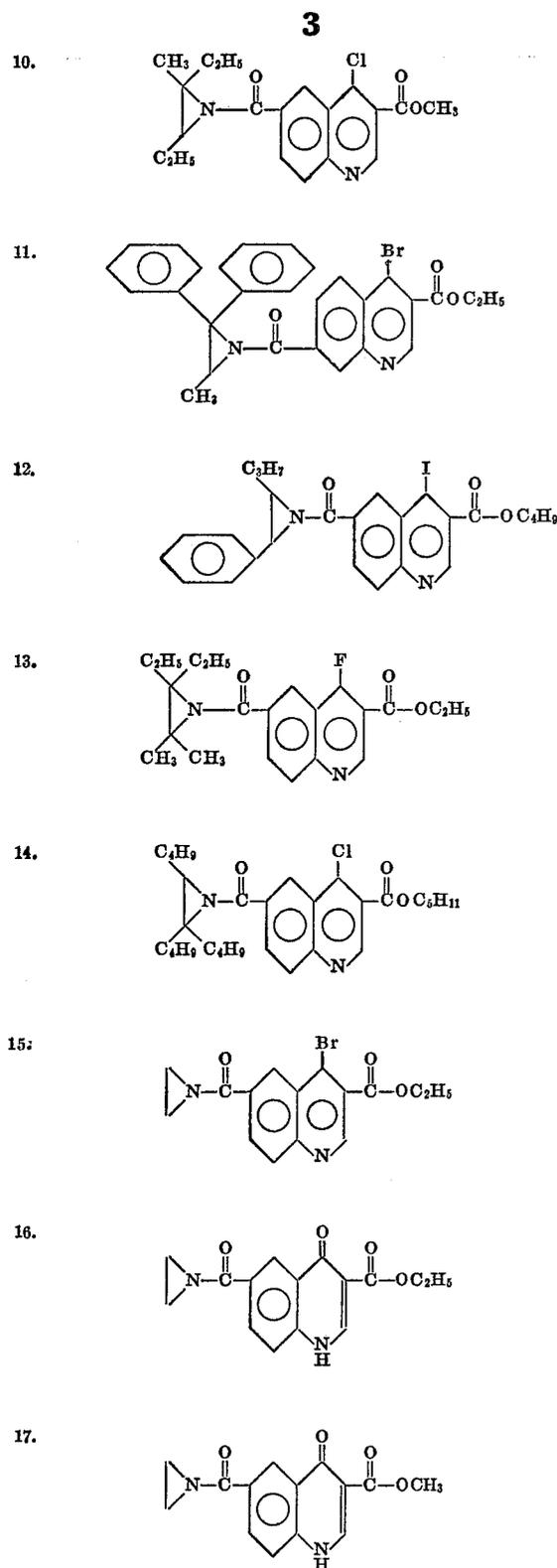
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9.

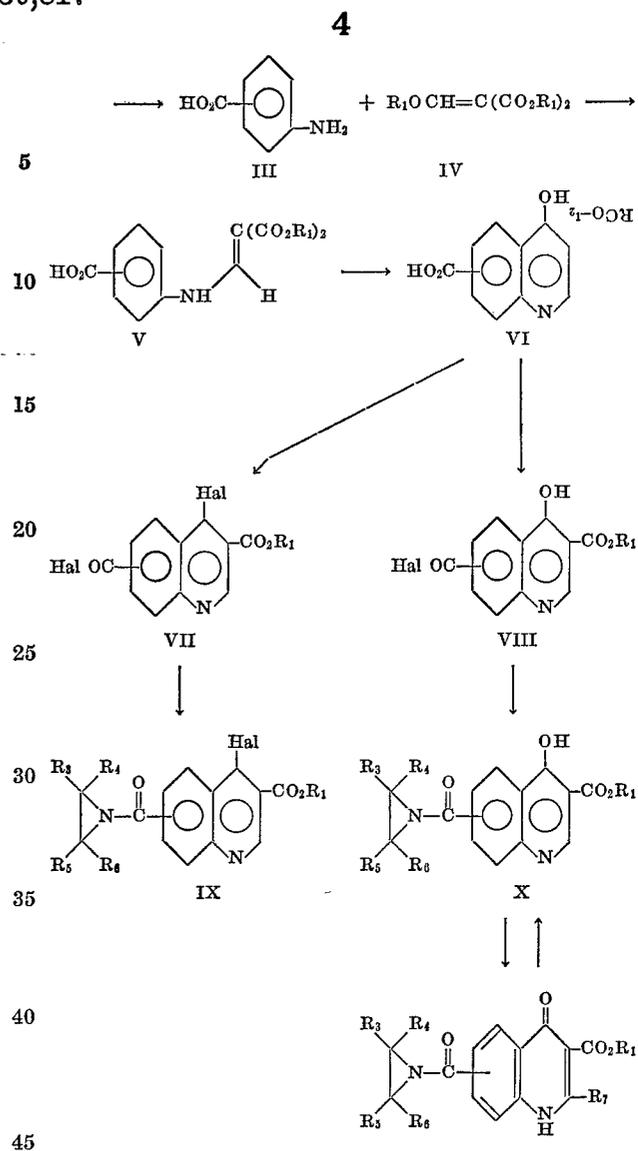
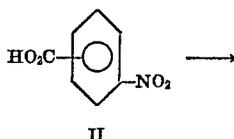


