



PATENT SPECIFICATION

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COMPLETE SPECIFICATION

1,8-Naphthyridine-3-Carboxylic Acids and Derivatives

We, STERLING DRUG INC., a corporation organised under the laws of the State of Delaware, United States of America, of 1450, Broadway, New York, State of New York, United States of America, 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:—

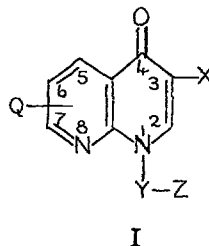
In accordance with the present invention there is provided a process for the preparation of a 3—X—4-oxo-1,4-dihydro-1,8-naphthyridine having a molecular structure in which an organic radical having the formula —YZ as defined herein is attached through a saturated carbon atom thereof to the 1-nitrogen atom of the naphthyridine nucleus, where X stands for hydroxycarbamyl, acyloxycarbamyl, carboxy or a salt thereof, carbalkoxy having from two to eleven carbon atoms inclusive, carbo - [(lower - tertiary - amino) - (polycarbon - lower - alkoxy)], cyano, carbamyl, aminocarbamyl, carbophenoxy, carbo - [(lower - secondary - amino) - (polycarbon - lower - alkoxy)], carbo(hydrocarbon mercapto), C(=NH)O - (lower - alkyl), C(=NH)NH₂, C(=NH)NH(lower - alkyl), C(=S)OH, or C(=S)SH, which comprises reacting the corresponding 3—X—4-hydroxy-1,8-naphthyridine with an organic ester of a strong acid providing the desired 1-substituent, and, if desired, obtaining a salt of a free product obtained.

The present invention also provides a 3—X—4-oxo-1,4-dihydro-1,8-naphthyridine having a molecular structure in which an

organic radical having the formula —YZ as defined herein is attached through a saturated carbon atom thereof to the 1-nitrogen atom of the naphthyridine nucleus where X is hydroxycarbamyl, acyloxycarbamyl, carboxy or a salt thereof, carbalkoxy having from two to eleven carbon atoms inclusive, carbo - [(lower - tertiary - amino) - (polycarbon - lower - alkoxy)], cyano, carbamyl, aminocarbamyl, carbophenoxy, carbo - [(lower - secondary - amino) - (polycarbon - lower - alkoxy)], carbo(hydrocarbon mercapto), C(=NH)O - (lower - alkyl), C(=NH)NH₂, C(=NH)NH(lower - alkyl), C(=S)OH, or C(=S)SH; or a bis-ester of said compound wherein X is carboxy with an aliphatic diol having 2—10 carbon atoms.

The physical embodiments of our invention have been tested by standard bacteriological and pharmacological evaluation procedures and found to have antibacterial and sedative properties. They are also useful as intermediates in organic syntheses.

Formula I (a preferred embodiment) is as follows:



Y is divalent aliphatic hydrocarbon attached

to the ring-nitrogen atom through a saturated carbon atom and having from one to ten carbon atoms inclusive, Z is hydrogen, hydroxy, halo, carboxy, lower-carbalkoxy, cyano, carbamyl, lower-aliphatic-hydrocarbon-oxy, (monocarbocyclic - aryl)-(lower-alkoxy), lower - secondary - amino, lower - tertiary-amino, lower-cycloalkyl, lower-aromatic or Q—3—X—4 - oxo - 1,4 - dihydro - 1,8-naphthyridinyl-1, and Q represents hydrogen or from one to four low-molecular weight substituents at positions 2, 5, 6 and 7 of the naphthyridine nucleus, said substituents being independently selected from lower-alkyl, lower-alkoxy, lower-alkylmercapto, lower-alkylsulphinyl, lower alkylsulphonyl, halo, hydroxy, hydroxy - (lower - alkyl), lower-alkyl - amino, di - (lower - alkyl)amino, nitro, amino, hydrazino, lower-carboxylic-acylamino, trihalomethyl, lower - alkanoyl, lower-alkanoyloxy - lower - alkyl, (lower-tertiary - amino) - (polycarbon - lower-alkyl), (lower - secondary - amino) - (polycarbon - lower - alkyl), (lower - tertiary-amino) - (polycarbon - lower - alkyl - amino), (lower - secondary - amino) - (polycarbon-lower - alkyl - amino), (lower - tertiary-amino) - (polycarbon - lower - alkoxy), (lower - secondary - amino) - (polycarbon-lower - alkoxy), monocarbocyclic - aryl, monocarbocyclic - aryloxy, monocarbocyclic-arylmercapto, monocarbocyclic - arylamino, (monocarbocyclic - aryl) - (lower - alkyl), (monocarbocyclic - aryl) - (lower - alkenyl), (monocarbocyclic - aryl) - (halo - lower-alkenyl), (monocarbocyclic - aryl) - (lower-alkynyl), monocarbocyclic - aroyl, (monocarbocyclic - aryl) - (lower - alkoxy), cyano, amino - (lower - alkyl), (lower - alkanoyl-amino) - (lower - alkyl), carbamyl, carboxy and lower-carbalkoxy. Unless otherwise indicated hereinabove or hereinbelow, the word "lower" when used with an alkyl moiety means alkyl, either straight- or branch-chained, having from one to six carbon atoms, e.g., lower-alkoxy includes methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, 2-butoxy, iso-butoxy, n-pentoxo, 3-pentoxo and n-hexoxy. Particularly preferred embodiments of our invention because of their relative ease of preparation due to ready availability of intermediates and because of their high antibacterial and/or sedative properties are the compounds having formula I where Q is one or two substituents other than hydrogen and at least one is in the 7-position of the naphthyridine ring.

When Z of formula I is hydrogen, Z—Y means aliphatic-hydrocarbon radicals having from one to ten carbon atoms inclusive and having a saturated carbon atom linked to the 1-nitrogen atom of the 1,8-naphthyridine ring, and comprehends alkyl, alkenyl and alkynyl radicals.

The term "lower-carbalkoxy," as used

herein, e.g., for Z in formula I, means carbalkoxy radicals where the alkoxy portion can be straight- or branch-chained and has from one to six carbon atoms, as illustrated by carbomethoxy and carbisopropoxy.

The term "lower-aliphatic-hydrocarbon-oxy," as used herein, means aliphatic hydrocarbonoxy radicals having from one to eight carbon atoms where aliphatic hydrocarbon is, for instance, alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl.

The term "lower-cycloalkyl," as used herein, means cycloalkyl radicals having from three to eight ring-carbon atoms and having up to a total of eight carbon atoms.

The term "lower-aromatic," as used herein means radicals having one or two aromatic rings which can be benzenoid or five- or six-membered hetero-aromatic, as illustrated by phenyl, naphthyl, biphenyl, pyridyl, pyrimidyl, furyl, thiazolyl, oxazolyl, triazinyl and thienyl. Preferred embodiments have as "lower - aromatic" monocarbocyclic - aryl radicals having six ring-carbon atoms, that is, aryl radicals of the benzene series. These embodiments, which are preferred primarily because of their commercial practicability due to availability of intermediates, include compounds where "lower-aromatic" is the unsubstituted phenyl radical and phenyl radicals substituted by low-molecular weight substituents such as lower-alkyl, lower-alkoxy, lower - alkylmercapto, lower - alkylsulphinyl, lower - alkylsulphonyl, halo, lower - alkyl-amino, di - (lower - alkyl)amino, nitro, amino, lower - carboxylic - acylamino, trihalomethyl, phenoxy, benzyloxy, benzoyl, lower - alkanoyl, (lower - tertiary - amino)-(polycarbon - lower - alkyl), (lower-secondary - amino) - (polycarbon - lower-alkyl), (lower - tertiary - amino) - (polycarbon - lower - alkylamino), (lower-secondary - amino) - (polycarbon - lower-alkylamino), (lower - tertiary - amino)-(polycarbon - lower - alkoxy), (lower-secondary - amino) - (polycarbon - lower-alkoxy), hydroxy, cyano, aminomethyl, carbamyl, carboxy, lower-carbalkoxy, phenylmercapto, benzyl or 4-methoxyphenoxy. The substituted phenyl radicals have preferably from one to three substituents which can be in any of the available positions of the phenyl nucleus, and where more than one substituent is present, they can be the same or different and they can be in any of the various position combinations relative to each other.

The term "lower-secondary-amino," as used herein, means secondary-amino radicals having from one to eight carbon atoms, as illustrated by: monocycloalkylamino radicals where the cycloalkyl group has from three to eight ring-carbon atoms, such as cyclopropyl-amino; mono - (lower - hydroxyalkyl)amino radicals where the lower-hydroxyalkyl group has two to six carbon atoms, such as 2-

hydroxyethylamino; mono-(lower-alkyl)amino radicals where the lower-alkyl group has from one to six carbon atoms such as methylamino; and mono - [(monocarbocyclic - aryl)methyl]-amino radicals, such as 2-chlorobenzylamino.

The term "lower-tertiary-amino," as used herein means tertiary-amino radicals having two nitrogen substituents such as those illustrated above for the lower-secondary-amino radicals, with preferred tertiary-amino radicals being di-(lower-alkyl)amino radicals where the lower-alkyl radicals are alike or different and each alkyl radical has from one to six carbon atoms as dimethylamino and saturated N-heteromonocyclic radicals having five or six ring atoms including alkylated derivatives, such as 1-piperidyl, 2-methyl-1-pyrrolidyl, 4-morpholinyl and 1-piperazyl.

When Z stands for lower-secondary-amino or lower-tertiary-amino, Y is preferably polycarbon - lower - alkyl and Z—Y may be 2 - (2 - hydroxyethylamino) - ethylamino, 4-dimethylaminobutyl and 3-(1-piperidyl)-propyl.

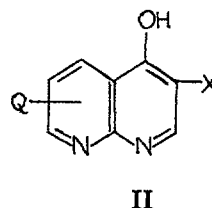
The term "polycarbon-lower-alkyl," as used herein, means lower-alkylene radicals having from two to six carbon atoms and having its connecting linkages on different carbon atoms.

The term "lower-carboxylic-acylamino," as used herein, e.g., as Q, means lower-alkanoylamino (having one to six carbon atoms) and monocarbocyclic - aroylamino (having six to eight carbon atoms), such as acetylamino and 3-chlorobenzoylamino.

The compounds of the invention are generally provided by reacting a 3—X—4-hydroxy-1,8-naphthyridine with an appropriate organic ester of a strong acid, i.e., an acid which is practically completely dissociated in aqueous solution. The organic moiety of the ester has up to and including eighteen carbon atoms, has a molecular weight not over 700 and is attached to the anionic portion of the ester through a saturated carbon atom thereof. Illustrative and preferred organic esters are esters of a strong inorganic acid or an organic sulphonic acid, said ester having the formula Z—Y—An, where An is an anion of a strong inorganic acid or an organic sulphonic acid, e.g., chloride, bromide, iodide, sulphate, benzenesulphonate and para-toluenesulphonate, and Z and Y have the meanings given above for formula I. The chloride, bromide or iodide is preferred because of the more ready availability of the requisite Z-(aliphatic-hydrocarbon) halides; and the reaction is carried out preferably in the presence of an acid-acceptor. The acid-acceptor is a basic substance which preferably forms freely water-soluble by-products easily separable from the product of the reaction, including for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium alkoxides, potassium alk-

oxides and sodium amide. The purpose of the acid-acceptor is to take up the hydrogen halide (or HAn) which is split out during the course of the reaction. The reaction can be carried out either in the presence or absence of a suitable solvent, but preferably in a solvent such as water, a lower-alkanol, acetone, dioxane, dimethyl formamide, or a mixture of such solvents, e.g., a mixture of water and a lower-alkanol. The reaction is generally carried out at a temperature between about room temperature (about 25° C.) and 150° C., preferably at reflux, in a lower-alkanol solvent or a mixture of water and a lower-alkanol.

To illustrate the preparation of the preferred 1,3-disubstituted-4-oxo-1,4-dihydro-1,8-naphthyridines of our invention having formula I, our process comprises reacting the corresponding 3—X—4-hydroxy-1,8-naphthyridine having the formula II



where Q and X have the meanings given above for formula I, with an ester having the formula Z—Y—An, where Z and Y have the meanings given above for formula I and An is an anion of a strong inorganic acid or an organic sulphonic acid, in the presence of an acid-acceptor.

When X is carboxy, i.e., when the intermediate is a 4-hydroxy-1,8-naphthyridine-3-carboxylic acid, the reaction is conveniently carried out by refluxing the acid with a Z-(aliphatic - hydrocarbon) ester, preferably halide, in aqueous ethanol in the presence of potassium or sodium hydroxide to yield the corresponding 1—(Z—Y)—4-oxo-1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid; the same 3-carboxylic acid is also obtained using these reaction conditions and a lower - alkyl 4 - hydroxy - 1,8 - naphthyridine - 3 - carboxylate as the intermediate, the ester hydrolyzing under the reaction conditions to form the acid. If the final product is desired in ester form, e.g., the ethyl ester, the intermediate ethyl 4-hydroxy-1,8-naphthyridine - 3 - carboxylate is reacted as above using refluxing ethanol as the solvent and sodium ethoxide as the acid-acceptor. The alkylation of the 4-hydroxy-1,8-naphthyridine - 3 - carboxylic acid can be carried out in the absence of an acid-acceptor by using its di-salt, e.g., by heating a mixture of the anhydrous dipotassium or disodium salt

with diethyl sulphate followed by acidification to obtain the 1-ethyl-4-oxo-1,8-naphthyridine-3-carboxylic acid.

