United States Patent Office

3,591,697

Patented July 6, 1971

3,591,697

1,4-DIHYDRO - 1 - SUBSTITUTED-6,7-METHYLENE-DIOXY-4-OXO - 3 - QUINOLINE CARBOXYLIC ACID ANTIBACTERIAL AGENTS

Daniel Kaminsky, Parsippany, and Robert I. Meltzer, Rockaway, N.J., assignors to Warner-Lambert Pharmaceutical Company, Morris Plains, N.J.

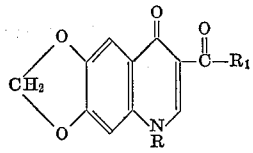
No Drawing. Continuation-in-part of application Ser. No. 639,304, May 18, 1967. This application June 19, 1970, Ser. No. 47,893

Int. Cl. A61k 27/00

U.S. Cl. 424—258 4 Claims

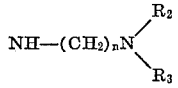
ABSTRACT OF THE DISCLOSURE

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



wherein R represents alkyl, substituted lower alkyl, cycloalkyl, alkenyl and aralkyl; R_1 represents O-alkyl, O-mono or dialkylaminoalkyl, O-cycloalkyl, NH-alkyl, NH-aryl,

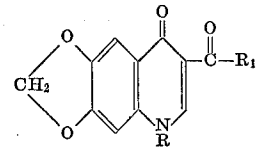




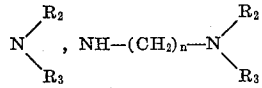
$NHCOOR_2$, NHOR, or any readily hydrolyzable group. These compounds are useful as anti-microbial agents.

This application is a continuation-in-part application of our copending application, U.S. Ser. No. 639,304, filed May 18, 1967, now U.S. Pat. No. 524,858.

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



wherein R represents lower alkyl, substituted lower alkyl, preferably hydroxy lower alkyl, carboxy lower alkyl, lower alkenyl and cycloalkyl; R_1 represents O-alkyl, O-mono or dialkylaminoalkyl, NH-lower alkyl, NH-aralkyl, NH-aryl,



where *n* is 1 to 4, —$NHCOOR_2$, 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 piperazino, etc., and R_1 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 monohomocyclic 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 group, for example, *E. coli* and the Proteus group, for example, *P. vulgaris*. 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 an inert pharmaceutical carrier such as lactose, starch, dicalcium phosphates, 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.

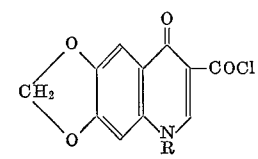
The compounds of this invention may also be administered in admixture with animal food stuffs, for example, they may be mixed from 1 to 25% by weight with food stuffs such as corn meal, water, and the like.

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 hydrophobic or hydrophilic 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 nitro-furans, the sulfa drugs, and the like to enhance their anti-bacterial spectrum.

Among the preferred compositions are those compositions containing as active ingredients an anti-bacterially effective amount of a compound according to Structure 1 above wherein R is lower alkyl, hydroxy-lower alkyl, carboxy-lower alkyl, lower alkenyl and cycloalkyl, in which cycloalkyl contains from 3 to 8 carbon atoms; R_1 is O-alkyl, preferably O-lower alkyl, O-mono alkyl or dilower-alkyl or O-cycloalkyl in which cycloalkyl contains from 3 to 8 cabon atoms and NHOH, $NHCOOR_2$; in which R_2 is lower alkyl in an inert pharmaceutical carrier.

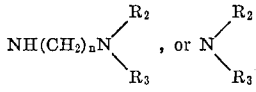
The active ingredients of this invention are prepared by four different methods. In the first method (referred to as Method A in the examples below) a compound of the formula:



(II)

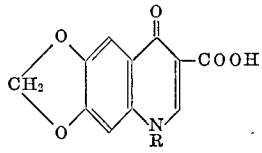
is treated with an alcohol, for example, methanol, diethylaminoethanol, cyclohexanol, and the like, to yield these compounds wherein R_1 is O-lower alkyl, O-dialkylaminoalkyl, O-cycloalkyl, and O-lower alkenyl.

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,



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 R_1 is NHOH or NHOR.

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 R_1 is NHCOOR. Starting compound II is obtained by treating quinolines of the formula:



(III)

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. No. 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

Thionyl 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. dry benzene and the mixture was refluxed for 12 hrs. 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. 235–236° (dec.). The crude solid was refluxed with 500 ml. of CH_2Cl_2 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° (dec.).

Analysis.—Calcd. for $C_{13}H_{10}ClNO_4$ (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-quinoline - 3 - carbonyl chloride, 6 g. (0.06 mole) of freshly distilled cyclohexanol and 30 g. of pyridine was heated for 2 hrs. 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 3:1 CCl_4:Skellysolve 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°.

Analysis.—Calcd. for $C_{19}H_{21}NO_5$ (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 ethyl 1-ethyl-1,4-dihydro-6,7-methylenedioxy - 4 - oxo - 3 - quinolinecarboxylate, M.P. 177–178°.

Analysis.—Calcd. for $C_{15}H_{15}NO_5$ (percent): C, 62.28; H, 5.23; N, 4.48. Found (percent): C, 61.99; H, 5.07; N, 4.71.

