United States Patent [19]

Santilli et al.

[11] **3,853,864**

[45] **Dec. 10, 1974**

[54] **1,7-DIALKYL-1,2-DIHYDRO-4-HYDROXY-1,8-NAPHTHYRIDINE-3-CARBOXYLIC ACID ALKYL ESTERS**

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[21] Appl. No.: **313,048**

[52] **U.S. Cl.** ..... **260/295.5 B,** 260/295.5 R, 260/294.8 F, 424/266

[51] **Int. Cl.** **C07c 31/36**

[58] **Field of Search** ..... 260/295.5 B

[56] **References Cited**

UNITED STATES PATENTS

3,590,036	6/1971	Lesher et al.	260/295.5 B
3,786,043	1/1974	Brundage et al.	260/295.5 B
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OTHER PUBLICATIONS

Lesher et al., Journal of Medicinal And Pharmaceutical Chemistry, Vol. 5, No. 5, Pages 1063–1065, Sept. 1962 Rsl J5.

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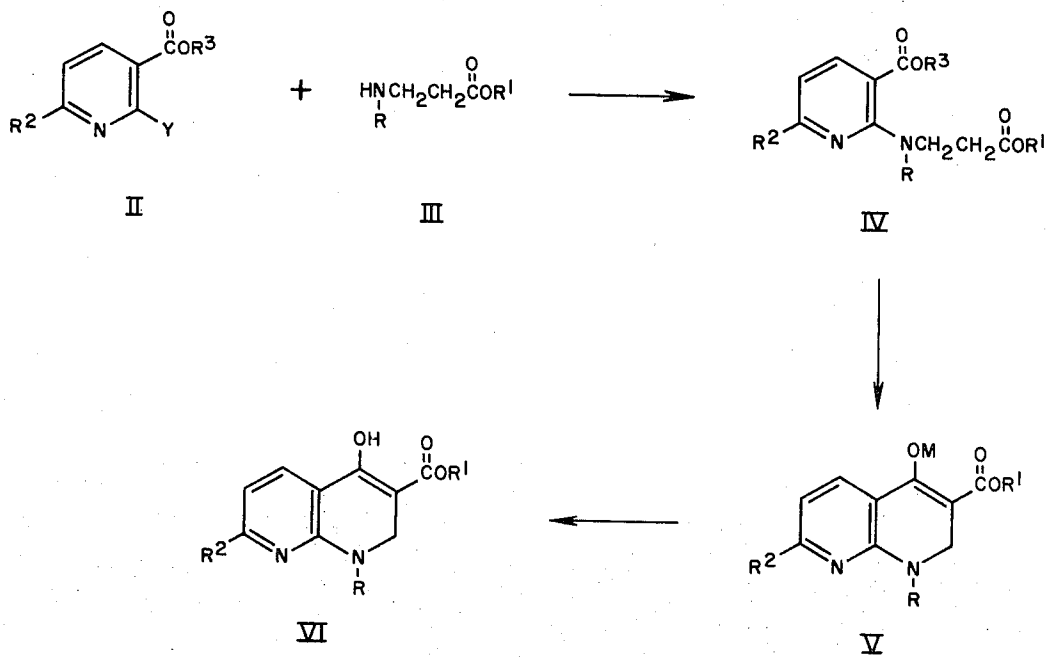
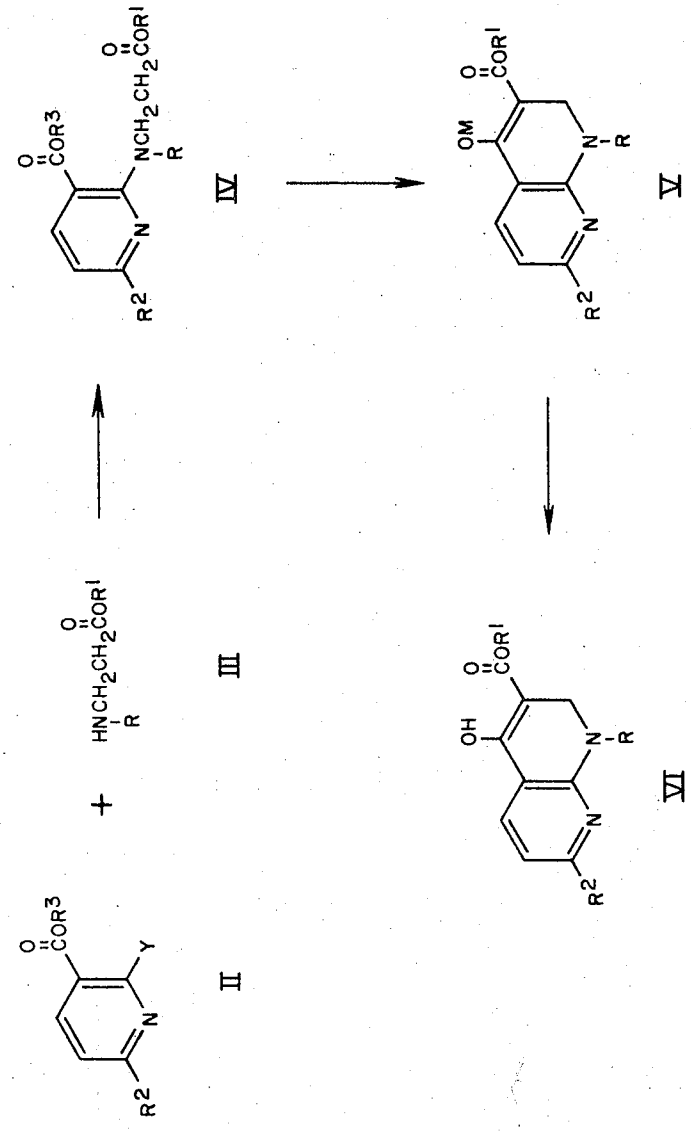
Attorney, Agent, or Firm—David E. Frankhouser