Some of the intermediate 4-hydroxy-1,8-naphthyridine - 3 - carboxylic acids and derivatives are known, e.g., 4-hydroxy-7-methyl - 1,8 - naphthyridine - 3 - carboxylic acid and ethyl ester, 7-ethoxy-4-hydroxy-1,8-naphthyridine - 3 - carboxylic acid and ethyl ester, and 4-hydroxy-1,8-naphthyridine-3-carboxylic acid. Other such intermediates, where novel, are prepared by known methods which are illustrated in the examples or by novel methods which are described further hereinbelow and illustrated in the examples.

For example, the intermediate lower-alkyl 4 - hydroxy - 1,8 - naphthyridine - 3 - carboxylate is obtained in two steps by first reacting a 2-aminopyridine with one molar equivalent of a dialkyl ethoxymethylene-malonate, preferably the diethyl ester, to yield a dialkyl N-(2-pyridylamino)methylene-malonate and then cyclizing this compound by heating it in an appropriate solvent, e.g., diethyl phthalate, "Dowtherm"—registered Trade Mark—A (eutectic mixture of diphenyl and diphenyl ether), or mineral oil to obtain the intermediate lower-alkyl 4-hydroxy-1,8-naphthyridine - 3 - carboxylate. To obtain the lower - alkyl 7 - acylamino - 4 - hydroxy - 1,8 - naphthyridine - 3 - carboxylate one starts with the 2,6-diaminopyridine and an acyl anhydride, preferably acetic anhydride, is included in the cyclizing step.

Also within the scope of the invention are salts of our above-described 1-substituted-4-oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acids. Preferred types of salts are those having cations which do not increase the toxicity of the compound as a whole toward animal organisms. These comprise the alkali metal salts, e.g., the sodium or potassium salts; the lower-alkaline earth metal salts, e.g., magnesium or calcium salts; and, the ammonium or organic amine salts, e.g., diethanolamine or N-methylglucamine salts. Although medicinally acceptable salts are preferred, other and all cationic salts are within the scope of our invention. All such salts, including those having toxic cations, are useful in characterizing the free acids and as intermediates in purification of the free acids. The salts are prepared from the acids using methods illustrated hereinbelow in the example.

Preferred ester embodiments of our 1-substituted - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylic acids are those derived from alkanols and phenols having up to ten carbon atoms, (lower-tertiary - amino) - (polycarbon - lower-alkanols), (lower - secondary - amino) - (polycarbon - lower - alkanols). Other ester embodiments are the corresponding thiol esters prepared from the corresponding alkyl-

mercaptans, substituted-alkylmercaptans and thiophenols. These esters and their preparation are further illustrated in the examples hereinbelow. Although medicinally acceptable esters are preferred, other and all esters are encompassed by the scope of the invention. All esters are useful in characterizing the free acids and/or as intermediates in purification of the free acids.

Similarly, like the salts and esters, all amide and hydrazide derivatives are within the scope of the invention, and they have the same utilities as the salts and esters. Preferred amide and hydrazide embodiments, which are prepared as illustrated in the examples, are those derived from ammonia or hydrazine, unsubstituted or substituted by one or more low-molecular weight substituents, e.g., lower-alkyl and monocarbocyclic-aryl.

Other compounds encompassed by our invention are bis-compounds prepared by our process using bis-esters having the formula An—Y—An where Y has the meaning given above for formula I and where, in each instance, An is attached to a saturated carbon atom, e.g., the reaction of 4-hydroxy-7-methyl-1,8 - naphthyridine - 3 - carboxylic acid with 1,3-diiodopropane, 1,6-dibromohexane or 1,4-diiodo-2-butene to yield, respectively, 1,3 - bis(3 - carboxy - 7 - methyl - 4 - oxo-1,4 - dihydro - 1,8 - naphthyridyl - 1)propane, 1,6 - bis(3 - carboxy - 7 - methyl - 4 - oxo-1,4 - dihydro - 1,8 - naphthyridyl - 1)hexane or 1,4 - bis(3 - carboxy - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridyl - 1)-2-butene. Other bis-compounds encompassed by our invention are those where the two naphthyridine rings are connected by a bis-ester grouping through the 3—X substituents by condensing, with an aliphatic diol having 2 to 10 carbon atoms, the X functions of a compound having the general formula I as defined above, e.g., the bis-ester obtained by first reacting 1-ethyl-7-methyl-4-oxo-1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid with oxalyl chloride to form the corresponding 3-carboxylic acid chloride and then reacting two molar equivalents of the acid chloride with a diol, e.g., 1,3-propanediol, 1,4 - dihydroxy - 2 - butene and 1,6-hexane-diol.

Our 1 - substituted - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acids and derivatives have the further utility as intermediates in the preparation of other of our 1-substituted-4-oxo-1,4-dihydro-1,8-naphthyridine - 3 - carboxylic acids and derivatives, as illustrated below for the preparation of preferred 7-substituted-naphthyridine embodiments.

For example, the 7-amino-4-oxo-1-substituted - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acids and derivatives are conveniently converted into the corresponding 7-diazonium salts which in turn are converted

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- into other 7-substituted-4-oxo-1-[Z-(aliphatic-hydrocarbyl)] - 3 - carboxylic acids and derivatives, e.g., the corresponding 7-halo and 7-hydroxy compounds. The 7-amino-4-oxo-1-substituted - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acids are prepared by reacting a lower-alkyl 7-acylamino-4-hydroxy - 1,8 - naphthyridine - 3 - carboxylate, e.g., the ethyl 7-acetylamino compound, with a Z-(aliphatic hydrocarbonating) agent, e.g., ethyl iodide or benzyl chloride, to obtain the lower - alkyl 7 - acylamino - 4 - oxo - 1 - substituted - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate, e.g., the ethyl 7 - acetyl - amino - 4 - oxo - 1 - (ethyl or benzyl) - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylate, which is then hydrolyzed with an acidic agent, e.g., HCl, to remove both the ester and N-acyl groups.
- 7 - Hydroxy - 4 - oxo - 1 - substituted-1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acids and derivatives are also useful as intermediates for preparation of the corresponding 7-halo compounds by their reaction with a halogenating agent effective to convert hydroxy to halo, e.g., phosphorus oxychloride, thionyl chloride, phosphorus tri- or pentachloride to produce the corresponding 7-chloro compound or phosphorus tribromide to produce the 7-bromo compound.
- The 7 - halo - 4 - oxo - 1 - substituted-1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acids and derivatives, in turn, are useful for the preparation of other corresponding 7-substituted compounds, for example, the 7-alkoxy, 7-alkylmercapto, 7-alkylamino, 7 - dialkylamino, 7 - hydrazino, 7 - [(lower - tertiary - amino- or lower-secondary - amino) - (polycarbon - lower-alkyl)amino], 7 - [(lower - tertiary - amino or lower - secondary - amino) - (polycarbon - lower - alkyloxy)] compounds by reacting the corresponding 7-halo compound respectively, for example, with sodium alkoxide, sodium alkylmercaptide, alkylamine, dialkylamine, hydrazine, tertiary-amino- or secondary-amino-alkylamine, sodium tertiary-amino- or secondary-amino-alkoxide. The 7-halo compound also can be catalytically reduced to remove the 7-halo substituent to yield the corresponding 7-unsubstituted-4-oxo - 1 - [Z - (aliphatic - hydrocarbyl)] - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid and derivatives.
- As pointed out above, the 4-oxo-1-substituted - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acids are useful for the preparation of their salt, ester, amide and hydrazide derivatives using methods for converting carboxylic acids into said derivatives. These methods are illustrated in the specific exemplary disclosure hereinbelow. These derivatives also have antibacterial and sedative properties, as illustrated in the specific examples below.
- The lower-alkyl esters of our 4-oxo-1-substituted - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acids, especially methyl and ethyl esters, are useful in their reaction with hydrazines and ammonia or amines to form the corresponding hydrazides and amides, respectively. Also, they can be reacted with higher homologous alkanols, e.g., n-butanol, 1,3-dimethylhexanol, n-decanol, or with an aminoalcohol, e.g., 3-(1-piperidyl)propanol or 4-di-methylaminobutanol, by an ester exchange reaction to yield the corresponding higher alkyl or aminoalkyl ester, e.g., n-butyl, 1,3-dimethylhexyl, n-decyl, 3-(1-piperidyl)-propyl or 4-dimethylaminobutyl ester, respectively.
- Our application No. 32669/63 (Serial No. 1,000,893) has as its subject the intermediate 4 - hydroxy - 7 - [2 - (lower - aromatic)-ethenyl] - 1,8 - naphthyridine - 3 - carboxylic acids and derivatives and their preparation. These compounds are prepared by reacting the corresponding lower-alkyl 4-hydroxy-7-methyl - 1,8 - naphthyridine - 3 - carboxylate with a lower-aromatic-aldehyde, e.g., benzaldehyde, or pyridine-2-aldehyde, in the presence of a mixture of a lower-alkanoic acid and anhydride, e.g., acetic acid and acetic anhydride, preferably by heating in the range of about 100° C. to about 150° C., thereby yielding the corresponding lower-alkyl 4-hydroxy - 7 - [2 - (lower - aromatic)-ethenyl] - 1,8 - naphthyridine - 3 - carboxylate, e.g., the corresponding 7-(2-phenyl-ethenyl) (i.e., 7-styryl) or 7-[2-(2-pyridyl)-ethenyl]ester. The corresponding acid is obtained by saponification of the ester and, in turn, can be converted into other esters or salt, amide or hydrazine derivatives, e.g., those defined hereinabove for our 1-substituted-4-oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acids.
- The 4 - oxo - 1 - substituted - 7 - [2-(lower - aromatic) - ethenyl] - 1,4 - dihydro - 1,8 - naphthyridines can be further reacted by reducing or oxidizing to obtain respectively the corresponding 7-[2-(lower-aromatic)ethenyl]- or 7-carboxy- compounds respectively. The 7-carboxy compounds can then be decarboxylated to produce the 7-unsubstituted compounds.
- Our 4 - oxo - 1 - substituted - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acids and derivatives when containing a basic residue, i.e., a lower-tertiary- or -secondary-amino residue, for example, a 2-diethyl-aminoethyl ester, a 1 - [3 - (1 - piperidyl)-propyl] compound or a 7-(4-n-propylamino-butoxy) compound, are useful both in the free base form and in the form of acid-addition salts; and both forms are within the purview of the present invention. The acid-addition salts are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the base form.

The acids which can be used to prepare the acid-addition salts include those which produce, when combined with the free base, medicinally acceptable salts, that is, salts whose anions are relatively innocuous to the animal organism in medicinal doses of the salts, so that the beneficial physiological or antibacterial properties inherent in the free base are not vitiated by side effects ascribable to the anions. In practising our invention, we found it convenient to form the hydrochloride salts. However, other appropriate medicinally acceptable salts within the scope of the invention are those derived from mineral acids such as hydrobromic acid, hydriodic acid, nitric acid, phosphoric acid, sulphamic acid, and sulphuric acid; and organic acids such as acetic acid, citric acid, tartaric acid, lactic acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid, *p*-toluenesulphonic acid and quinic acid, giving the hydrobromide, hydriodide, nitrate, phosphate, sulphamate, sulphate, acetate, citrate, tartrate, lactate, methanesulphonate, ethanesulphonate, benzenesulphonate, *p*-toluenesulphonate and quinate, respectively.

The acid-addition salts of said basic compounds are prepared either by dissolving the free base in aqueous or aqueous-alcohol solution containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

Although medicinally acceptable salts of said basic compounds are preferred, all acid-addition salts are within the scope of our invention. All acid-addition salts are useful as sources of the free base form even if the particular salt *per se* is desired only as an intermediate product as for example when the salt is formed only for purposes of purification or identification, or when it is used as an intermediate in preparing a medicinally acceptable salt by ion exchange procedures.

Also encompassed by our invention are quaternary-ammonium salts of the aforesaid compounds containing a lower-tertiary-amino moiety. These salts are useful for further identification of the aforesaid tertiary-amino compounds. The quaternary ammonium salts are obtained by the addition of esters having a molecular weight less than 200 to the free base form of the compounds. A preferred class of esters comprises alkyl, alkenyl or aralkyl esters of inorganic acids or organic sulphonc acids, and include such compounds as methyl chloride, methyl bromide, methyl iodide, ethyl bromide, propyl chloride, 2-hydroxyethyl bromide, allyl chloride, allyl bromide, dimethyl, sulphate, methyl benzenesulphonate, methyl *p*-toluenesulphonate, benzyl chloride, benzyl bromide, and substituted benzyl halides, such as *p*-chlorobenzyl

chloride, *p*-nitrobenzyl chloride, *o*-chlorobenzyl chloride and *p*-methoxybenzyl chloride. The quaternary ammonium salts are prepared by mixing the free base and the alkyl, alkenyl or aralkyl esters in an organic solvent inert under the conditions of reaction, for example, ethanol, methanol, ether and acetonitrile. Heating can be used to facilitate the reaction, although salt formation usually takes place readily at room temperature. The quaternary ammonium salt separates directly or can be obtained by concentration of the solution.

The molecular structures of the final products and intermediates of our invention are established by their mode of synthesis and confirmed by the correspondence of calculated and found values for the elementary analyses for representative examples and by infrared and ultraviolet spectral analyses.

