The present invention relates to compositions of matter containing quinolines of the formula:

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R}
\end{align*}
\]

wherein \( R \) represents alkyl, substituted lower alkyl, cycloalkyl, naphthyl, and aralkyl; \( R \) represents O-alkyl, O-monoo or dialkylaminoalkyl, O-cycloalkyl, NH-alkyl, NH-aryl, NHCOOR, NHOR, or any readily hydrolyzable group. These compounds are useful as anti-microbial agents.

The present invention relates to anti-bacterial compositions containing as active ingredients, 1,4-dihydro-1-R-6,7-methylenedioxy-4-oxo-3-quinoline carboxylic acid derivatives of the formula:

\[
\begin{align*}
\text{CH} & \quad \text{O} \\
\text{R} & \quad \text{R}
\end{align*}
\]

where \( n \) is 1 to 4, \(-\text{NHCOOR}_2\), in which \( R_2 \) is lower alkyl or aralkyl and \( R_3 \) is lower alkyl or \( R_2 \) and \( R_3 \) taken together with the nitrogen atom may constitute a cyclic moiety such as morpholino, piperidino, or piperazine, etc., and \( R_4 \) may also be any readily hydrolyzable group, such as a thioester nitrile, or the like.

In the above definitions of \( R, R_1, R_2, \) and \( R_3 \), alkyl is meant to include those alkyl groups containing 1 to 12 carbon atoms in a straight or branch chain such as methyl, ethyl, propyl, isopropyl, and the like; cycloalkyl is meant to include from 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclohexyl, and the like; aralkyl is meant to include both mono- and dihydrogenated ring systems, such as benzyl, as well as heteroaromatic ring systems such as pyridyl, furyl, and the like. The definitions \( R, R_1, R_2 \) and \( R_3 \) as used hereinafter are to be considered to have the meanings defined above.

The compositions of this invention exhibit potent anti-bacterial activity particularly against gram negative bacteria, such as the Escherichia coli strain and the Proteus group. Accordingly, they are useful as anti-bacterial agents in the treatment of mammals, such as dogs, guinea pigs, cats, monkeys, and the like, which are infected with bacteria susceptible to these agents. In order to use these compounds, they are combined with known pharmaceutical carriers, such as lactose, starch, dicalcium phosphate, syrup, and the like, to yield various dosage forms such as tablets, suspensions and the like, with the active ingredient being present in amounts of from about 100 to 500 mg. per dosage unit. They may also be combined with sterile vehicles, such as sterile water, or sterile isotonic saline to form dosage forms suitable for parenteral administration.

These dosage forms may be compounded according to standard pharmaceutical art. Generally, a dosage regimen of about 100 mg. to 1500 mg., preferably about 250 mg., 3 or 4 times daily, orally or by injection are recommended to treat bacterial infections caused by these gram-negative bacteria. A surprising property of these compositions resides in the discovery that they are more slowly metabolized in the mammalian body and consequently, they are longer acting when compared with other quinoline compounds such as those disclosed in U.S. Pat. No. 3,287,458. Because of this prolonged activity, the dosage that is necessary to be administered to a host may be considerably reduced.

The compounds of this invention may also be administered in admixture with animal foodstuffs, for example, they may be mixed from 1 to 25% by weight with foodstuffs such as corn meal, water, and the like.

The compounds of this invention may also be used in a form suitable for topical application. Such compositions may comprise from about 1 to 20% by weight of the selected active ingredient and such standard pharmaceutical diluents which are commonly used in the manufacture of topical compositions, such as talc, Vaseline, or other hydrophilic or hydrophobic ointment bases, and the like. These compositions are applied to infected sites.

The compositions of this invention may also include other known anti-bacterials, such as the tetracyclines, the nitrofurans, the sulfa drugs, and the like to enhance their anti-bacterial spectrum.

The active ingredients of this invention are prepared by four different methods. In the first method (referred to as Method A in the examples below) a compound of the formula:

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R}
\end{align*}
\]

is treated with an alcohol, for example, methanol, diethylamine, ethanol, cyclohexanol, and the like to yield these compounds wherein \( R_1 \) is O-lower alkyl, O-dialkylaminoalkyl, O-cycloalkyl, and O-lower aralkenyl.