[57] **ABSTRACT**

1,7-Dialkyl-1,2-dihydro-4-hydroxy-1,8-naphthyridine-3-carboxylic acid alkyl esters are prepared by cyclization of 2-[(2-alkoxycarbonylethyl)alkylamino]-6-alkylnicotinic acid alkyl esters. The compounds so produced exhibit in vivo antibacterial activity.

8 Claims, 1 Drawing Figure



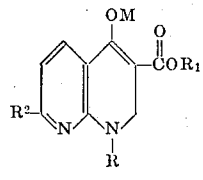

II
III
IV
V
VI
VII

1,7-DIALKYL-1,2-DIHYDRO-4-HYDROXY-1,8-NAPHTHYRIDINE-3-CARBOXYLIC ACID ALKYL ESTERS

This invention relates to new and pharmacologically active chemical compounds classified in the art of chemistry as alkyl esters of 1,7-dialkyl-1,2-dihydro-4-hydroxy-1,8-naphthyridine-3-carboxylic acids.

1,7-Dialkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids and esters thereof are described in U.S. Pat. No. 3,590,036 and in an article by G. Lesher et al. J. Med. Pharm. Chem, 5, 1063 (1962).

The invention sought to be patented in its broadest aspect comprises chemical compounds of the structural formula



I

wherein R is a straight-chain lower alkyl group, R^1 and R^2 are each a straight-chain or branched lower alkyl group, and M is hydrogen or an alkali metal, and, when M is hydrogen, the non-toxic, pharmaceutically acceptable acid addition salts thereof.

Preferred embodiments of the compounds of Formula I are those wherein R is ethyl, R^2 is methyl, R^1 is a straight-chain or branched lower alkyl group, and M is hydrogen.