Our 1 - [Z - (aliphatic - hydrocarbyl)] - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acids and derivatives when tested according to standard *in vitro* bacteriological evaluation procedures possess antibacterial activity, for example, against organisms such as *Staphylococcus aureus*, *Eberthella typhi*, *Clostridium welchii*, as illustrated below in the examples. Preferred embodiments also were found to have significant *in vivo* activity against gram-negative bacteria, e.g., *Klebsiella pneumoniae*, *Salmonella typhimurium*, in mice when administered orally and/or subcutaneously at dose levels in the range of about 100 to 400 mg. per kg. per day. Embodiments were found to increase the hexobarbital-induced sleeping time in mice when administered intraperitoneally forty minutes before intraperitoneal administration of 40 mg. per kg. of hexobarbital. Results in the following examples are given in terms of the number of animals caused to exhibit a loss of righting reflex for one minute or more at a given dose level, e.g., 200 mg. per kg. or in terms of ED₅₀, i.e., the effective dose in mg. per kg. that causes fifty per cent of the animals to exhibit a loss of righting reflex for one minute or more. Positive results in this barbitol-potentiating test indicate the compound tested has central nervous system depressant activity and is useful as a potentiator for barbiturates.

The compounds of the invention are usually administered in pharmaceutical compositions comprising the compounds and suitable pharmaceutical carriers, as known in the art.

The following examples will further illustrate the invention without, however, limiting it thereto.

EXAMPLE 1.

1 - Ethyl - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 11.6 g. of 4-hydroxy-7-methyl-1,8-naphthyridine - 3 - carboxylic acid, 11.1 g. of potassium hydroxide, 230 cc. of ethanol (95% here and elsewhere unless otherwise

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- indicated) and 81 cc. of water was refluxed until the solids dissolved. To this solution was added 28 cc. of ethyl iodide and the resulting mixture was refluxed for 5 days. The reaction mixture was cooled in an ice bath; and the resulting precipitate was collected, recrystallized from acetic acid, washed with water and dried in a vacuum oven (at about 70° C.) to yield 8.7 g. (66% yield) of the crystalline product, 1 - ethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 226.8—230.2° C. (corr.).
- Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.05; H, 5.21; N, 12.06; N.E. (neutral equivalent), 232.
- Found: C, 62.12; H, 5.47; N, 11.92; N.E., 229.

The foregoing preparation was carried out using a shorter reaction period as follows: A

warm solution containing 41 g. of 4-hydroxy-7 - methyl - 1,8 - naphthyridine - 3 - carboxylic acid and 39 g. of potassium hydroxide in one liter of ethanol and 200 cc. of water was treated with 50 cc. of ethyl iodide and the resulting mixture was refluxed gently overnight, acidified with hydrochloric acid and cooled. The resulting precipitate was collected and recrystallized twice from acetonitrile to yield 26 g. (56% yield) of 1-ethyl-7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 229—230° C.

1 - Ethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, as follows:

40	Organism	Log Reciprocal Minimum Effective Concentration (mg./cc.)	
		Bacteriostatic	Bactericidal
	<i>Staphylococcus aureus</i>	4.3	<3.3
	<i>Eberthella typhi</i>	4.3	3.9
	<i>Clostridium welchii</i>	4.6	<3.3

- 45 1 - Ethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was found to have significant *in vivo* activity against *Klebsiella pneumoniae* in mice when administered orally or subcutaneously at dose levels as low as 100 mg. per kg. per day and, also, against *Salmonella typhimurium* in mice when administered subcutaneously at a dose level as low as 100 mg. per kg. per day. This compound when tested according to the procedure described hereinabove for potentiation of hexobarbital sleeping time in mice was found to have an ED_{50} of less than 50 mg. per kg. This same compound was found to have an acute oral toxicity (LD_{50}) in mice of 4000 mg. per kg. after 24 hours and 3300 ± 975 after 7 days and an acute subcutaneous toxicity (LD_{50}) in mice of 500 ± 52 mg. per kg.

- Also prepared using the above procedure are 1 - (4 - carboxybutyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1 - (2 - carbethoxyethyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1 - cyclopropylmethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1 - cinnamyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1 - (3 - bromobenzyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1 - (4 - biphenylmethyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 7 - methyl - 4 - oxo - 1 - (2 - thienylmethyl) - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid and 1 - (3 - dimethylaminopropyl) - 7 - methyl - 4 - oxo - 1,4 -

dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, and 1 - (4 - ethoxybenzyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid.

EXAMPLE 2.

Sodium 1 - ethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate was prepared by warming on a steam bath a mixture of 6.9 g. of 1-ethyl-7-methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1.1 g. of sodium hydroxide and 150 cc. of ethanol until dissolution resulted. The warm solution was filtered, the filtrate allowed to cool, and the solid collected and air-dried. There was thus obtained 7.5 g. of sodium 1-ethyl-7-methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate, m.p. 270.6—272.0° C. (corr.) with decomposition.

Anal. Calcd. for $C_{12}H_{11}N_2NaO_3$: N, 11.02; Na, 9.06.

Found: H_2O , 5.95; N (dry basis), 10.68; Na (dry basis), 9.00.

Sodium 1 - ethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate was found to have significant *in vivo* activity against *Klebsiella pneumoniae* in mice when administered orally at dose levels as low as 100 mg. per kg. per day.

EXAMPLE 3.

Calcium 1 - ethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate was prepared as follows: To a solution containing 12 g. of 1-ethyl-7-methyl-4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acid, 25 cc. of 10% aqueous potassium hydroxide solution and 300 cc. of water was added with stirring a solution con-

- taining 30 g. of calcium acetate dihydrate. The reaction mixture was stirred at room temperature for about 10 minutes; and the resulting precipitate was collected, washed with water and air-dried. The solid was recrystallized once from methanol-water (4:1), a second time from methanol-water (5:1), and then air-dried to yield 5.5 g. of calcium di-
- 5 (1 - ethyl - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylate), M.P. $>300^{\circ}$ C. (corr.).
- 10 Anal. Calcd. for $C_{21}H_{22}CaN_4O_6$: C, 57.40; H, 4.40; N, 11.14.
- Found: C, 57.16; H, 4.67; N, 11.35.
- 15 Calcium di - (1 - ethyl - 7 - methyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylate) was found to have significant *in vivo* activity against *Klebsiella pneumoniae* in mice when administered orally at a dose level
- 20 as low as 100 mg. per kg. per day. This same compound when tested according to the procedure described hereinabove for potentiation of hexobarbital sleeping time in mice was found to have an ED_{50} of 120 ± 20 mg. per
- 25 kg.
- EXAMPLES 4—10.
- The following compounds were prepared following the procedure described in Example 1:
- 30 1,7 - Dimethyl - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid, m.p. $>300^{\circ}$ C. (corr.), when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have
- 35 bacteriostatic (Bs) and bactericidal (Bc) values (given here and hereinafter as log reciprocal minimum effective concentrations, mg. per cc.) of 4.0 and 3.12, respectively, against *Clostridium welchii*.
- 40 7 - Methyl - 4 - oxo - 1 - n - propyl - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. $209.4\text{--}210.2^{\circ}$ C. (corr.), when tested according to standard *in vitro* bacteriological evaluation procedures was found to
- 45 possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 4.3 and <3.0 against *Staphylococcus aureus*, of 5.0 and 3.6 against *Eberthella typhi* and of 5.0 and 4.0 against *Clostridium welchii*. This
- 50 same compound was found to have significant *in vivo* activity against *Klebsiella pneumoniae* in mice when administered orally or subcutaneously at a dose level as low as 100 mg. per kg. per day and, also, against *Salmonella typhimurium* in mice when administered
- 55 orally at a dose level as low as 200 mg. per kg. per day.
- 1 - n - Butyl - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. $220.4\text{--}222.0^{\circ}$ C. (corr.), when
- 60 tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity for example, to have Bs and Bc values (as defined herein-
- above) of 3.6 and 3.12 against *Eberthella typhi*.
- 1 - Isobutyl - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. $234.8\text{--}236.8^{\circ}$ C. (corr.), when
- 70 tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example to have Bs and Bc values, respectively, of 4.3 and 3.6 against *Staphylococcus aureus*, of 4.3 and 3.3 against *Eberthella typhi* and of 4.6
- 75 and 3.0 against *Clostridium welchii*. This same compound when tested as described above was found to potentiate hexobarbital sleeping time in three out of six mice at a dose level of 200 mg. per kg.
- 80 7 - Methyl - 4 - oxo - 1 - n - pentyl 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylic acid, m.p. $171.4\text{--}172.8^{\circ}$ C. (corr.), when tested according to standard *in vitro* bacteriological evaluation procedures
- 85 was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 4.12 and 3.12 against *Staphylococcus aureus* and of 4.12 and 3.3 against *Clostridium welchii*.
- 90 1 - n - Hexyl - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, a pale yellow solid, m.p. $146.2\text{--}148.2^{\circ}$ C. (corr.), when tested according to standard *in vitro* bacteriological evaluation procedures
- 95 was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 4.6 and 3.0 against *Staphylococcus aureus*, of 5.0 and 4.12 against *Clostridium welchii* and of 4.12 and 4.12 against *Mycobacterium tuberculosis*.
- 100 1 - n - Decyl - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. $129.2\text{--}130.4^{\circ}$ C. (corr.).
- EXAMPLE 11.
- 105 5,7 - Dimethyl - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared by refluxing for 4 hours a mixture containing 21.8 g. of 5,7-dimethyl-4-hydroxy - 1,8 - naphthyridine - 3 - carboxylic acid, 120 cc. of 10% aqueous potassium
- 110 hydroxide solution, 300 cc. of ethanol and 25 cc. of ethyl iodide. The reaction mixture was made acidic and the resulting precipitate was collected, recrystallized from acetic acid-water and then from acetic acid to yield 10.6
- 115 g. of 5,7-dimethyl-1-ethyl-4-oxo-1,4-dihydro-1,8 - naphthyridine - 3 - carboxylic acid, as yellow needles, m.p. $243.6\text{--}244.8^{\circ}$ C. (corr.).
- Anal. Calcd. for $C_{13}H_{14}N_2O_3$: N, 11.38; N.E., 246.
- Found: N, 11.11; N.E., 240.
- 120 5,7 - Dimethyl - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid when tested according to standard *in vitro* bacteriological evaluation procedures
- 125 was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 4.6 and 3.12 against *Eberthella*

typhi, of 5.3 and 3.6 against *Clostridium welchii* and of 4.0 and 3.6 against *Mycobacterium tuberculosis*.

- 5 The intermediate 5,7-dimethyl-4-hydroxy-1,8-naphthyridine-3-carboxylic acid was prepared in several steps starting with 2-amino-4,6-dimethylpyridine as follows: A mixture containing 92 g. of 2-amino-4,6-dimethylpyridine and 166 g. of ethoxymethylenemalonate ester was heated for 2 hours on a steam bath. The ethanol formed by the reaction was distilled off *in vacuo* and the remaining material was poured into a evaporating dish and cooled. The resulting solid was recrystallized two times from ethanol to yield 170 g. of diethyl N-(4,6-dimethyl-2-pyridyl)aminomethylenemalonate, m.p. 96.8—98.6° C. (corr.).

10 *Anal.* Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.62; H, 6.90; N, 9.59.

Found: C, 61.52; H, 7.07; N, 9.55.

- 15 A mixture containing 29.2 g. of diethyl N-(4,6-dimethyl-2-pyridyl)aminomethylenemalonate and 180 cc. of "Dowtherm" A (eutectic mixture of diphenyl and diphenyl ether) was refluxed for about 30 minutes and allowed to cool. The solid that separated was collected, washed with benzene and recrystallized from ethanol using decolorizing charcoal.
- 20 There was thus obtained, as a yellow solid, ethyl 5,7-dimethyl-4-hydroxy-1,8-naphthyridine-3-carboxylate, m.p. 235.8—236.6° C. (corr.).

30 *Anal.* Calcd. for $C_{15}H_{11}N_2O_3$: C, 63.40; H, 5.73; N, 11.38.

Found: C, 63.66; H, 5.75; N, 11.16.

- 35 A mixture containing 49 g. of ethyl 5,7-dimethyl-4-hydroxy-1,8-naphthyridine-3-carboxylate, 450 cc. of 10% aqueous potassium hydroxide solution and 250 cc. of ethanol was heated on a steam bath for about 2 hours after which the volume of the reaction mixture had been reduced to about 500 cc. The resulting solution was poured into a solution containing 150 cc. of 6N hydrochloric acid and about 1 litre of water. The yellow solid that separated was collected and washed successively with water, ethanol and ether, and then dried *in vacuo* at 60° C. to yield 45 g. of 5,7-dimethyl-4-hydroxy-1,8-naphthyridine-3-carboxylic acid, a yellow solid, m.p. 285° C. with decomposition.

EXAMPLE 12.

- 55 6-Bromo-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid was prepared as follows: A mixture containing 14.2 g. of 6-bromo-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid, 9.8 g. of potassium hydroxide, 230 cc. of ethanol and 80 cc. of water was refluxed until the solids dissolved. To this solution was added 20 cc. of ethyl iodide and the resulting reaction mixture was refluxed on a steam bath for 19 hours. The reaction mixture was then cooled in an ice

bath and the resulting precipitate was collected, washed with acetone, recrystallized from dimethylformamide, washed with acetone and dried in a vacuum oven (70° C.) to yield 10.7 g. of 6-bromo-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, m.p. 279.6—280° C. (corr.) with decomposition.