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The compounds of formula I can be prepared in accordance with the following reaction scheme.



In accordance with the above reaction scheme, a nitrobenzoic acid II is reduced to the corresponding amino-benzoic acid III by reaction with hydrogen in the presence of a catalyst for reduction, such as palladium or platinum on charcoal. The aminobenzoic acid III is reacted with an alkoxymethylene malonic acid or ester IV (in a molar ratio of III:IV of within the range of from about 0.8:1 to about 1.2:1) at a temperature within the range of from about 80 to about 140° C. to form compounds of structure V. Compound V is cyclized by heating it above about 200° C. in an inert solvent such as Dowtherm, triethylene glycol, or nitrobenzene, for a period ranging from about 0.5 to about 3 hours, to yield a hydroxy quinoline of formula VI. The hydroxy quinoline VI can then be reacted with a halogenating agent such as oxalyl chloride, thionyl chloride, phosphorus pentachloride, phosphorus pentabromide, thionyl bromide, oxalyl bromide or the like under appropriate conditions as described below, to yield either compound VII or compound VIII.

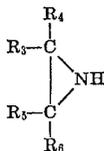
To form compound VII, the alkali metal salt of compound VI is reacted with a halogenating agent such as oxalyl chloride or thionyl bromide, in a molar ratio of VI:halide of within the range from about 2:1 to about 50:1 at a temperature within the range of from about 20 to about 90° C.

To form compound VIII, compound VI is reacted with halogenating agent, such as oxalyl chloride or thionyl bromide, in a molar ratio of VI:halide of within the range of from about 1:1 to about 20:1, at a temperature within the range of from about 30 to about 80° C.

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Compound VII and compound VIII can then be reacted with an ethyleneimine of the structure

XI



in a molar ratio of VII or VIII:imine of within the range of from about 1:1 to about 5:1 in the presence of an organic or inorganic base such as triethylamine, pyridine, sodium hydroxide, potassium hydroxide or ethyleneimine, at a temperature within the range of from about 0° to about 30° C.

Compounds of formula I where R₁ is H may be conveniently prepared from compounds of formula I where R₁ is lower alkyl like methyl or ethyl by hydrolysis under acidic or basic conditions by standard procedures.

In the foregoing formulas the symbols have the same meaning and limitations defined earlier.

The starting material of formula II may be either *m* or *p*-nitrobenzoic acid.

Illustrative starting materials of formula XI include aziridine; 2-ethylaziridine; 2,2-dimethylaziridine; 2,2,3,3-tetramethylaziridine; 2,3 - dimethylaziridine; 2 - phenylaziridine, 2,3-diphenylaziridine; 2-phenyl-2-ethylaziridine and the like.

The bases of formula I form pharmaceutically acceptable acid-addition salts by reaction with the common inorganic and organic acids. Such inorganic salts as the hydrohalides, e.g., hydrobromide, hydrochloride, hydroiodide, sulfates, nitrates, phosphates, borates, etc., and organic salts as acetate, tartrate, malate, citrate, succinate, benzoate, ascorbate, salicylate, theophyllinate, camphor-sulfonate, alkanesulfonate, e.g., methanesulfonate, aryl-sulfonate, e.g., benzenesulfonate, toluenesulfonate and the like are also within the scope of the invention. It is frequently convenient to effect the purification of the product by forming the acid salt. The base may be obtained therefrom by neutralization with an alkali hydroxide such as sodium hydroxide and the base in turn can be transformed into a different salt by reaction with the appropriate acid.