The compounds of Formula I exhibit in vivo anti-bacterial effects as demonstrated by evaluation in standard in vivo anti-bacterial test procedures.

In describing the invention herein, reference will be made to the annexed Drawing which shows the preparation of the 1,7-di(lower)alkyl-1,2-dihydro-4-hydroxy-1,8-naphthyridine-3-carboxylic acid, (lower-)alkyl esters. In the Drawing, R, R^1 and R^2 have the meanings hereinbefore set forth in Formula I, M is an alkali metal, and Y is chloro, bromo, iodo, benzenesulfonyloxy, p-methylbenzenesulfonyloxy, or p-bromobenzenesulfonyloxy.

Referring now to the Drawing, where the compounds are assigned Roman numerals for identification, the compounds of the invention are prepared according to the following methods:

In the first step, a nicotinic acid ester (II), having a displaceable substituent in the 2-position, is reacted with a 3-[N-alkylamino]propionic acid ester (III) to produce a nicotinic acid ester compound (IV) having an (alkoxycarbonylethyl)alkylamino substituent in the 2-position. The reaction is carried out in the presence of an acid acceptor, such as sodium carbonate, in a reaction-inert solvent, such as dimethylformamide (DMF) or dimethyl-acetamide (DMA), at a temperature ranging from 150°C to 175°C. With DMF or DMA as solvents, it is convenient to perform the reaction at the reflux temperature.

In the second step, the 2-nicotinic acid ester compound (IV) is cyclized under Dieckmann reaction conditions to afford an alkyl 1,7-dialkyl-1,2-dihydro-4-hydroxy-1,8-naphthyridine-3-carboxylate.

The cyclization reaction is preferably effected by heating the intermediate (IV) at a temperature ranging from 50°C to 100°C, (preferably 60°C to 80°C) in the presence of an alkali metal lower alkoxide in a non-reactive organic solvent, preferably a lower alkanol.

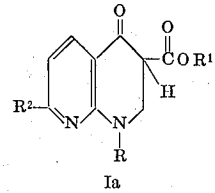
Under these conditions, the product is obtained as the alkali metal enolate salt (V). It will be appreciated that, to prevent transesterification, best results will be obtained when the alkoxide reagent and the alkanol employed as solvent contain the same alkyl moiety (R^1) that is present in the alkyl ester function at the 3-position of the cyclized product. The alkali metal alkoxide can conveniently be prepared in situ by dissolving the alkali metal in the desired alkanol solvent, and thereafter adding the intermediate to be cyclized.

The enol salt (V) can be converted to the enol (VI) by acidification with an acid whereby the alkali metal (M) is replaced by hydrogen. When a weak acid (i.e., one which will not protonate the amine function) is employed, the product is obtained in the form of the free amine. If desired, the free amine can be converted to an acid addition salt by treatment with a strong acid. The acid employed for formation of the acid addition salt must be non-toxic and acceptable for pharmaceutical use. Among the suitable acids are hydrochloric, hydrobromic, sulfuric, nitric, sulfonic, benzenesulfonic, p-toluenesulfonic, methanesulfonic, or phosphoric.

As used herein and in the appended claims, "lower alkyl" means an alkyl group having from one to six carbon atoms. The term "lower alkoxide" means an alkoxy group having from one to six carbon atoms. "Alkali metal" means sodium or potassium.

The starting compounds for the processes described herein are either known compounds or can be prepared from known compounds by procedures well known in the art.

It will be appreciated by those skilled in the art that the compounds of the invention can exist as tautomers. Hence, the compounds can be depicted in the enol form as in Formula I or in the keto form as in Formula Ia:



Ia

Infrared and nuclear magnetic resonance spectrographic data indicate that the enol form (I) is the predominate form. Hence, the compounds of the invention are depicted and named herein in the enol form as 1,2-dihydro-4-hydroxy-1,8-naphthyridine-3-carboxylic acids rather than as 1,2,3,4-tetrahydro-4-oxo-1,8-naphthyridine-3-carboxylic acids. It is understood that both the enol and keto forms are equivalent for the purposes of the invention.