Anal. Calcd. for $C_{12}H_{11}BrN_2O_3$: Br, 25.69, N, 9.00.

Found: Br, 25.50; N, 9.28.

6-Bromo-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 4.6 and 3.0 against *Staphylococcus aureus*, of 4.12 and 3.6 against *Eberthella typhi* and of 4.6 and 3.3 against *Clostridium welchii*.

The intermediate 6-bromo-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid was prepared in several steps starting with 6-amino-3-bromo-2-methylpyridine as follows: A mixture containing 91.4 g. of 6-amino-3-bromo-2-methylpyridine and 105.5 g. of diethyl ethoxymethylenemalonate was heated under vacuum on a steam bath overnight (about 15 hours). The reaction mixture, which had solidified to a yellow solid, was recrystallized from ethanol to yield 121.5 g. of diethyl N-(5-bromo-6-methyl-2-pyridyl)aminomethylenemalonate, m.p. 133—134.5° C. For analysis a 20 gram portion was recrystallized a second time from 95% ethanol and dried in a vacuum oven whereupon there was obtained 18.3 g of the white crystalline product having the same melting point, the corrected melting point being 130.8—132.6° C.

Anal. Calcd. for $C_{14}H_{17}BrN_2O_4$: Br, 22.37; N, 7.85.

Found: Br, 22.50; N, 7.94.

"Dowtherm" A (700 cc) was heated to reflux with stirring and to it was added 101.4 g. of diethyl N-(5-bromo-6-methyl-2-pyridyl)aminomethylenemalonate dissolved in 200 cc. of warm "Dowtherm" A. The reaction mixture was then refluxed for 2 hours, allowed to cool and then allowed to stand overnight at room temperature. The solid that separated was collected and washed successively with n-pentane and acetone, dried in an oven at about 80° C. and recrystallized from dimethylformamide using decolorizing charcoal to yield 26.8 g. of ethyl 6-bromo-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate, m.p. 288—289° C. with decomposition.

The foregoing ester was hydrolyzed to the corresponding acid as follows: A mixture containing 26.8 g. of ethyl 6-bromo-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate and 145 cc. of 10% aqueous

- potassium hydroxide solution was refluxed for 2 hours and then allowed to stand at room temperature overnight. The reaction mixture was then brought to boiling and filtered to remove a small amount of tan solid. The filtrate was cooled and acidified with hydrochloric acid to yield a copious pale yellow precipitate. The mixture was chilled in an ice bath and the yellow solid was collected, washed with water and dried to yield 21.0 g. of 6-bromo-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid, m.p. 294—296° C. with decomposition.

EXAMPLE 13.

- 6-Bromo-5,7-dimethyl-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid was prepared as follows: A mixture containing 31 g. of ethyl 6-bromo-5,7-dimethyl-4-hydroxy-1,8-naphthyridine-3-carboxylate, 98 cc. of 10% aqueous potassium hydroxide solution, 400 cc. of ethanol, 500 cc. of water and 15 cc. of ethyl iodide was refluxed for 3 hours. An additional 1 liter of ethanol, 1 liter of water, 50 cc. of 10% aqueous potassium hydroxide solution and about 10 cc. of ethyl iodide were added and refluxing was continued for an additional 2 hours. The reaction mixture was then poured into 1 liter of water containing 100 cc. of 6N hydrochloric acid. The finely divided precipitate that separated was collected, dried in a vacuum oven at 60° C. for about 4 hours and then recrystallized from dimethylformamide to yield 20.5 g. of 6-bromo-5,7-dimethyl-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, m.p. 235.2—237.8° C. (corr.).

Anal. Calcd. for $C_{13}H_{13}BrN_2O_3$: Br, 24.58; N, 8.61.

- Found: Br, 24.40; N, 8.87.
- The intermediate ethyl 6-bromo-5,7-dimethyl-4-hydroxy-1,8-naphthyridine-3-carboxylate was prepared in several steps starting with 6-amino-3-bromo-2,4-dimethylpyridine as follows: A mixture of 84.5 g. of 6-amino-3-bromo-2,4-dimethylpyridine and 93 g. of diethyl ethoxymethylenemalonate was heated on a steam bath for 1 hour. To the reaction mixture, which had caked, was added about 500 cc. of ethanol and the resulting mixture was refluxed and then allowed to cool to room temperature. The solid that separated was collected and washed with ethanol. There was thus obtained 125 g. of diethyl N-(5-bromo-4,6-dimethyl-2-pyridyl)aminomethylenemalonate, m.p. 134—135.5° C. A 19 gram sample was recrystallized from ethanol to yield 17 g. of the product having the same melting point, the corrected m.p. being 132.6—133.4° C.

Anal. Calcd. for $C_{15}H_{19}BrN_2O_4$: Br, 21.53; N, 7.55.

Found: Br, 21.53; N, 7.60.

- A mixture containing 45 g. of diethyl N-(5-bromo-4,6-dimethyl-2-pyridyl)amino-

methylenemalonate and 360 cc. of "Dowtherm" A was refluxed with stirring at the temperature of 250—252° C. Refluxing was continued for about 75 minutes and the ethanol formed by the reaction was removed by distillation. The cooled reaction mixture was filtered and the solid thus obtained was washed with benzene and n-pentane to yield 31 g. of the product. The 31 g. of product was combined with a 27 g. portion obtained in another run and the mixture was recrystallized from dimethylformamide and subsequently triturated with ethanol and dried to yield 48 g. of product, ethyl 6-bromo-5,7-dimethyl-4-hydroxy-1,8-naphthyridine-3-carboxylate, m.p. 282.0—284° C. (corr.) with decomposition.

Anal. Calcd. for $C_{13}H_{13}BrN_2O_3$: Br, 24.58; N, 8.62.

Found: Br, 24.30; N, 8.66.

6-Bromo-5,7-dimethyl-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 5.3 and 4.12 against *Staphylococcus aureus*, of 4.3 and 3.12 against *Eberthella typhi* and of 5.12 and 3.3 against *Clostridium welchii*.

EXAMPLE 14.

1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid hydrazide was prepared as follows: A mixture of 17 g. of ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate and 75 cc. of hydrazine hydrate was heated on a steam bath for about 15 minutes, cooled and allowed to stand at room temperature overnight. The reaction mixture was then heated to near boiling for about 5 minutes and cooled; the resulting precipitate was collected, recrystallized twice from isopropyl alcohol, the second time using decolorizing charcoal, and air-dried to yield 14 g. of the product, 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid hydrazide, m.p. 184.2—186.0° C. (corr.).

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.50; H, 5.74; N, 22.76.

Found: C, 58.40; H, 5.72; N, 23.03.

1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid hydrazide when tested as described above for potentiation of hexobarbital sleeping time in mice was found to have an ED₅₀ of 65±11 mg. per kg.

EXAMPLE 15.

1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide was prepared as follows: A reaction mixture containing 7.5 g. of 1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide, 80 g. of Raney nickel and 150 cc. of ethanol was refluxed on a steam

bath for 4 hours, and then allowed to cool to room temperature and stand overnight. The reaction mixture was heated to boiling, the catalyst filtered off, and the filtrate evaporated to dryness. The resulting crystalline material was recrystallized from acetic acid-water (1:1) and washed with acetone to yield 3 g. of the product, 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide, m.p. 224.8—246.4° C.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.36; H, 5.66; N, 18.16.

Found: C, 62.23; H, 5.60; N, 17.90.

1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide was found to have significant *in vivo* activity against *Klebsiella pneumoniae* in mice when administered subcutaneously at a dose level of 200 mg. per kg. per day.

EXAMPLE 16.

Ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate was prepared as follows: A 6.9 g. portion of sodium was dissolved in 300 cc. of absolute ethanol (to produce a solution of sodium ethoxide in ethanol) and to the resulting solution was added 23.2 g. of ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate. The reaction mixture was brought to reflux on a steam bath and to the resulting suspension was added 35 cc. of ethyl iodide. The resulting reaction mixture was refluxed for 16 hours and chilled in an ice bath; and, when no solid separated, it was evaporated to about one-third its volume on a steam bath under reduced pressure, acidified, diluted and shaken well with four volumes of water, and filtered. The solid that separated from the filtrate was collected and recrystallized three times from ethyl acetate, the second time using decolorizing charcoal. There was thus obtained 7.0 g. of the product, ethyl 1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate, m.p. 120.8—121.6° C. (corr.).

Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 64.60; H, 6.19; N, 10.77.

Found: C, 64.58; H, 6.03; N, 10.93.

Ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate was found to have significant *in vivo* activity against *Klebsiella pneumoniae* in mice when administered orally or subcutaneously at dose levels as low as 100 mg. per kg. per day.

Also prepared by the above procedure are ethyl 7-methyl-4-oxo-1-(3-phenoxypropyl)-1,4-dihydro-1,8-naphthyridine-3-carboxylate, 1-(3-dimethylamino-propyl)-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, and ethyl 1-carbo-n-hexyloxymethyl-4-oxo-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylate.

EXAMPLE 17.

n-Butyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate was prepared as follows: A mixture containing 13 g. of ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate, 25 cc of n-butanol and 0.3 g. of sodium methoxide was heated in an oil bath at about 122—125° C. for a period of 48 hours. The reaction mixture was then cooled, filtered, and the filtrate concentrated *in vacuo* to remove the solvent. The remaining reaction mixture solidified on cooling. The solid was collected and recrystallized from cyclohexane using decolorizing charcoal. The air-dried product, n-butyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate, m.p. 98.0—99.4° C. (corr.), weighed 8.8 g. (61% yield).

Anal. Calcd. for $C_{16}H_{20}N_3O_3$: C, 66.66; H, 6.98; N, 9.71.

Found: C, 66.49; H, 6.72; N, 9.64.

n-Butyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate when tested as described above was found to potentiate hexobarbital sleeping time in six out of six mice at a dose level of 200 mg. per kg. This same compound was found to have significant *in vivo* activity against *Klebsiella pneumoniae* in mice when administered orally at a dose level of 100 mg. per kg. per day.

EXAMPLE 18.

1,3-Dimethylbutyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate was prepared as follows: A mixture containing 11 g. of ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate, 25 cc. of 4-methyl-2-pentanol and 0.1 g. of sodium methoxide was heated for about 16 hours in an oil bath kept at about 130—135° C. The reaction mixture was cooled, filtered, and concentrated *in vacuo* to remove the solvent. The resulting solidified reaction mixture was recrystallized twice from cyclohexane, once from di-isopropyl ether, washed with n-pentane and dried *in vacuo* at 70° C. to yield 6.5 g. of product, 1,3-dimethylbutyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate, m.p. 114.6—119.4° C. (corr.).

Anal. Calcd. for $C_{17}H_{21}N_3O_3$: C, 68.36; H, 7.64; N, 8.84.

Found: C, 68.68; H, 7.25; N, 8.87.

1,3-Dimethylbutyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate when tested as described above for potentiation of hexobarbital sleeping time in mice was found to have an ED_{50} of 152 ± 28 mg. per kg. This same compound was found to have significant *in vivo* activity against *Klebsiella pneumoniae* in mice when adminis-

tered orally at a dose level of 100 mg. per kg. per day.

EXAMPLE 19.

2 - Dimethylaminoethyl 1 - ethyl - 7-methyl - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylate was prepared as follows: A mixture containing 11 g. of ethyl 1 - ethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylate, 25 cc. of 2-dimethylaminoethanol and 0.1 g. of sodium methoxide was heated in an oil bath kept at about 135—140° C. for about 16 hours. The reaction mixture was concentrated *in vacuo* to remove the solvent and remaining oily material was taken up in chloroform. The chloroform solution was washed twice with water, dried over anhydrous potassium carbonate, treated with decolorizing charcoal, filtered, and concentrated *in vacuo* to remove the chloroform. The remaining oily material was dissolved in 40 cc. of acetonitrile; to this solution was added 6 cc. of 15% ethanolic hydrogen chloride; and the resulting mixture was cooled. The solid that separated was collected and recrystallized once from acetonitrile and once from isopropyl alcohol. There was thus obtained 3 g. of product, 2 - dimethylaminoethyl 1 - ethyl - 7-methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate in the form of its hydrochloride, m.p. 228.6—230.2° C. (corr.).

Anal. Calcd. for $C_{16}H_{21}N_3O_3 \cdot HCl$: C, 56.52; H, 6.52; Cl, 10.44.

Found: C, 56.38; H, 6.55; Cl, 10.49.

2 - Dimethylaminoethyl 1 - ethyl - 7-methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate hydrochloride when tested as described above was found to potentiate hexobarbital sleeping time in four out of six mice at a dose level of 200 mg. per kg. This same compound was found to have significant *in vivo* activity against *Klebsiella pneumoniae* in mice when administered orally at a dose level of 200 mg. per kg. per day or subcutaneously at a dose level of 100 mg. per kg. per day.

EXAMPLES 20—23.

The following compounds prepared following the procedure described in Example 1: 1 - benzyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 255.2—256.8° C. (corr.), when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 4.3 and 3.6 against *Staphylococcus aureus* and of 4.0 and 3.3 against *Clostridium welchii*.

1 - (2 - Chlorobenzyl) - 7 - methyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylic acid, m.p. 219.6—222.0° C. (corr.) with decomposition, when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial

activity, for example, to have Bs and Bc values, respectively, of 5.0 and 3.3 against *Staphylococcus aureus*, of 3.3 and 3.0 against *Eberthella typhi* and of 4.6 and 3.3 against *Clostridium welchii*.