The new compounds of this invention are useful in combatting coccidiosis, a disease affecting primarily poultry, caused by protozoa of the genus *Eimeria*, especially *E. tenella*, *E. necatrix* and *E. acervulina*. This disease causes severe and frequently fatal infection in poultry flocks. It constitutes a serious economic hazard.

A current practice in poultry raising is the feeding of coccidiostatic preparations in the general diet as a prophylactic measure and the compounds of this invention may be used in this manner. Compounds of this invention are administered at levels about 0.05% by weight of the feed for this purpose. However, they are used in a therapeutic manner to combat the disease when it occurs.

Compositions containing one or more compounds of this invention may be formulated by intimately dispersing the active coccidiostatic ingredient or mixture of active ingredients throughout a carrier or diluent which is either solid or liquid. Preferably, the compound is thoroughly admixed with a major proportion of poultry feed supplied to the fowl, e.g., chick starter feed, broiler and grower feeds, laying mash, breeder and turkey breeder mash, turkey starter and grower feeds and the like.

The active material may also be incorporated in pre-mixes wherein higher proportions of the active ingredients are present. The concentrated premix is then diluted with additional feed by the feed supplier or poultry grower, for example, one pound of premix per ton of feed, to obtain a feed containing the requisite amount of coccidiostat.

It will also be appreciated that the active ingredients may be supplied in combination with an inert carrier or

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diluent such as Attapulgus clay, bentonite or edible vegetable materials, distillers dried grains, corn meal, fermentation residue and the like. Liquid dispersions in water can be prepared by using emulsifiers and/or surface active agents.

The amount of compound of formula I incorporated in the food or water is in the range of about 0.005 to 0.5% (by weight), preferably about 0.02 to 0.04%. In addition, the incorporation of a tetraalkylthiuram disulfide, e.g., tetramethylthiuram disulfide and the like, frequently enhance the action of a compound of formula I and thus conserve the amount of the latter required. Thus, a total of about 0.005 to 0.1% (by weight) preferably about 0.01 to 0.03% of the combined substances in the feed is usually adequate. Approximately equal proportions (percent by weight) of the two components is sufficient, but a ratio of about 1 to 3 of the quinoline derivative to about 1 to 3 parts of the disulfide may be used. The preferred composition contains quinoline derivative as the single active substance or in combination with tetraethylthiuram disulfide.

The compounds are also of value as nematocides. Nematodes like ascarides or pinworms are effectively controlled by feeding infected animal diets containing about 0.05% by weight of a compound of the class described.

The following examples are illustrative of the invention. All temperatures are on the centigrade scale.

EXAMPLE 1

6-(1-Aziridinylcarbonyl)-4-chloro-3-quinolinecarboxylic acid, ethyl ester

A. [(p-Carboxyanilino)methylene]malonic acid, diethyl ester.—A mixture of 13.7 g. (0.1 mole) of p-aminobenzoic acid and 21.6 g. (0.1 mole) of diethyl ethoxymethylene malonate is heated slowly to 130° C. The liquid begins to reflux and the mixture gradually solidifies. The mixture is kept at this temperature for approximately 30 min. After cooling, the solid is thoroughly mixed with ether and the insoluble material filtered to give 28 g. of product. Recrystallization from MeOH gives white needles, mp 220–223° C.,

$$\lambda_{\text{Nujol}}^{\text{max}} 1760 \text{ cm.}^{-1}$$

broad C=O; τ DMSO triplet at 8.75 τ (—CH₃'s) multiplet at 5.6–6.1 τ (CH₂'s); 2-doublets 2.1 τ , 2.6 τ , J=30 c.p.s. (Aromatic H's), doublet 1.5 τ , 1.74 τ (—CH=C<), doublet —0.6, —0.9 τ (NH), broad absorption —2.6 τ (OH).

Anal.

Calc. for C₁₅H₁₇NO₅: C, 58.63; H, 5.58; N, 4.56.
Found: C, 58.91; H, 5.67; N, 4.52.

B. 4 - Hydroxy - 3,6 - quinolinedicarboxylic acid, 3-ethyl ester.—A mixture of 10 g. (0.032 m.) of [(p-carboxyanilino)methylene]-malonic acid, diethyl ester and 30 ml. of Dowtherm is refluxed for 3 hours at 250–260° C. The mixture is cooled, filtered, rinsed with hexane and then methanol.