In the second method (referred to as Method B in the examples) employing analogous reaction conditions, compound II above is treated with a suitable amine to yield compounds wherein \( R_1 \) is NH-alkyl, NH-aryl, NH-aralkyl,
3

In the third method, (referred to as Method C in the examples) compound II is treated with hydroxylamine or substituted hydroxylamines to yield compounds wherein R₂ is NH₂OH or NH₂OR.

In the fourth method (referred to as Method D in the examples) compound II is treated with a carbamate ester (such as ethyl carbamate) to yield compounds wherein R₂ is NHCOOR. Starting compound II is obtained by treating quinolines of the formula:

\[
\begin{align*}
\text{CH}_2\text{O} & \\
\text{O} & \\
\text{N} & \\
\text{COOH} & \\
\text{(III)} & 
\end{align*}
\]

with thionyl chloride, oxalyl chloride or other agents generally used to convert acids to acid chlorides. Compound III is described and disclosed in U.S. Pat. 3,287,458.

The following examples are included in order further to illustrate the invention.

METHOD A

Example 1

1 - ethyl - 1,4 - dihydro-4-oxo-6,7-methylenedioxy-quinoline-3-carbonyl chloride. - Thiophenyl chloride (13.2 g., 0.11 mole) was added to a slurry of 26.1 g. (0.1 mole) of pure 1-ethyl-1,4-dihydro-4-oxo-6,7-methylenedioxy-3-quinoline carboxylic acid in 100 ml. of dry benzene and the mixture was refluxed for 12 hr. Petroleum ether (250 ml.) was added and the mixture filtered to yield 29 g. of 1-ethyl-1,4 - dihydro - 4-oxo-6,7-methylenedioxy - quinoline - 3 - carbonyl chloride as yellow brown solid, M.P. 255-256°C (dec.). The crude solid was re-refined with 500 ml. of CH₂Cl₂ and filtered hot to yield 24.3 g. (87%) of light brown solid, 1-ethyl-1,4-dihydro-4-oxo-6,7-methylenedioxy - quinoline - 3 - carbonyl chloride, M.P. 245°C (dec.).

Analysis. - Calcd. for C₂₃H₂₂ClNO₄ (percent): C, 55.83; H, 3.60; N, 5.01; Cl, 12.68. Found (percent): C, 56.03; H, 3.87; N, 4.94; Cl, 12.87.

Example 2

Cyclohexyl 1-ethyl-1,4 - dihydro - 4 - oxo-6,7-methylenedioxy-quinoline-3-carboxylate. - A mixture of 14 g. (0.05 mole) of 1-ethyl-1,4-dihydro-4-oxo-6,7-methylenedioxy-3-quinoline carboxylic acid and 6 g. (0.06 mole) of freshly distilled cyclohexanol and 30 g. of pyridine was heated for 2 hr. on a steam bath. The volatiles were removed in vacuo and the residue was triturated several times with water and filtered. The crude product was recrystallized from 1:1 CCl₄:Cellsol B yielding 15.4 g. (90%) of cyclohexyl 1-ethyl-1,4-dihydro-6,7-methylenedioxy - 4 - oxo - 3 - quinoline-carboxylate, M.P. 204-206°C.

Analysis. - Calcd. for C₂₃H₂₃NO₄ (percent): C, 66.46; H, 6.16; N, 4.08. Found (percent): C, 66.46; H, 6.24; N, 3.91.

Example 3

Following the procedure of Example 2 and employing analogous reaction conditions, but using ethanol, instead of cyclohexanol, there was obtained propyl 1-ethyl-1,4 - dihydro - 6,7 - methylenedioxy - 4 - oxo-3-quinolinecarboxylate, M.P. 158-160°C.


Example 5

Following the procedure of Example 2 and employing analogous reaction conditions, but using n-butanol instead of cyclohexanol, there was obtained butyl 1-ethyl-1,4 - dihydro - 6,7 - methylenedioxy - 4-oxo-3-quinoline carboxylate, M.P. 131-133°C.