When the compounds of the invention are employed as in vivo anti-bacterial agents, they may be administered alone or in combination with pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets or capsules containing such excipients as starch, lactose, magnesium stearate, and so forth. They may be administered orally in the form of solution or they may be injected parenterally, e.g. intramuscularly. For parenteral administration, they may be used in the form of a sterile solution or suspensions containing other solutes, for ex-

ample, enough saline or glucose to make the solution isotonic.

The dosage of the present pharmacologically active agents will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular subject under treatment. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. It will generally be found that when the composition is administered orally, larger quantities of the active agent will be required to produce the same effect as a smaller quantity given parenterally. In general, the compounds of this invention are most desirably administered at a dosage that will generally afford effective results without causing any harmful or deleterious side effects.

The manner and processes for making and using the compounds of the invention are illustrated in the following examples, wherein all temperatures are expressed as degrees Centigrade.

EXAMPLE I

2-Chloro-6-Methylnicotinic Acid Methyl Ester

A mixture of 25 g. of 2-hydroxy-6-methyl nicotinic acid in 125 ml. of phosphorus oxychloride is heated under reflux for 2.5 hours. The phosphorus oxychloride is then removed in a rotary evaporator. The residue is slowly poured into 600 ml. of cold methanol. The methanol is evaporated and the residue dissolved in 250 ml. of water and extracted with 150 ml. of chloroform. The chloroform layer is dried over magnesium sulfate, filtered and evaporated to give 29.5 g. of the title compound as an oil.

Analysis for $C_8H_8NClO_2$

Calculated: C, **51.77**; H, **4.34**; N, **7.55**

Found: C, **51.92**; H, **4.65**; N, **7.04**

EXAMPLE II

2-[(2-Ethoxycarbonylethyl)Ethylamino]-6-Methylnicotinic Acid Methyl Ester

A mixture of 12 g. of 2-chloro-6-methylnicotinic acid, methyl ester, 0.5 g. of ethyl-3-(ethylamino)propionate [D. W. Adamson, J. Chem. Soc., 1949 Suppl. Issue 1 S 144] and 7 g. of sodium carbonate in 100 ml. of dimethylformamide (DMF) is heated under reflux for 18 hours. The mixture is filtered and the DMF evaporated. The residue is partitioned between 250 ml. of ether and 250 ml. of water. The ether layer is dried over magnesium sulfate, filtered, and evaporated to give an oil which is used directly in Example III.

EXAMPLE III

1-Ethyl-1,2-Dihydro-4-Hydroxy-7-Methyl-1,8-Naphthyridine-3-Carboxylic Acid Ethyl Ester, Hydrochloride

The oil from Example II is added to a sodium ethoxide solution prepared by dissolving 3.0 g. of sodium in 250 ml. of absolute ethanol. The mixture is heated at reflux temperature for 10 minutes. The mixture is cooled. The insoluble material is collected and triturated with 200 ml. of 20% aqueous acetic acid solution. The insolubles are collected and recrystallized from petroleum ether. The free base (m.p. 75°–80°) is dissolved in ethyl acetate and acidified with ethereal hydrochloric acid to yield 1.3 g. of the title compound, m.p. 161°–164°.

Analysis for $C_{14}H_{19}N_2ClO_3$

Calculated: C, 56.28; H, 6.41; N, 9.38

Found: C, 56.52; H, 6.54; N, 9.62

EXAMPLE IV

2-[(2-n-Butoxycarbonylethyl)Ethylamino]-6-Methylnicotinic Acid Methyl Ester

A mixture of 18.5 g. of 2-chloro-6-methylnicotinic acid methyl ester, 17.3 g. of butyl 3-ethylaminopropionate and 10.6 g. of sodium carbonate in 100 ml. of dimethylformamide (DMF) is heated under reflux for 20 hours. The mixture is filtered and the DMF evaporated. The residue is partitioned between 250 ml. of ether and 250 ml. of water. The ether layer is dried over magnesium sulfate, filtered and evaporated to afford an oil which is used directly in Example V.