1 - (3,4 - dichlorobenzyl) - 7 - methyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acid, m.p. 261.6—263.6° C. (corr.); 7 - methyl - 1 - (1 - naphthylmethyl) - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylic acid, m.p. 244.6—246.2° C. (corr.), when recrystallized from acetic acid using decolorizing charcoal.

EXAMPLE 24.

1 - (2 - Cyclohexylethyl) - 7 - methyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylic acid was prepared as follows: A mixture containing 20.4 g. of 4-hydroxy-7-methyl - 1,8 - naphthyridine - 3 - carboxylic acid, 19.5 g. of potassium hydroxide, 385 cc. of ethanol, 150 cc. of water and 40 cc. of 2-cyclohexylethyl bromide was refluxed on a steam bath for about 18 hours. To the basic reaction mixture was added 25 cc. of 22% ethanolic hydrogen chloride; the acidic mixture was cooled in an ice bath; and the resulting precipitate was collected, washed with water, dried in a vacuum oven at 65° C., and recrystallized from absolute ethanol to yield 21.6 g. (69%) of the product, 1-(2-cyclohexylethyl) - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 186.0—187.0° C. (corr.).

Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.76; H, 7.05; N, 8.91.

Found: C, 69.06; H, 6.80; N, 9.01.

1 - (2 - Cyclohexylethyl) - 7 - methyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylic acid when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 5.0 and 3.3 against *Staphylococcus aureus* and of 4.12 and 3.12 against *Clostridium welchii*.

Also prepared according to the above procedure are 1 - (3 - ethoxypropyl) - 7-methyl - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylic acid and 1-(2 - benzyloxyethyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylic acid.

EXAMPLE 25.

1 - (2 - Ethoxyethyl) - 7 - methyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylic acid was prepared following the procedure described in Example 24, m.p. 182.6—183.4° C. (corr.), when recrystallized twice from acetonitrile using decolorizing charcoal and once from dioxane, when tested according to standard *in vitro* bacteriological evaluation procedures, it was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 3.6 and <3.3

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against *Staphylococcus aureus* and of 3.6 and <3.3 against *Clostridium welchii*.

EXAMPLES 26—28.

The following examples were prepared following the procedure described in Example 1:

1 - Allyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 207.6—208.2° C. (corr.) when recrystallized from absolute ethanol, and when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values respectively, of 4.3 and 3.6 against *Eberthella typhi* and of 4.12 and 3.0 against *Clostridium welchii*. This same compound was found to have significant *in vivo* activity against *Klebsiella pneumoniae* in mice when administered orally at a dose level of 400 mg. per kg. per day or subcutaneously at a dose level of 200 mg. per kg. per day. Also, when tested for potentiation of hexobarbital sleeping time in mice this compound was found to have an ED₅₀ of 60±7 mg. per kg.

1 - (2 - Chloro - 2 - propenyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 185.2—186.2° C. (corr.) when recrystallized three times from absolute ethanol, and when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 4.3 and 3.3 against *Staphylococcus aureus* and of 4.6 and 3.6 against *Eberthella typhi*. This same compound when tested as described above for potentiation of hexobarbital sleeping time in mice was found to have an ED₅₀ of 86±15.6 mg. per kg.

7 - Methyl - 4 - oxo - 1 - (2 - propynyl) - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 253.4—254.0° C. (corr.) with decomposition, when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 4.3 and <3.0 against *Eberthella typhi* and of 4.12 and <3.0 against *Clostridium welchii*. This same compound when tested as described above for potentiation of hexobarbital sleeping time in mice was found to have an ED₅₀ of 71±9.9 mg. per kg.

EXAMPLE 29.

1 - Carboxymethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: 20.4 g. of 4 - hydroxy - 7 - methyl - 1,8 - naphthyridine - 3 - carboxylic acid and 19.5 g. of potassium hydroxide were dissolved in 60 cc. of water. To this solution was added 9.5 g. of chloroacetic acid and the resulting solution was evaporated by heating with stirring on a hot plate until a stiff paste was obtained. This required about thirty minutes.

The reaction mixture was dissolved in hot water, treated with decolorizing charcoal, filtered, and filtrate acidified with acetic acid. The acidic solution was chilled in an ice bath; and the resulting precipitate was collected, washed with water, dried in a vacuum oven at 65° C. and then recrystallized from 90% aqueous acetic acid. There was thus obtained 16.0 g. (61%) of the product, 1-carboxymethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 292.4—294° C. (corr.) with decomposition.

Anal. Calcd. for C₁₂H₁₀N₂O₅: C, 54.96; H, 3.85; N, 10.68.

Found: C, 55.22; H, 4.17; N, 10.69.

EXAMPLE 30.

1 - (2 - Diethylaminoethyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: To a solution containing 20.4 g. of 4-hydroxy - 7 - methyl - 1,8 - naphthyridine - 3 - carboxylic acid, 26.0 g. of potassium hydroxide, 385 cc. of ethanol and 150 cc. of water was added 34.4 g. of 2-diethylaminoethyl chloride hydrochloride and the resulting reaction mixture was refluxed for about 2 hours and then allowed to stand at room temperature overnight. The reaction solution was chilled in an ice bath; and, when no precipitate resulted, it was then evaporated to dryness by heating on a steam bath *in vacuo*. The residual material was taken up in ethanol and the resulting solution treated with decolorizing charcoal and filtered. To the filtrate was added 25 cc. of 20% ethanolic hydrogen chloride and the resulting solution was chilled in an ice bath. The precipitate that separated was collected and recrystallized from methanol and dried in a vacuum oven at 70° C. to yield 16.1 g. (47% yield) of the product, 1 - (2 - diethylaminoethyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid in the form of its hydrochloride salt, m.p. 268.4—270° C. (corr.) with decomposition.

Anal. Calcd. for C₁₆H₂₁N₃O₃·HCl: Cl, 10.43; N, 12.37.

Found: Cl, 10.51; N, 12.45.

Also prepared according to the above procedure are 1 - (2 - di - n - butylaminoethyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 7 - methyl - 4 - oxo - 1 - [2 - (1 - piperidyl)ethyl] - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1 - (4 - diethylaminobutyl) - 4 - oxo - 7 - styryl - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid and 1 - [3 - (1 - pyrrolidyl) - propyl] - 4 - oxo - 7 - styryl - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid.

EXAMPLE 31.

7 - Methyl - 1 - (2 - methyl - 2 - propenyl) - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A

- mixture containing 14.7 g. of 4-hydroxy-7-methyl - 1,8 - naphthyridine - 3 - carboxylic acid, 14.0 g. of potassium hydroxide, 280 cc. of ethanol, 110 cc. of water and 30 cc. of 3-chloro - 2 - methyl - 1 - propene was refluxed on a steam bath and then allowed to stand overnight at room temperature. The reaction mixture was acidified with concentrated hydrochloric acid and chilled in an ice bath. The crystalline precipitate that separated was collected, washed with water, dried in a vacuum oven (70° C.) and recrystallized from acetonitrile using decolorizing charcoal. After drying the recrystallized product in a vacuum oven at 70° C., there was obtained 9.6 g. (52%) of 7 - methyl - 1 - (2 - methyl - 2 - propenyl) - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 218.4—219.6° C. (corr.).
- Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.84.
Found: C, 65.25; H, 5.43; N, 10.96.
- 7 - Methyl - 1 - (2 - methyl - 2 - propenyl) - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acid when tested as described above was found to potentiate hexobarbital sleeping time in four out of six mice at a dose level of 200 mg. per kg.
- EXAMPLE 32.
- 1 - (2 - Butenyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared following the procedure described in Example 1 using 10.2 g. of 4 - hydroxy - 7 - methyl - 1,8 - naphthyridine - 3 - carboxylic acid, 16.3 g. of potassium hydroxide, 190 cc. of ethanol, 75 cc. of water, 25 cc. of 1-chloro-2-butene and a reflux period of 3 hours. There was thus obtained about 7 g. of the product, 1-(2-butenyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 215.2—216.0° C. (corr.) when recrystallized twice from acetonitrile and dried in a vacuum oven (70° C.).
- Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.84.
Found: C, 65.03; H, 5.50; N, 10.98.
- 1 - (2 - Butenyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid when tested as described above was found to potentiate hexobarbital sleeping time in three out of six mice at a dose level of 200 mg. per kg.
- EXAMPLE 33.
- 1 - Ethyl - 4 - oxo - 7 - styryl - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 14.6 g. of 4-hydroxy-7-styryl-1,8-naphthyridine - 3 - carboxylic acid, 9.8 g. of potassium hydroxide, 230 cc. of ethanol, 80 cc. of water, and 20 cc. of ethyl iodide was refluxed on a steam bath for about 16 hours. The reaction mixture was then chilled in an ice bath and the solid that separated was collected, washed with acetone, dried in
- a vacuum oven (70° C.) and recrystallized from acetic acid to yield 12.8 g. of the product, 1 - ethyl - 4 - oxo - 7 - styryl - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, a light yellow solid, m.p. 265.0—266.8° C. (corr.).
- Anal. Calcd. for $C_{19}H_{16}N_2O_3$: N, 8.75; N.E., 320.
Found: N, 8.89; N.E., 316.
- The intermediate 4 - hydroxy - 7 - styryl-1,8 - naphthyridine - 3 - carboxylic acid was prepared in two steps as described in Example I of our copending application No. 32669/63 (Serial 1,000,893).
- 1 - Ethyl - 4 - oxo - 7 - styryl - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 5.6 and 4.6 against *Staphylococcus aureus* and of 5.6 and 4.3 against *Clostridium welchii*. This same compound when tested as described above for potentiation of hexobarbital sleeping time in mice was found to have an ED_{50} of 39±13 mg. per kg.
- Also prepared according to the above procedure are 1 - cyclohexylmethyl - 7 - (3,4-dimethoxystyryl) - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid, 7 - (4 - chlorostyryl) - 1 - [3 - (N,N - dimethylcarbarnyl)propyl] - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1 - (2 - methoxyethyl) - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 7 - (4 - methylmercaptostyryl) - 4-oxo - 1 - (3 - phenylpropyl) - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid, 4 - oxo - 7 - styryl - 1 - (3 - thienylmethyl)-1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 4 - oxo - 1 - [3 - (4-pyridyl)propyl] - 7 - styryl - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid, 1 - ethyl - 4 - oxo - 7 - [2 - (3 - pyridyl)-ethenyl] - 1,4 - dihydro - 1,8 - naphthyridine-3 - carboxylic acid, and 1 - ethyl - 7 - (4-nitrostyryl) - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine-3-carboxylic acid.
- EXAMPLE 34.
- Ethyl 1 - ethyl - 4 - oxo - 7 - styryl-1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate was obtained together with the corresponding carboxylic acid in the following synthesis: A mixture containing 64 g. of ethyl 4 - hydroxy - 7 - styryl - 1,8 - naphthyridine - 3 - carboxylate, 52 g. of potassium hydroxide, 920 cc. of ethanol, 320 cc. of water, and 80 cc. of ethyl iodide was refluxed for about 16 hours. The acidic reaction mixture was cooled in an ice bath; and the resulting precipitate was collected, washed twice with acetone and dried to yield 39.0 g. of solid (see below). The acetone washings were diluted with water and the yellow precipitate that separated was collected, washed

with boiling water, recrystallized once from acetic acid-water and a second time from absolute ethanol to yield 6.1 g. of ethyl-1-ethyl-4-oxo-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylate, m.p. 174.2—176.6° C. (corr.).

Anal. Calcd. for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.79; N, 8.04.

Found: C, 72.15; H, 5.49; N, 8.30.

- 10 The above 39 g. of solid was washed with hot 10% aqueous potassium carbonate solution and the resulting suspension was acidified with hydrochloric acid and filtered.

- 15 The filtered product was washed with water and dried in an oven (70° C.) to yield about 39 g. (62%) of 1-ethyl-4-oxo-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, the same product prepared above in Example 33.

- 20 Ethyl 1-ethyl-4-oxo-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylate when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 5.3 and 4.6 against *Staphylococcus aureus* and of 5.6 and 5.0 against *Clostridium welchii*. This same compound when tested as above for potentiation of hexobarbital sleeping time in mice was found to have an ED_{50} of 2.28 ± 0.7 mg. per kg.

- 30 The ethyl esters of 1-cyclohexylmethyl-7-(3,4-dimethoxystyryl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and of 1-(4-diethylaminobutyl)-4-oxo-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid are prepared by the above procedure.

EXAMPLE 35.

- 40 n-Propyl 1-ethyl-4-oxo-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylate was prepared as follows: A mixture containing 14.0 g. of ethyl 1-ethyl-7-styryl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate, 200 cc. of n-propanol and 0.5 g. of sodium methoxide was refluxed on a steam bath over the week end in a flask equipped with a drying tube containing anhydrous calcium sulphate. The reaction mixture was cooled well in an ice bath and the resulting white precipitate was collected and recrystallized using decolorizing charcoal from ethanol-water to yield 7.4 g. (51%) of the product, a white solid, n-propyl 1-ethyl-4-oxo-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylate, m.p. 181.8—183.0° C. (corr.).

Anal. Calcd. for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73.

- 60 Found: C, 73.14; H, 6.18; N, 7.73.
n-Propyl 1-ethyl-4-oxo-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylate when tested as above for potentiation of hexobarbital sleeping time in mice was found to have an ED_{50} of about 8 mg. per kg.