The product is recrystallized from dimethylformamide to give white crystals melting above 270°.

$$\lambda_{\text{Nujol}}^{\text{max}} 1660-1730 \text{ cm.}^{-1}$$

broad C=O, 2520–2720 cm.⁻¹, —H-bonded OH.

Anal.

Calc. for C₁₃H₁₁NO₅: C, 59.77; H, 4.24; N, 5.36.
Found: C, 59.72; H, 4.54; N, 5.29.

C. 6-(1-Aziridinylcarbonyl) - 4 - chloro - 3 - quinolinecarboxylic acid, ethyl ester.—A suspension of 2 g. of 4-hydroxy-3,6-quinoline-dicarboxylic acid, ethyl ester in 500 ml. of ethyl alcohol is neutralized with 1N potassium hydroxide using phenolphthalein as indicator. The residue left after evaporating the solvent is dried *in vacuo* over P₂O₅. The dried potassium salt is ground to a powder and treated with a solution of 3 ml. of oxalyl chloride in 50 ml. of benzene. After stirring overnight at room temperature, the insoluble solid is filtered off and

the solution concd. to give 1.1 g. of the 4-chloro-quinolinecarboxylic acid chloride.

A suspension of the above acid chloride in 200 ml. of benzene is added dropwise with stirring to a mixture of 0.2 g. of sodium hydroxide, 75 g. of ice, 50 ml. of benzene and 0.2 g. of ethyleneimine. The reaction temperature is maintained at 0-5° for 2 hr. The benzene layer is separated, washed with water, dried (MgSO₄) and evaporated to give 0.7 g. of yellowish-white solid, mp 90-100°. Recrystallization from acetonitrile gives an analytical sample: mp 107-110°;

$$\lambda_{\text{Nujol}}^{\text{max.}} 1718 \text{ cm.}^{-1}$$

(ester C=O), 1653 cm.⁻¹ (amide C=O); τ CDCl₃ 8.5 (t, CH₃), 7.48 (aziridine protons), 5.45 (CH₂).

Anal.

Calc. for C₁₅H₁₃N₂O₃Cl: C, 59.13; H, 4.31; N, 9.21; Cl, 11.6

Found: C, 58.91; H, 4.49; N, 9.15; Cl, 11.9

EXAMPLE 2

6-(1-Aziridinylcarbonyl)-4-hydroxy-3-quinolinecarboxylic acid, ethyl ester

To a suspension of 6 g. of 4-hydroxy-3,6-quinolinedicarboxylic acid, ethyl ester (Example 1, A and B) in 200 ml. of dry benzene and 100 ml. of dry chloroform, 18 ml. of oxalyl chloride is added and the mixture is refluxed for 2 hr. The oil obtained after evaporation of the solvent and excess oxalyl chloride *in vacuo*, is triturated with ether to give 2.5 g. of the 4-hydroxyquinolinecarboxylic acid chloride, mp 180-190°.

A suspension of 2.5 g. of the above compound is 200 ml. of benzene is added dropwise with stirring to a mixture of 0.49 g. of sodium hydroxide, 75 g. of ice, 50 ml. of benzene and 0.43 g. of ethyleneimine (addition time 1 hr., temp. 0-5°). The mixture is allowed to warm up to room temperature and stirred at room temperature for 0.5 hr. The benzene layer is separated, washed with water, dried (MgSO₄) and evaporated to give 1.79 g. of solid. Two recrystallizations from acetonitrile gives yellow crystals, mp 184-187°;

$$\lambda_{\text{Nujol}}^{\text{max.}} \text{C=O at } 1680 \text{ cm.}^{-1} \text{ and } 1660 \text{ cm.}^{-1}$$

with a shoulder at 1710 cm.⁻¹; τ CDCl₃ 8.6 (t, CH₃) 7.6 (s, aziridine protons), 5.7 (q, CH₂), 2.5-1.8 (aromatic protons), 1.4 (d, vinyl) and 2,3 (d, NH). The compound exists as the keto tautomer.

EXAMPLE 3

Following the procedure of Example 1, but substituting dimethyl methoxymethylene malonate for diethyl ethoxymethylene malonate, there is obtained 6-(1-aziridinylcarbonyl)-4-chloro-3-quinolinecarboxylic acid, methyl ester.