Analysis. - Calcd. for C₂₅H₂₅NO₄ (percent): C, 64.35; H, 6.04; N, 4.41. Found (percent): C, 64.23; H, 5.94; N, 4.23.

Example 6

Following the procedure of Example 2 and employing analogous reaction conditions, but using t-amyl alcohol instead of cyclohexanol, there was obtained tert-amyl 1-ethyl-1,4 - dihydro - 6,7 - methylenedioxy - 4-oxo-3-quinolinecarboxylate, M.P. 172-173°C.


Example 7

Following the procedure of Example 2 and employing analogous reaction conditions, but using n-hexyl alcohol instead of cyclohexanol, there was obtained hexyl 1-ethyl-1,4 - dihydro - 6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate, M.P. 90-92°C.

Analysis. - Calcd. for C₂₇H₂₇NO₄ (percent): C, 66.07; H, 7.71; N, 4.06. Found (percent): C, 65.90; H, 6.81; N, 4.19.

Example 8

Following the procedure of Example 2 and employing analogous reaction conditions, but using n-decyl alcohol instead of cyclohexanol, there was obtained decyl 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate, M.P. 99-101°C.

Analysis. - Calcd. for C₃₀H₃₄NO₄ (percent): C, 68.80; H, 7.78; N, 3.49. Found (percent): C, 69.07; H, 7.89; N, 3.70.

Example 9

Following the procedure of Example 2 and employing analogous reaction conditions, but using diethylaminoethanol, instead of cyclohexanol, there was obtained 2-(diethylamino)ethyl 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate, M.P. 108-109°C.

Analysis. - Calcd. for C₂₃H₂₃NO₄ (percent): C, 63.32; H, 7.61; N, 7.77. Found (percent): C, 63.52; H, 7.65; N, 7.48.

Example 10

The acid chloride obtained by treatment of 1,4-dihydro-1 - methyl - 6,7 - methylenedioxy-4-oxo-3-quinolinecarboxylic acid with thionyl chloride as in Method A, Example 1, was treated, without isolation, with ethanol to yield 1-ethyl-1,4 - dihydro - 1-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate, M.P. 202-203°C.


Example 11

The acid chloride obtained by treatment of 1,4-dihydro-6,7-methylenedioxy-4-oxo-1-propyl-3-quinoline carboxylic acid with thionyl chloride, as in Method A, Example 1, was treated, without isolation, with ethanol to yield ethyl 1,4 - dihydro - 6,7 - methylenedioxy-4-oxo-1-propyl-3-quinolinecarboxylate, M.P. 147-149°C.

Analysis. - Calcd. for C₂₆H₂₅NO₄ (percent): C, 63.36; H, 5.65; N, 4.26. Found (percent): C, 63.34; H, 5.80; N, 4.44.

Example 12

The acid chloride obtained by treatment of 1-butyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinoline carboxylic acid.
acid with thionyl chloride, as in Method A, Example 1, was treated, without isolation, with ethanol to yield ethyl 1-buty1-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinoline carboxylate, M.P. 117-119\degree.

**Analysis.**—Calcd. for C₁₀H₁₄NO₅ (percent): C, 64.35; H, 6.04; N, 4.41. Found (percent): C, 64.51; H, 6.23; N, 4.50.

**METHOD B**

**Example 1**

N - (2-diethylaminoethyl)-1-ethyl-1,4-dihydro-4-oxo-6,7-methylenedioxy-quinoline-3-carboxamide.—A mixture of 8.4 g. (0.03 mole) of 1-ethyl-1,4-dihydro-4-oxo-6,7-methylenedioxy quinoline-3-carbonyl chloride, 4.6 g. (0.04 mole) of N,N-diethyl ethylenediamine and 150 ml. of benzene was refluxed for 8 hr. The volatiles were removed under aspirator vacuum and the residue was triturated with 5% NaOH solution and recrystallized from aqueous isopropyl alcohol yielding 10.2 g. (94%), M.P. 192-195\degree of N - (2-diethylaminoethyl) - 1-ethyl-1,4-dihydro - 6,7-methylenedioxy-4-oxo-3-quinoline carboxamide, M.P. 199-201\degree.