EXAMPLE V

1-Ethyl-1,2-Dihydro-4-Hydroxy-7-Methyl-1,8-Naphthyridine-3-Carboxylic Acid Butyl Ester, Hydrochloride

The oil from Example IV is added to a solution of sodium n-butoxide prepared by dissolving 2.3 g. of sodium in 400 ml. of butanol. The mixture is heated at reflux temperature for 10 minutes. The precipitate is collected and dissolved in 150 ml. of 10% aqueous acetic acid. The solution is extracted with 150 ml. of ether. The ether layer is dried over magnesium sulfate, filtered, and diluted with 15 ml. of ethyl acetate. On acidification of this solution with ethereal hydrochloric acid a precipitate separates. Recrystallization of the precipitate from ethyl acetate gives 0.8 g. of the title compound, m.p. 124°–127°.

Analysis for $C_{16}H_{23}N_2O_3Cl$

Calculated: C, 58.80; H, 7.09; N, 8.57; Cl, 10.85

Found: C, 58.44; H, 7.16; N, 8.60; Cl, 10.96

EXAMPLE VI

2-[(2-Ethoxycarbonylethyl)n-Butylamino]-6-Methylnicotinic Acid Methyl Ester

A mixture of 3.7 g. of 2-chloro-6-methylnicotinic acid methyl ester, 3.4 g. of ethyl 3-butylaminopropionate and 2.12 g. of sodium carbonate in 40 ml. of dimethylformamide (DMF) is heated under reflux for 6 hours. The mixture is filtered and the filtrate is partitioned between 500 ml. of water and 100 ml. of chloroform. The chloroform layer is dried over magnesium sulfate, filtered, and evaporated to give an oil which is used directly in Example VII.

EXAMPLE VII

1-Butyl-1,2-Dihydro-4-Hydroxy-7-Methyl-1,8-Naphthyridine-3-Carboxylic Acid Ethyl Ester, Hydrochloride

The oil from Example VI is added to a sodium ethoxide solution prepared by dissolving 0.46 g. of sodium in 50 ml. of ethanol. After warming for 5 minutes the mixture is filtered and the filtrate cooled in an ice bath. The precipitate thus formed is triturated with 100 ml. of 10% aqueous acetic acid. The insolubles are collected and dissolved in ethyl acetate. Acidification with ethereal hydrochloric acid gives a precipitate which is

filtered. The filtrate is cooled in ice to afford a second crop of the title compound, m.p. 112°–118°.

Analysis for $C_{16}H_{23}N_2O_3Cl$

Calculated: C, 58.80; H, 7.09; N, 8.57

Found: C, 58.78; H, 6.99; N, 8.60

EXAMPLE VIII

2-Benzenesulfonyloxy-6-Methylnicotinic Acid Methyl Ester

To a solution of 0.45 g. of sodium in 150 ml. of ethanol is added 3.34 g. of 2-hydroxy-6-methylnicotinic acid methyl ester. After stirring for 30 minutes the insoluble material is collected and suspended in 100 ml. of N,N-dimethylformamide. To this suspension is added 3.53 g. of benzenesulfonyl chloride. The mixture is warmed on a steam bath for a few minutes and filtered. The filtrate is diluted with 100 ml. of water. On cooling, a precipitate develops. Recrystallization from benzenepetroleum affords the title compound, m.p. 61°–64°.