EXAMPLE 36.

1-Methyl-4-oxo-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid was prepared following the procedure described in Example 33 using 38.0 g. of 4-hydroxy-7-styryl-1,8-naphthyridine-3-carboxylic acid, 25.4 g. of potassium hydroxide, 600 cc. of ethanol, 200 cc. of water, 50 cc. of methyl iodide and a reflux period of 1 and $\frac{1}{2}$ hours. There was thus obtained 26.5 g. (67%) of the product, a cream-colored cottony solid, 1-methyl-4-oxo-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, m.p. >300° C. (corr.), when recrystallized from acetic acid.

Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15.

Found: C, 70.56; H, 4.25; N, 9.06.

EXAMPLE 37.

4-Oxo-1-n-propyl-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid was prepared following the procedure described in Example 33 using 38.0 g. of 4-hydroxy-7-styryl-1,8-naphthyridine-3-carboxylic acid, 25.4 g. of potassium hydroxide, 600 cc. of ethanol, 210 cc. of water, 50 cc. of n-propyl bromide and a reflux period of 28 hours. After two recrystallizations from acetonitrile, there was obtained 25.1 g. of the product, a pale yellow solid, 4-oxo-1-n-propyl-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, m.p. 236.6—238.0° C. (corr.).

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.42; N, 8.38.

Found: C, 72.18; H, 5.19; N, 8.41.

EXAMPLE 38.

Ethyl 4-oxo-1-n-propyl-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylate was prepared as follows: 19.3 g. of 4-oxo-1-n-propyl-7-styryl-1,8-naphthyridine-3-carboxylic acid was dissolved in 500 cc. of chloroform and to this stirred solution was added 22.1 g. of oxalyl chloride. A yellow precipitate formed immediately. The reaction mixture was refluxed for 6 hours on a steam bath and then allowed to stand at room temperature over the week end in a flask sealed with a drying tube containing anhydrous calcium sulfate. To the reaction mixture was added 30 cc. of ethanol. The resulting solution was stirred, refluxed for 30 minutes, allowed to cool to room temperature, and filtered. The filtrate was washed once with 10% potassium carbonate and twice with water, dried over anhydrous potassium carbonate, and evaporated in a steam bath *in vacuo*. The dark residual oily material solidified on cooling. This solid was recrystallized twice from absolute ethanol, each time using decolorizing charcoal, and then dried in an oven (80° C.) to yield 13.1 g. of the product, ethyl 4-oxo-1-n-propyl-7-styryl-1,4-dihydro-1,8-naphthyridine-



3-carboxylate, m.p. 134.8—136.8° C. (corr.).
Anal. Calcd. for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73.

Found: C, 72.99; H, 6.04; N, 7.67.

- 5 Ethyl 4 - oxo - 1 - n - propyl - 7 - styryl-
 1,4 - dihydro - 1,8 - naphthyridine - 3-
 carboxylate when tested as above for potentia-
 tion of hexobarbital sleeping time in mice
 was found to have an ED_{50} of about 2.05
 10 mg. per kg.

EXAMPLES 39—42.

- The following compounds were prepared
 following the procedure described in Example
 38: ethyl 1 - methyl - 4 - oxo - 7 - styryl-
 15 1,4 - dihydro - 1,8 - naphthyridine - 3-
 carboxylate, m.p. 200.5—201.4° (corr.), after
 2 recrystallizations from acetonitrile using de-
 colorizing charcoal, when tested as above for
 potentiation of hexobarbital sleeping time in
 mice was found to have an ED_{50} of 41 ± 12
 20 mg. per kg. Methyl 1-ethyl-4-oxo-7-styryl-
 1,4 - dihydro - 1,8 - naphthyridine - 3-
 carboxylate, m.p. 211.6—214.2° C. (corr.),
 when tested as above for potentiation of hexo-
 25 barbital sleeping time in mice was found to
 have an ED_{50} of about 100 mg. per kg.

- Isopropyl 1 - ethyl - 4 - oxo - 7 - styryl-
 1,4 - dihydro - 1,8 - naphthyridine - 3-
 30 carboxylate, m.p. 183.2—184.0° C. (corr.)
 when recrystallized from ethanol using de-
 colorizing charcoal, when tested as above for
 potentiation of hexobarbital sleeping time in
 mice was found to have an ED_{50} of 2.7 ± 0.2
 mg. per kg. Ethyl 1-ethyl-7-(4-methoxy-
 35 styryl) - 4 - oxo - 1,4 - dihydro - 1,8-
 naphthyridine - 3 - carboxylate was pre-
 pared, m.p. 184.2—186.8° C. (corr.) after 3-
 recrystallizations from acetonitrile using de-
 colorizing charcoal.

EXAMPLE 43.

- 1 - Ethyl - 7 - (4 - methoxystyryl) - 4-
 oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-
 carboxylic acid was prepared following the
 procedure described in Example 33, m.p.
 45 282.6—286.7° C. (corr.), after one recrystal-
 lization from acetic acid. The intermediate 4-
 hydroxy - 7 - (4 - methoxystyryl) - 1,8-
 naphthyridine - 3 - carboxylic acid was
 prepared in two steps following the procedure
 described in Example II of our copending
 50 application No. 32669/63 (Serial 1,000,893).

EXAMPLE 44.

- 1 - Ethyl - 4 - oxo - 7 - (2 - phenylethyl)-
 1,4 - dihydro - 1,8 - naphthyridine - 3-
 55 carboxylic acid was prepared by catalytic
 hydrogenation of the corresponding 7-styryl
 compound as follows: A mixture containing
 10.0 g. of 1 - ethyl - 4 - oxo - 7 - styryl-
 1,4 - dihydro - 1,8 - naphthyridine - 3-
 60 carboxylic acid, platinum oxide, 400 cc. of
 acetic acid were placed in a steel bomb and
 heated at a temperature of about 114—119°
 C. at a pressure of about 125 lbs. of hydrogen.
 The reaction took about 30 minutes and 1.76
 65 mole equivalents of hydrogen were taken up.

The contents of the bomb were emptied into
 a large beaker and rinsed with fresh acetic
 acid. The reaction mixture was then filtered
 through diatomaceous earth to remove the
 platinum catalyst. The clear yellow filtrate
 was evaporated to dryness on a steam bath
 under reduced pressure to yield a yellow
 solid. The solid was recrystallized using de-
 colorizing charcoal from 500 cc. of absolute
 ethanol and then recrystallized a second time
 from ethyl acetate to yield 3.7 g. of the pro-
 duct, 1 - ethyl - 4 - oxo - 7 - (2 - phenyl-
 ethyl) - 1,4 - dihydro - 1,8 - naphthyridine-
 3-carboxylic acid, m.p. 178.0—179.2° C.
 (corr.).

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: N, 8.69;
 N.E., 322.

Found: N, 8.73; N.E., 322.

1 - Ethyl - 4 - oxo - 7 - (2 - phenylethyl)-
 1,4 - dihydro - 1,8 - naphthyridine - 3-
 85 carboxylic acid when tested according to
 standard *in vitro* bacteriological evaluation
 procedures was found to possess antibacterial
 activity, for example, to have Bs and Bc
 values, respectively, of 5.0 and 4.6 against
 90 *Staphylococcus aureus* and of 5.0 and 4.6
 against *Clostridium welchii*. This same com-
 pound when tested as described above for
 potentiation of hexobarbital sleeping time in
 mice was found to have an ED_{50} of 48 ± 13.7
 95 mg. per kg.

EXAMPLE 45.

1 - Ethyl - 4 - oxo - 1,4 - dihydro - 1,8-
 naphthyridine - 3,7 - dicarboxylic acid was
 prepared as follows: To a stirred suspension
 containing 28.0 g. of 1-ethyl-4-oxo-7-styryl-
 1,4 - dihydro - 1,8 - naphthyridine - 3-
 carboxylic acid in 192 cc. of pyridine and 35
 cc. of water cooled to 15—20° C. in an ice
 bath was added portionwise over a period of
 about 1 hour 36.8 g. of potassium per-
 manganate. The temperature was kept at 15—
 20° C. during the addition of the per-
 manganate. After two 90 cc. portions of water
 were added to the reaction mixture, one after
 half of the permanganate had been added
 and the other after completion of the addition
 of the permanganate, the reaction mixture
 was stirred for an additional 30 minutes.
 After an unsuccessful attempt to remove the
 colloidal manganese dioxide by filtration,
 sodium bisulphite solution was added until
 all manganese dioxide had been destroyed.
 The mixture was then acidified with 6N
 sulphuric acid whereupon pale yellow solid
 separated. The solid was collected and dis-
 solved in 10% aqueous potassium carbonate
 solution. This solution was filtered and to the
 filtrate was added hydrochloric acid to re-
 precipitate the product. The solid was
 collected, washed with water and recrystal-
 lized from acetic acid using decolorizing
 charcoal. It was then washed with acetone and
 dried in a vacuum oven at 70° C. to yield
 12.6 g. (57%) of the product, 1-ethyl-4-oxo-
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1,4 - dihydro - 1,8 - naphthyridine - 3,7-dicarboxylic acid, m.p. 282—283.4° C. (corr.) with decomposition.

5 *Anal.* Calcd. for $C_{12}H_{10}N_2O_5$: N, 10.68; N.E., 131. and 262.

Found: N, 10.76; N.E., 129 and 273.

EXAMPLE 46.

1 - Ethyl - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 10 5.8 g. of 1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine - 3,7 - dicarboxylic acid and 0.29 g. of 2-pyridone suspended in 58 cc. of "Dowtherm" A was refluxed for about 20 15 minutes. The supernatant liquid was decanted into a clean flask and allowed to cool to room temperature. The solid that separated was collected, washed three times with ether, and recrystallized three times from acetonitrile, 20 the first time using decolorizing charcoal, to yield 1.1 g. of the product, 1-ethyl-4-oxo-1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 231.0—231.8° C. (corr.).

25 *Anal.* Calcd. for $C_{11}H_{10}N_2O_5$: C, 60.54; H, 4.62; N, 12.84.

Found: C, 60.36; H, 4.33; N, 12.95.

EXAMPLE 47.

30 7 - Amino - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: 14 g. of ethyl 7 - acetamido - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylate was dissolved by boiling with a mixture 35 of 50 cc. of 6N hydrochloric acid and 50 cc. of water. About 10 minutes after dissolution, solid separated and to this mixture was added 100 cc. of water plus 150 cc. of 6N hydrochloric acid. The mixture was heated near 40 boiling for about 30 minutes to dissolve most of the solid and the resulting mixture was filtered. The filtrate was poured into a slight excess of potassium hydroxide solution and ice. When no solid separated, hydrochloric 45 acid was added till acidic and the resulting solid was collected, recrystallized from 6N hydrochloric acid, dried in a vacuum oven at 60° C. to yield 8.4 g. of the product, a white solid, 7 - amino - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. >300° C. (corr.).

50 *Anal.* Calcd. for $C_{11}H_{11}N_3O_3$: N, 18.02; N.E., 233.

Found: N, 17.97; N.E., 231.

55 Ethyl 7 - acetamido - 1 - ethyl - 4 - oxo-1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate was prepared in several steps starting with 2,6-diaminopyridine as follows: To a solution containing 327 g. of 2,6-diaminopyridine in 1500 cc. of ethanol kept at about 40—45° C. was added 627 g. of diethyl ethoxymethylenemalonate and the resulting 60 reaction solution was kept at 45—55° C. for about 25 minutes and then refluxed on a steam bath for 10 minutes. The reaction solu-

tion was then cooled and the solid that separated was collected, washed well with cold ethanol, recrystallized from benzene and dried in a vacuum oven at 60° C. to obtain about 450 g. of diethyl N-(6-amino-2-pyridyl)-aminomethylenemalonate, m.p. 114—116° C.

Anal. Calcd. for $C_{13}H_{11}N_3O_4$: N, 15.05.

Found: N, 15.08, 15.07.

A mixture containing 14 g. of diethyl N-(6 - amino - 2 - pyridyl) - aminomethylene-malonate, 10 cc. of acetic anhydride and 10 cc. of "Dowtherm" A was heated first at 140° C. for about 15 minutes, then from 140° C. to about 250° C. over a period of 30 80 minutes and finally at 250° C. for about 15 minutes. The reaction mixture was cooled to 100° C. and the solid that separated was collected, washed with benzene and n-pentane, recrystallized from dimethylformamide, washed well with ethanol and dried in a vacuum oven at 60° C. There was thus obtained 7.2 g. of ethyl 7-acetamido-4-hydroxy - 1,8 - naphthyridine - 3 - carboxylate, m.p. >300° C. (corr.).

90 *Anal.* Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.73; H, 4.76; N, 15.27.

Found: C, 56.69; H, 4.59; N, 15.42.

Ethyl 7 - acetamido - 1 - ethyl - 4 - oxo-1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate was prepared as follows: A mixture containing 27.5 g. of ethyl 7-acetamido-4 - hydroxy - 1,8 - naphthyridine - 3 - carboxylate, 58 cc. of 10% aqueous potassium hydroxide solution, 350 cc. of water, 500 cc. of ethanol and 30 cc. of ethyl iodide was refluxed for 1 and $\frac{1}{2}$ hours. The neutral reaction mixture was concentrated by heating on a steam bath to remove the ethanol. To the resulting thick white slurry was added about 500 cc. of water; and the solid was collected and recrystallized twice from ethanol to yield 18.5 g. of the product, ethyl 7-acetamido - 1 - ethyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate, m.p. 192—195° C. This material was used in the above preparation without further purification.