EXAMPLE 4

Following the procedure of Example 2 and employing analogous reaction conditions, but using n-propanol instead of cyclohexanol, there was obtained propyl 1-ethyl-1,4-dihydro-6,7-methylenedioxy - 4 - oxo - 3 - quinolinecarboxylate, M.P. 159–160°.

Analysis.—Calcd. for $C_{16}H_{17}NO_5$ (percent): C, 63.36; H, 5.56; N, 4.62. Found (percent): C, 63.13; H, 5.72; N, 4.74.

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 - quinolinecarboxylate, M.P. 131–133°.

Analysis.—Calcd. for $C_{17}H_{19}NO_5$ (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-dhydro - 6,7 - methylenedioxy-4-oxo-3-quinolinecarboxylate, M.P. 172–173°.

Analysis.—Calcd. for $C_{18}H_{21}NO_5$ (percent): C, 65.24; H, 6.39; N, 4.23. Found (percent): C, 65.16; H, 6.36; N, 4.46.

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°.

Analysis.—Calcd. for $C_{19}H_{23}NO_5$ (percent): C, 66.07; H, 6.71; 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°.

Analysis.—Calcd. for $C_{23}H_{31}NO_5$ (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°.

Analysis.—Calcd. for $C_{19}H_{24}N_2O_5$ (percent): C, 63.32; H, 6.71; N, 7.77. Found (percent): C, 63.52; H, 6.75; 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 ethyl 1,4-dihydro-1-methyl - 6,7 - methylenedioxy-4-oxo-3-quinolinecarboxylate, M.P. 202–203°.

Analysis.—Calcd. for $C_{14}H_{13}NO_5$ (percent): C, 61.09; H, 4.76; N, 5.09. Found (percent): C, 61.26; H, 4.99; N, 5.08.

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°.

Analysis.—Calcd. for $C_{16}H_{17}NO_5$ (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 with thionyl chloride, as in Method A, Example 1, was treated, without isolation, with ethanol to yield ethyl 1-butyl-1,4-dihydro - 6,7 - methylenedioxy-4-oxo-3-quinoline carboxylate, M.P. 117–119°.

Analysis.—Calcd. for $C_{17}H_{19}NO_5$ (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 hrs. 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° of N - (2-diethylaminoethyl)-1-ethyl-1,4-dihydro-6,7-methylenedioxy - 4 - oxo - 3 - quinoline carboxamide, M.P. 199–201°.

Analysis.—Calcd. for $C_{19}H_{25}N_3O_4$ (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°.

Analysis.—Calcd. for $C_{20}H_{18}N_2O_5$ (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°. The analytical sample from 95% ethanol had M.P. 269–270°.

Analysis.—Calcd. for $C_{13}H_{12}N_2O_5$ (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-methylenedioxy-quinoline-3-yl)carbonyl]carbamates

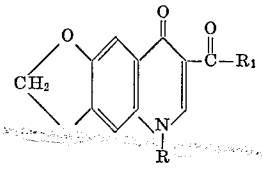
A mixture of 8.4 g. (0.03 mole) of 1-ethyl-1,4-dihydro-

4 - oxo-6,7-methylenedioxyquinoline-3-carbonyl chloride, 5.3 g. (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° (dec.). The analytical material had M.P. 276–277° (dec.).

Analysis.—Calcd. for $C_{16}H_{16}N_2O_6$ (percent): C, 57.83; H, 4.85; N, 8.43. Found (percent): C, 57.54; H, 4.94; N, 8.25.

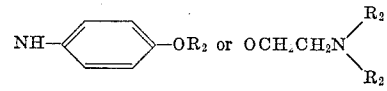
We claim:

1. An anti-bacterial composition containing as active ingredient an anti-bacterially effective amount of a compound of the formula:



wherein R is lower alkyl, hydroxy-lower alkyl, carboxy-lower alkyl, lower alkenyl, or cycloalkyl, in which cycloalkyl contains from 3 to 8 carbon atoms; R_1 is

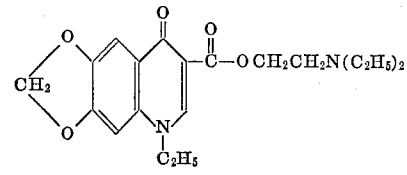
NHOH, $NHCOOR_2$



in which R_2 is lower alkyl in an inert pharmaceutical carrier.

2. A method for treating gram negative bacterial infections in a mammal which comprises administration to said mammal an effective anti-bacterial amount of a composition according to claim 1.

3. A method according to claim 1 wherein said composition contains as active ingredient the compound having the following structural formula:



at a dose of about 25 mg. to 1500 mg. several times daily.

4. A method according to claim 3 wherein the composition of claim 1 is administered at a dose of about 250 mg. several times daily.

References Cited

UNITED STATES PATENTS

2,614,121	10/1952	Price et al.	260—287
3,172,811	3/1965	Kaminsky et al.	260—287
3,290,315	12/1966	Watson	260—287
3,397,208	8/1968	Berman	260—287

JEROME D. GOLDBERG, Primary Examiner