Analysis for $C_{14}H_{13}NO_5S$

Calculated: C, 54.71; H, 4.26; N, 4.56

Found: C, 54.55; H, 4.20; N, 4.31

EXAMPLE IX

1-Ethyl-1,2-Dihydro-4-Hydroxy-7-Methyl-1,8-Napythyridine-3-Carboxylic Acid Ethyl Ester (Alternative Method)

A stirred mixture of 3.07 g. of 2-benzenesulfonyloxy-6-methylnicotinic acid, methyl ester, 1.45 g. of ethyl 3-ethyl-aminopropionate, and 1.06 g. of sodium carbonate in 25 ml. of N,N-dimethylformamide is heated under reflux for 6 hours. The mixture is filtered and the filtrate partitioned between 500 ml. if water and 100 ml. of ether. The ether layer is dried over magnesium sulfate, filtered and evaporated. The residue is added to a solution of 0.23 g. of sodium in 30 ml. of ethanol and is warmed to reflux temperature for a few minutes. The precipitate is collected and triturated with 50 ml. of 10% aqueous acetic acid to afford 1-ethyl-1,2-dihydro-4-hydroxy-7-methyl, 1,8-naphthyridine-3-carboxylic acid, ethyl ester. A mixture m.p. with the free base prepared in Example III showed no depression, and the infrared spectra of both samples are identical.

EXAMPLE X

The in vivo therapeutic activity of the compounds of Formula I against bacterial infections is demonstrated and elicited by employing the following test procedure:

Forty male mice, weighing 18 g. ± 1 g., are divided into four separate groups containing ten mice in each group. Each animal is injected intraperitoneally with 0.5 ml. of a standardized suspension of the infective agent in 5% gastric mucin. Six hours post infection, each mouse is given a single oral dose of the test compound.

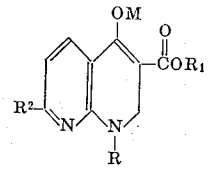
The amount of compound given varies in each of the four groups; i.e., 4 graded doses are administered. The animals are observed for 14 days and deaths recorded daily. The CD_{50} (curative dose) values are determined by acceptable statistical procedures. [See Reed and Muensch, Amer. J. of Hygiene, 27, 493 (1938)].

When tested as above-described, 1-ethyl-1,2-dihydro-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid ethyl ester hydrochloride showed therapeutic activity, as measured by CD_{50} values, against infections caused by the following gram-negative organisms at a dosage level in the range of 2 to 6 mg/mouse: *Escherichia coli* 920, *Salmonella typhimurium* SaB-1, *Salmonella typhosa* SaD–12, *Proteus vulgaris* 347, and *Proteus mirabilis* 3.

1-Ethyl-1,2-dihydro-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid n-butyl ester, hydrochloride, showed activity (CD_{50}) against *Escherichia coli* 920 at about 2 mg/mouse.

What is claimed is:

1. A compound of the formula



I

wherein R is a straight-chain lower alkyl group, R^1 and R^2 are each a straight-chain or branched lower alkyl group, and M is hydrogen or an alkali metal, and, when M is hydrogen, the non-toxic, pharmaceutically acceptable acid addition salts thereof.

2. A compound as defined in Formula I wherein R is ethyl, R^2 is methyl, R^1 is a straight-chain or branched lower alkyl group, and M is hydrogen, and the non-toxic, pharmaceutically acceptable acid addition salts thereof.

3. A compound as defined in claim **2** which is 1-ethyl-1,2-dihydro-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid ethyl ester.

4. A compound as defined in claim **2** which is 1-ethyl-1,2-dihydro-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid ethyl ester, hydrochloride.

5. A compound as defined in claim **2** which is 1-ethyl-1,2-dihydro-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid butyl ester.

6. A compound as defined in claim **2** which is 1-ethyl-1,2-dihydro-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid butyl ester, hydrochloride.

7. A compound as defined in claim **1** which is 1-butyl-1,2-dihydro-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid ethyl ester.

8. A compound as defined in claim **1** which is 1-butyl-1,2-dihydro-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid ethyl ester, hydrochloride.

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