EXAMPLE 4

Following the procedure of Example 2, but substituting 2,2,3,3-tetramethylaziridine for aziridine, there is obtained 6-(2,2,3,3-tetramethyl-1-aziridinylcarbonyl)-4-hydroxy-3-quinolinecarboxylic acid, ethyl ester.

EXAMPLE 5

Following the procedure of Example 1, but substituting 2-phenylaziridine for aziridine, there is obtained 6-(2-phenyl-1-aziridinylcarbonyl)-4-chloro-3-quinolinecarboxylic acid, ethyl ester.

EXAMPLE 6

Following the procedure of Example 1, but substituting dibutylbutoxymethylene malonate for diethylethoxymethylene malonate, there is obtained 6-(1-aziridinylcarbonyl)-4-chloro-3-quinolinecarboxylic acid, butyl ester.

EXAMPLE 7

Following the procedure of Example 2, but substituting 2,3-diphenylaziridine for aziridine there is obtained 6-(2,3-diphenyl-1-aziridinylcarbonyl)-4-hydroxy-3-quinolinecarboxylic acid, ethyl ester.

EXAMPLE 8

Following the procedure of Example 1, but substituting 2,2-diphenylaziridine for aziridine there is obtained 6-(2,2-diphenyl-1-aziridinylcarbonyl)-4-chloro-3-quinolinecarboxylic acid.

EXAMPLE 9

Following the procedure of Example 2, but substituting 2-phenyl-2-ethylaziridine for aziridine there is obtained 6-[(2-phenyl-3-ethyl)-1-aziridinylcarbonyl]-4-hydroxy-3-quinolinecarboxylic acid, ethyl ester.

EXAMPLE 10

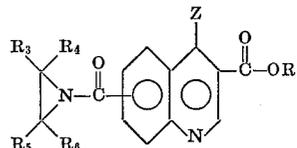
6-(1-Aziridinylcarbonyl)-4-chloro-3-quinolinecarboxylic acid

To a solution of 3.05 g. (0.01 mole) of 6-(1-aziridinylcarbonyl)-4-chloro-3-quinolinecarboxylic acid ethyl ester in 100 ml. of ethyl alcohol, 10 ml. of 0.1N alcoholic sodium hydroxide is added and the mixture refluxed for an hour. The solvent is removed *in vacuo*, the residue neutralized with 0.1N HCl to give 6-(1-aziridinylcarbonyl)-4-chloro-3-quinolinecarboxylic acid. It may be crystallized from dilute methyl alcohol.

It will be apparent to those skilled in the art that the ethyleneimine employed in preparing the compounds of the invention can include substituents such as alkyl or aryl as defined hereinbefore so that the aziridinyl group in any of the Examples can include as R₃, R₄, R₅ and R₆ such alkyl and/or aryl groups.

What is claimed is:

1. A compound of the structure



wherein Z is selected from the group consisting of hydroxy, chlorine and bromine; R₁ is selected from the group consisting of hydrogen and lower alkyl of 1 to 8 carbons; R₃, R₄, R₅, and R₆ are the same or different and are selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbons and phenyl, not more than two of R₃, R₄, R₅, and R₆ being phenyl and wherein neither of the carbon atoms in the aziridinyl ring contains two branched chain lower alkyl groups; and wherein the aziridinyl carbonyl group is located in either the 6 or 7 position; and pharmaceutically acceptable salts thereof.

2. A compound in accordance with claim 1 wherein R₃, R₄, R₅ and R₆ are selected from the group consisting of hydrogen and lower alkyl of 1 to 4 carbons.

3. A compound in accordance with claim 1 wherein R₃, R₄, R₅ and R₆ are all hydrogen.

4. A compound in accordance with claim 1 wherein Z is hydroxyl.

5. A compound in accordance with claim 1 wherein Z is chlorine or bromine.

6. A compound in accordance with claim 2 wherein R₁ is lower alkyl of 1 to 8 carbons.

7. A compound in accordance with claim 1 having the name 6-(1-aziridinylcarbonyl)-4-chloro-3-quinolinecarboxylic acid, ethyl ester.

8. A compound in accordance with claim 1 having the

name 6-(1-aziridinylcarbonyl)-4-hydroxy - 3 - quinoline-
 carboxylic acid, ethyl ester.

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DONALD G. DAUS, Primary Examiner

U.S. Cl. X.R.

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