**Analysis.**—Calcd. for C₁₆H₂₁N₃O₄ (percent): C, 63.49; H, 7.01; N, 11.69. Found (percent): C, 63.57; H, 7.05; N, 11.76.

**Example 2**

Following the procedure of Method C, Example 1, and using m-anisidine there was obtained 1-ethyl-1,4-dihydro-N - (m-methoxyphenyl)-6,7-methylenedioxy-4-oxo-3-quinoline carboxamide, M.P. 240-241\degree.

**Analysis.**—Calcd. for C₁₉H₂₁N₂O₂ (percent): C, 65.56; H, 4.95; N, 7.65. Found (percent): C, 65.50; H, 5.02; N, 7.41.

**METHOD C**

1-ethyl-1,4-dihydro-4-oxo-6,7-methylenedioxyquinoline-3-hydroxamic acid.—Hydroxylamine hydrochloride (2.1 g., 0.03 mole) was added to a mixture of 4.2 g. (0.015 mole) of 1-ethyl-1,4-dihydro-4-oxo-6,7-methylenedioxyquinoline-3-carbonyl chloride in 25 ml. of pyridine. After stirring for 2 hr., the mixture was heated for 3 hr. on a steam bath. The pyridine was removed under aspirator vacuum and the residue was recrystallized from 90% aqueous ethanol to yield 4.0 g. of light yellow crystals (96%) of 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinoline hydroxamic acid, M.P. 265-268\degree. The analytical sample from 95% ethanol had M.P. 269-270\degree.

**Analysis.**—Calcd. for C₁₉H₂₁N₂O₄ (percent): C, 56.52; H, 4.38; N, 10.14. Found (percent): C, 56.77; H, 4.47; N, 10.10.

**METHOD D**

Ethyl[(1-ethyl-1,4-dihydro-4-oxo-6,7-methylenedioxyquinoline - 3 - yl)carbonyl]carbamates.—A mixture of 8.4 g. (0.03 mole) of 1-ethyl-1,4-dihydro-4-oxo-6,7-methylenedioxyquinoline-3-carbonyl chloride, 5.3 g. of (0.06 mole) of ethyl carbamate and 100 ml. of pyridine was refluxed for 8 hr. The solvent was removed in vacuo and the residue triturated with water and recrystallized from 90% aqueous dimethylformamide yielding 76% of colorless crystalline ethyl[(1-ethyl-1,4-dihydro-4-oxo-6,7-methylenedioxyquinoline-3-yl)carbonyl]carbamate, M.P. 273-275\degree (dec.). The analytical material had M.P. 276-277\degree (dec.).

**Analysis.**—Calcd. for C₉₁H₁₄N₂O₇ (percent): C, 57.83; H, 4.85; N, 8.43. Found (percent): C, 57.54; H, 4.94; N, 8.25.

It is understood that the foregoing detailed description is given merely by way of illustration and that many variations may be made therein without departing from the spirit of our invention.

Having described our invention, what we desire to secure by Letters Patent is:

1. A compound of the formula:

   ![Chemical Structure](image)

   wherein R is lower alkyl, hydroxy-lower alkyl, carboxylower alkyl, lower alkenyl, or cycloalkyl, in which cycloalkyl has from 3 to 8 carbon atoms; R₁ is NH₂OH, NHCOOR₂,

2. The compound of claim 1 wherein R is C₇H₈ and R₁ is NH₂OH.

3. The compound of claim 1 wherein R is C₇H₈ and R₁ is NHCOOC₃H₇₃.

4. The compound of claim 1 wherein R is C₇H₈ and R₁ is

5. The compound of claim 1 wherein R is C₇H₈ and R₁ is OCH₃CH₂N(C₃H₇)₂.

**References Cited**

**UNITED STATES PATENTS**

2,614,121 10/1952 Price et al. 260-287 X
3,290,315 12/1966 Watson 260-287 X
3,597,208 8/1968 Berman 260-287 X

**DONALD G. DAUS, Primary Examiner**

U.S. Cl. X.R. 424-258; 260-247.2, 268