7 - Amino - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 3.6 and <3.0 against *Staphylococcus aureus*, of 4.0 and 3.0 against *Eberthella typhi* 120 and of 4.3 and 3.0 against *Clostridium welchii*.

EXAMPLE 48.

7 - Amino - 1 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 27.5 g. of ethyl 7-acetamido-4-hydroxy - 1,8 - naphthyridine - 3 - carboxylate, 58 cc. of 10% aqueous potassium hydroxide, 500 cc. of ethanol, 350 cc. of 130

- water and 10 cc. of methyl iodide was refluxed on a steam bath for 3 hours, with occasional small additions of methyl iodide (to replace that lost by volatilization and hydrolysis). An additional 140 cc. of 10% aqueous potassium hydroxide was added to the reaction mixture and heating was continued on a steam bath without a condenser for an additional 3 hours. The thus partially concentrated reaction mixture was filtered and the filtrate poured with stirring into 50 cc. of 6N hydrochloric acid, adding water as needed to facilitate stirring. The resulting white precipitate was collected, washed with water, recrystallized from 6N hydrochloric acid and dried in a vacuum oven at 70° C. to yield 16.9 g. of the product, 7-amino - 1 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. >300° C. (corr.).
- Anal. Calcd. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17.
Found: C, 54.72; H, 4.65; N, 19.06.
- 7 - Amino - 1 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid when tested according to the procedure described above was found to potentiate hexobarbital sleeping time in four out of six mice at a dose level of 200 mg. per kg.

EXAMPLE 49.

- 7 - Amino - 1 - n - propyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 27.5 g. of ethyl 7-acetamido-4-hydroxy - 1,8 - naphthyridine - 3 - carboxylate, 58 cc. of 10% aqueous potassium hydroxide, 350 cc. of water, 500 cc. of ethanol and 25 cc. of n-propyl iodide was refluxed on a steam bath for a period of 5 hours. An additional 260 cc. of 10% aqueous potassium hydroxide solution was added to the acidic reaction mixture and refluxing was continued for an additional 5 hours, again adding about 25 cc. of n-propyl iodide. The reaction mixture was then refluxed for 1 hour without a condenser to allow removal of the excess n-propyl iodide and ethanol, filtered, and the filtrate treated with excess dilute aqueous hydrochloric acid. The solid that separated was collected, recrystallized once from ethanol and a second time from n-propanol, and dried in a vacuum oven at 60° C. to yield 10.5 g. of pale yellow solid, 7-amino - 1 - n - propyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 225.4—227.6° C. (corr.).
- Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00.
Found: C, 58.36; H, 5.27; N, 16.76.
- 7 - Amino - 1 - n - propyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 3.61 and <3.01 against *Staphylococcus*

aureus and of 4.31 and 3.31 against *Clostridium welchii*.

EXAMPLE 50.

7 - Acetamido - 1 - ethyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 18.7 g. of 7-amino-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, 200 cc. of acetic anhydride and 200 cc. of acetic acid was refluxed with stirring for 5 hours. To the reaction mixture was then added 4 drops of concentrated sulfuric acid and refluxing was continued overnight (for about 16 hours). The reaction mixture was filtered while hot and the filtrate was chilled in an ice bath. The precipitate that separated was collected, triturated with ethyl acetate and dried in a vacuum oven at 60° C. to yield 11.0 g. of the white product, 7 - acetamido - 1 - ethyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. >300° C. (corr.).

Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27.
Found: C, 56.68; H, 4.17; N, 15.31.

7 - Acetamido - 1 - ethyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 4.3 and 3.12 against *Eberthella typhi* and of 4.3 and 3.6 against *Clostridium welchii*. This same compound was found to have significant *in vivo* activity against *Klebsiella pneumoniae* in mice when administered orally at a dose level of 400 mg. per kg. per day or when administered subcutaneously at a dose level of 200 mg. per kg. per day.

EXAMPLE 51.

1 - Ethyl - 4 - oxo - 7 - propionamido - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 12.8 g. of 7-amino-1-ethyl-4-oxo-1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 200 cc. of propionic anhydride and 6 drops of sulfuric acid was refluxed for 6 hours, allowed to cool to room temperature and then slowly poured with stirring into 1 liter of methanol. The solid that separated was collected, recrystallized once from dimethylformamide using decolorizing charcoal and once from acetonitrile using decolorizing charcoal, and then dried in a vacuum oven at 70° C. to yield 4.0 g. of the product, 1-ethyl - 4 - oxo - 7 - propionamido - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 236.4—237.2° C. (corr.).

Anal. Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.10; H, 5.23; N, 14.52.
Found: C, 58.44; H, 5.29; N, 14.44.

1 - Ethyl - 4 - oxo - 7 - propionamido - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid when tested according to the procedure described above for potentiation of hexo-

barbital sleeping time in mice was found to have an ED_{50} of 230 ± 69.8 mg. per kg.

- Also prepared by the above procedure is
 5 7 - n - butanoylamino - 1 - ethyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid.

EXAMPLE 52.

- 1 - Ethyl - 7 - formamido - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 23.3 g. of 7-amino-1-ethyl-4-oxo-1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 75 cc. of formic acid and 75 cc. of acetic anhydride was refluxed for 2 hours and then
 10 allowed to stand at room temperature overnight (about 16 hours). The liquid was decanted from the separated solid; and the solid was stirred with 300 cc. of water for about $\frac{1}{2}$ hour, filtered and washed with water. The solid was then recrystallized from pyridine acetate using decolorizing charcoal, washed successively with water and acetone, and then
 15 dried for 5 hours in a vacuum oven at 70° C. to yield a white product, 1-ethyl-7-formamido - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. $293.8-294.6^\circ$ C. (corr.) with decomposition.

Anal. Calcd. for $C_{12}H_{11}N_3O_4$: C, 55.16; H, 4.24; N, 16.08.

- 30 Found: C, 55.22; H, 4.11; N, 16.18.

EXAMPLE 53.

- 7 - Bromo - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: 18.6 g. of 7-amino - 1 - ethyl - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid was partially dissolved in 192 cc. of 48% hydrobromic acid and the mixture was cooled to 0° C. To the stirred mixture kept at 0° C.
 35 was added dropwise first over a period of fifteen minutes 12 cc. of bromine and then over a period of 20 minutes a solution of 18.8 g. of sodium nitrite in 25 cc. of water. After the resulting mixture was stirred an additional 30 minutes, it was made alkaline with a solution containing 100 g. of sodium hydroxide in 500 cc of water, keeping the temperature below 27° C. There resulted a large gummy orange lump. This was separated
 40 by decanting the liquid and then triturated (in a mortar) in a dilute solution of aqueous sodium hydroxide and ethanol. The mixture was allowed to stand overnight whereupon it partially solidified. The solid was removed by filtration and the filtrate was acidified with hydrochloric acid. The solid that separated was collected, triturated with ethanol and then recrystallized from dimethylformamide twice to yield 2.5 g. (10%) of the white solid product, 7 - bromo - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. $255.0-256.0^\circ$ C. (corr.).

Anal. Calcd. for $C_{11}H_8BrN_2O_3$: Br, 26.92; N, 9.43.

- 65 Found: Br, 26.91; N, 9.28.

7 - Bromo - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was found to have significant *in vivo* activity against *Klebsiella pneumoniae* in mice when administered subcutaneously at a dose level of 100 mg. per kg. per day.

EXAMPLE 54.

1 - Ethyl - 7 - hydroxy - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: To a partial solution of 7.0 g. of 7-amino-1-ethyl-4-oxo-1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid in 35 cc. of concentrated sulfuric acid and 40 cc. of water kept at 0° C. was added portionwise 3 g. of sodium nitrite; and the resulting mixture was stirred for 1 hour at 0° C. To the reaction mixture was added about 300 cc. of boiling water whereupon a white solid separated. The mixture was heated to boiling and then cooled in an ice bath. The solid was collected, washed with water, recrystallized once from ethanol, once from dimethylformamide, and then washed with ethanol to yield the product, 1-ethyl - 7 - hydroxy - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid, m.p. $287.8-288.6^\circ$ C. (corr.), when dried at 60° C.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.95.

Found: C, 56.46; H, 4.19; N, 12.18.

1 - Ethyl - 7 - hydroxy - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 4.3 and 3.82 against *Staphylococcus aureus*, of 3.7 and <3.7 against *Eberthella typhi* and of 4.3 and 3.7 against *Clostridium welchii*.

EXAMPLE 55.

7 - Chloro - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 56 g. of 1-ethyl-7-hydroxy-4-oxo-1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid and 200 cc. of phosphorus oxychloride was refluxed for 30 minutes and then concentrated to remove about 125 cc. of the excess $POCl_3$. The concentrate was then poured into a mixture of water and ice; and the solid that separated was collected to yield 50 g. of the product, 7 - chloro - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. $252-255^\circ$ C. with decomposition. For analysis, a 12 gram portion of the product was recrystallized from acetonitrile using decolorizing charcoal to yield 9.3 g. of white solid product which melted at $249.8-250.4^\circ$ C. (corr.) and analysed as follows:

Anal. Calcd. for $C_{11}H_8ClN_2O_3$: Cl, 14.05; N, 11.09.

Found: Cl, 13.83; N, 11.24.

7 - Chloro - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic

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acid when tested according to standard *in vitro* bacteriological evaluation procedures was found to possess antibacterial activity, for example, to have Bs and Bc values, respectively, of 4.6 and <3.0 against *Staphylococcus aureus*, of 5.3 and 3.6 against *Eberthella typhi* and of 4.6 and 3.0 against *Clostridium welchii*.

EXAMPLE 56.

7 - Ethoxy - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A 5.0 g. portion of 7 - chloro - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was dissolved in 60 cc. of dry dimethylformamide at reflux. Heating was discontinued and to the solution was added over a 2 minute period 60 cc. of a 0.06 M solution of sodium ethoxide in dry ethanol. The reaction mixture was allowed to stand about 10 minutes and then poured into water. The aqueous mixture was made acidic with hydrochloric acid; and the solid that separated was collected, recrystallized once from ethanol and once from dimethylformamide to yield the product, 7 - ethoxy - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 226.8—227.8° C. (corr.).

Anal. Calcd. for $C_{15}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68.

Found: C, 59.72; H, 5.25; N, 10.91.

7 - Ethoxy - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid when tested as described above was found to potentiate hexobarbital sleeping time in four out of six mice at a dose level of 200 mg. per kg.

7 - Ethoxy - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid also can be obtained following the procedure described in Example 1 using molar equivalent quantities of 7-ethoxy-4-hydroxy-1,8-naphthyridine-3-carboxylic acid, potassium hydroxide, ethanol, water and ethyl iodide. The corresponding ethyl ester is obtained following the procedure described in Example 16 using ethyl 7 - ethoxy - 4 - hydroxy-1,8 - naphthyridine - 3 - carboxylate, sodium ethoxide, absolute ethanol and ethyl iodide.

Also prepared by the above procedure are 7 - n - butoxy - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid and 1 - ethyl - 4 - oxo - 7 - phenoxy-1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid.

EXAMPLE 57.

7 - (2 - Diethylaminoethoxy) - 1 - ethyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acid was prepared as follows: To a solution of 13.8 g. of 2-diethylaminoethyl chloride hydrochloride in 75 cc. of dry ethanol was added 200 cc. of one molar solution of sodium ethoxide in ethanol. This mixture was combined with a solution of 14 g. of 1-ethyl-7 - hydroxy - 4 - oxo - 1,4 - dihydro - 1,8-

naphthyridine - 3 - carboxylic acid in 100 cc. of dry dimethylformamide. The resulting slurry was refluxed on a steam bath for 3½ hours. Fifty cc. of water was added to the solid-liquid reaction mixture and it was concentrated to a syrupy solid which was dissolved in 100 cc. of water. The aqueous solution was treated with decolorizing charcoal and filtered. The filtrate was neutralized with acetic acid, chilled and filtered. The filtrate was concentrated to a tan tarry solid which was extracted with hot acetone. Addition of 18% ethanolic hydrogen chloride to the hot acetone extract and cooling yielded 20 g. of cream solid which was collected and dried. The solid was dissolved in 100 cc. of water and 35 cc. of 10% potassium bicarbonate was added (pH=6.4). The solution was extracted several times with chloroform, adjusting the pH from about 6 to 7.5 between extractions. The combined extracts were dried over anhydrous sodium sulfate and concentrated to yield 11.4 g. of cream colored solid which was recrystallized twice from ethyl acetate to yield 6.8 g. (34%) of pale cream colored solid product. 7 - (2 - diethylaminoethoxy) - 1 - ethyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acid, m.p. 163.6—165.4° C. (corr.).

Anal. Calcd. for $C_{17}H_{23}N_3O_4$: C, 61.24; H, 6.95; N, 12.61.

Found: C, 61.30; H, 6.74; N, 12.49.

EXAMPLE 58.

1 - Ethyl - 7 - ethylmercapto - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: 12.0 g. of 7-chloro - 1 - ethyl - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid was dissolved in 200 cc. of dry dimethylformamide by boiling. To this hot solution was added a mixture containing 18 g. of ethylmercaptan, 67 cc. of 10% aqueous potassium hydroxide solution and 100 cc. of ethanol. The resulting reaction mixture was allowed to stand for 5 minutes and then poured into about 1 liter of water containing excess hydrochloric acid. The precipitate that separated was collected, washed successively with water and a little ethanol and then recrystallized from dimethylformamide. The recrystallized solid was triturated in hot ethanol, collected, and dried to yield 10.2 g. of the product, 1-ethyl - 7 - ethylmercapto - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 217.2—218.4° C. (corr.).

Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: N, 10.17; S, 11.51.

Found: N, 10.32; S, 11.46.

1 - Ethyl - 7 - ethylmercapto - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid when tested as described above was found to potentiate hexobarbital sleeping time in four out of six mice at a dose level of 200 mg. per kg.

EXAMPLE 59.

7 - Dimethylamino - 1 - ethyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 12.6 g. of 7-chloro-1-ethyl-4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acid and 50 cc. of 25% aqueous dimethylamine was heated on a steam bath for about 25 minutes. The resulting turbid solution was diluted with water and then poured into an excess of very dilute hydrochloric acid solution. The solid that separated was collected, triturated first with water and then with ethanol, and recrystallized from dimethylformamide. The recrystallized solid was triturated with boiling ethanol, collected and dried to yield 11.0 g. of the white product, 7 - dimethylamino - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 271.4—272.2° C. (corr.).

Anal. Calcd. for $C_{15}H_{17}N_3O_3$: C, 59.76; H, 5.79; N, 16.08.

Found: C, 59.89; H, 5.50; N, 16.08.

Also prepared by the above procedure is 7 - n - butylamino - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid.

EXAMPLE 60.

7 - (5 - Diethylamino - 2 - pentylamino)-1 - ethyl - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 12.6 g. of 7-chloro-1-ethyl-4-oxo-1,4-dihydro-1,8 - naphthyridine - 3 - carboxylic acid, 15.9 g. of 5-diethylamino-2-pentylamine and 200 cc. of acetonitrile was refluxed for 4 hours, and the solvent was then removed by distilling *in vacuo* to yield a viscous, clear, oily material. The oily material was taken up in chloroform and extracted with aqueous potassium hydroxide solution. The alkaline solution was washed three times with chloroform, acidified with a slight excess of concentrated hydrochloric acid, washed with chloroform, neutralized with 10% aqueous potassium bicarbonate solution, and allowed to cool with stirring whereupon a solid slowly formed. The solid was collected and heated with isopropyl alcohol containing 20 cc. of 15% ethanolic hydrogen chloride. The hot solution was filtered, allowed to stand at room temperature, and the precipitate that formed was collected, washed with acetone, recrystallized from ethanol and air-dried to yield 5 g. of the product, 7-(5-diethylamino-2-pentylamino) - 1 - ethyl - 4 - oxo - 1,8 - naphthyridine - 3 - carboxylic acid in the form of its hydrochloride, m.p. 242.0—243.2° C. (corr.).

Anal. Calcd. for $C_{30}H_{40}N_4O_3 \cdot HCl$: C, 58.46; H, 7.60; N, 13.62.

Found: C, 58.46; H, 7.42; N, 13.58.

Also prepared by the above procedure is 1 - ethyl - 4 - oxo - 7 - [2 - (1 - piperidyl)-

ethylamino] - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acid.

EXAMPLE 61.

1 - Ethyl - 7 - hydrazino - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: 12.6 g. of 7-chloro - 1 - ethyl - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid and 50 g. of hydrazine hydrate were mixed at room temperature and then warmed on a steam bath for about 1 hour. The reaction mixture was then allowed to cool and the solid that separated was collected and dissolved in about 200 cc. of water by warming on a steam bath. The hot solution was filtered and poured into 200 cc. of concentrated hydrochloric acid. The resulting mixture was stirred at room temperature and then cooled. The solid that separated was collected, washed well with water and then dissolved in aqueous potassium hydroxide solution. The alkaline solution was treated with decolorizing charcoal, filtered, and to the filtrate was added a slight excess of 6N hydrochloric acid. The solid that separated was collected, washed with acetone and recrystallized from 6N hydrochloric acid using decolorizing charcoal to yield 6.5 g. of the yellow product, 1 ethyl-7-hydrazino-4-oxo-1,8 - naphthyridine - 3 - carboxylic acid in the form of its hydrochloride, m.p. >300° C. (corr.).

Anal. Calcd. for $C_{11}H_{12}N_4O_3 \cdot HCl$: Cl, 12.44; N, 19.68.

Found: Cl, 12.40; N, 19.67.

EXAMPLE 62.

1 - (3 - Hydroxypropyl) - 7 - methyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acid is obtained following the procedure described in Example 1 using molar equivalent quantities of 4-hydroxy-7-methyl-1,8 - naphthyridine - 3 - carboxylic acid, potassium hydroxide, ethanol, water and 3-hydroxypropyl iodide. The corresponding ethyl ester is obtained following the procedure described in Example 16 using ethyl 4-hydroxy - 7 - methyl - 1,8 - naphthyridine-3-carboxylate, sodium ethoxide, absolute ethanol and 3-hydroxypropyl iodide.

EXAMPLE 63.

Ethyl 1 - (3 - chloropropyl) - 7 - methyl-4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylate is obtained by reacting the corresponding 1 - (3 - hydroxypropyl) compound of the preceding example with a chlorinating agent, for example, phosphorus oxychloride.

EXAMPLE 64.

1 - Ethyl - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was obtained by alkylating the dipotassium salt of 4 - hydroxy - 7 - methyl-1,8 - naphthyridine - 3 - carboxylic acid as follows: A 4.6 g. portion of ethyl 4-hydroxy-7 - methyl - 1,8 - naphthyridine - 3 - carb-

oxylate was dissolved by warming it in an aqueous solution containing 2.6 g. of potassium hydroxide. The solution was then evaporated to dryness on a steam bath *in vacuo*. Benzene was added and distilled to remove the last traces of water. There was thus obtained the dipotassium salt of 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid. To this dipotassium salt was added 30 cc. of diethyl sulfate and the mixture was heated upon a steam bath in a flask sealed with a drying tube containing anhydrous calcium sulfate. The reaction mixture was heated for 4 hours and poured into water. The resulting mixture was heated with stirring and excess 10% aqueous potassium hydroxide solution was added to destroy the excess diethyl sulfate. The mixture was stirred for 30 minutes and then allowed to stand overnight. The solution was acidified with 6N hydrochloric acid solution and the precipitate that separated was collected, recrystallized from acetonitrile using decolorizing charcoal and air-dried to yield 2.2 g. (48%) of 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, m.p. 229—231° C. A mixed melting point of this product with the product obtained in Example 1 by reacting 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid with ethyl iodide gave no depression.

EXAMPLE 65.

1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-nitrile was prepared as follows: A mixture containing 23.1 g. of 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide, 19.4 g. of benzene-sulphonyl chloride and 20 g. of pyridine was stirred at room temperature for about 10 minutes with no rise in temperature noted. The reaction mixture was then warmed with stirring up to about 75° C. Stirring was continued with no external heating whereupon the inside temperature rose slowly to about 80° C. After dissolution had been completed, the reaction mixture was allowed to cool to room temperature whereupon it solidified. It was then broken up, taken up with water and a relatively large volume of chloroform, and the resulting mixture was filtered through diatomaceous earth. The chloroform layer was separated and washed successively with 1N hydrochloric acid, water and dilute ammonium hydroxide solution. It was then dried over anhydrous potassium carbonate, filtered, and evaporated to dryness. The resulting solid was recrystallized from ethanol using decolorizing charcoal and air-dried to yield 10 g. of the product, 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-nitrile, m.p. 220—226° C. (corr.).

Anal. Calcd. for $C_{15}H_{11}N_3O$: C, 67.60; H, 5.20; N, 19.70.

Found: C, 67.29; H, 5.15; N, 20.00.

EXAMPLE 66.

1,4-bis(3-carboxy-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridyl-1)-2-butene was prepared as follows: To a refluxed mixture containing 20.4 g. of 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid, 19.5 g. of potassium hydroxide, 150 cc. of water and 385 cc. of ethanol was added dropwise over a period of 90 minutes a solution containing 6.25 g. of 1,4-dichloro-2-butene dissolved in 25 cc. of ethanol. Refluxing was continued for an additional 90 minutes and the reaction mixture was then allowed to cool and stand overnight at room temperature. The crystalline solid that had separated was dissolved by heating the reaction mixture to reflux and the resulting solution was acidified with 19 cc. of concentrated hydrochloric acid. Some solid separated and the resulting mixture was cooled in an ice bath to yield more solid. The solid was collected, washed with water, recrystallized from formic acid using decolorizing charcoal and then recrystallized a second time from dimethyl sulfoxide to yield 1.1 g. of product, 1,4-bis(3-carboxy-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridyl-1)-2-butene, m.p. 365° C. with decomposition.

Anal. Calcd. for $C_{24}H_{20}N_4O_6$: C, 62.60; H, 4.38; N, 12.17.

Found: C, 62.56; H, 4.20; N, 12.22.

EXAMPLE 67.

1,4-Bis(3-carboxy-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridyl-1)-butane was prepared by catalytically hydrogenating the corresponding 2-butene derivative as follows: A mixture containing 0.8 g. of 1,4-bis(3-carboxy-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridyl-1)-2-butene, 4 cc. of 10% aqueous potassium hydroxide solution, 150 cc. of water and Raney nickel was shaken with hydrogen under pressure (50 lbs. per sq. in.) at room temperature (27° C.). After about 40 minutes the uptake of hydrogen had stopped. The mixture was shaken for an additional hour; and the catalyst was filtered and washed with dilute potassium hydroxide solution. The filtrate was heated to boiling and acidified with concentrated hydrochloric acid. The white solid that separated was collected, recrystallized from dimethyl sulfoxide using decolorizing charcoal, washed with acetone and dried *in vacuo* at 70° C. to yield 0.3 g. of the product, 1,4-bis(3-carboxy-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridyl-1)butane, m.p. 342—343° C. with decomposition.

Anal. Calcd. for $C_{24}H_{22}N_4O_6$: C, 62.33; H, 4.80; N, 12.12.

Found: C, 62.35; H, 4.99; N, 11.60.

Also encompassed by our invention are the following compounds: 1-(2-cyanoethyl)-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, 1-(2-carbamylethyl)-7-methyl-4-oxo-1,4-

- 5 dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, ethyl 1 - (2 - carbamylethyl) - 7-methyl - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylate, 7 - methyl-4 - oxo - 1 - [2 - (3 - pyridyl)ethyl] - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 7 - methyl - 4 - oxo - 1 - (2 - n-propylaminoethyl) - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylic acid, ethyl
- 10 1 - (5 - ethylaminopentyl) - 7 - methyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylate, 1 - [2 - (2 - chlorobenzylamino)-ethyl] - 7 - methyl - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid, ethyl
- 15 1 - (4 - cyanobutyl) - 4 - oxo - 7 - styryl-1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1-[3 - (3 - hydroxypropylamino)-propyl] - 4 - oxo - 7 - styryl - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, ethyl 4 - oxo - 1 - [2 - (2 - phenylethylamino)ethyl] - 7 - styryl - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylate, 7 - n-butoxy - 1 - ethyl - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid, 5,6 - dimethoxy - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1,7 - diethyl - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid, 4 - oxo - 1 - n - propyl - 7 - trifluoromethyl - 1,4 - dihydro - 1,8 - naphthyridine-3 - carboxylic acid, 7 - benzyl - 1 - ethyl-4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3 - carboxylic acid, 4 - oxo - 1,5,6,7-tetramethyl - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 2,7 - dimethyl - 1 - ethyl - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid, 7 - benzyloxy - 4 - oxo - 1 - n - propyl - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, ethyl 7 - acetamido - 1 - ethyl - 5-ethoxy - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate, 1 - ethyl - 7-fluoro - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1 - ethyl-4 - oxo - 7 - trichloromethyl - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid, 1 - ethyl - 6 - hydroxy - 7 - methyl - 4 - oxo-1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, phenyl 1 - ethyl - 7-methyl - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylate, 4 - chlorophenyl 1 - ethyl - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylate, 3 - methyl - phenyl 1 - ethyl - 7-methyl - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylic acid, phenyl 1-ethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid, ethyl 1 - ethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 6 - acetyl - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1 - ethyl - 6 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1 - ethyl - 5 - methyl - 4 - oxo - 1,4-
- dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 6,7 - dimethyl - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 6 - bromo - 1 - ethyl - 2,5,7 - trimethyl - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylic acid, 1-ethyl - 7 - ethylsulfinyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 7 - n - butylsulfonyl - 1 - ethyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylic acid, 1 - ethyl - 7 - methyl - 6-nitro - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1 - ethyl-7 - (3 - ethylaminopropyl) - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 1 - ethyl - 7 - [2 - (1 - piperidyl)-ethyl] - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, ethyl 1-ethyl - 7 - (2 - n - propylaminoethylamino)-4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3 - carboxylate, ethyl 1 - ethyl - 7 - (3-ethylaminopropoxy) - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylate, 1-ethyl - 7 - phenyl - 4 - oxo - 1,4 - dihydro-1,8 - naphthyridine - 3 - carboxylic acid, 1-ethyl - 7 - phenylmercapto - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 7 - (4 - ethoxyphenylamino) - 1 - n-propyl - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylic acid, 7-benzoyl - 1 - ethyl - 6 - methyl - 4 - oxo-1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylic acid, 7 - [2 - (3,4 - dimethoxyphenyl)ethoxy] - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 7 - cyano - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, ethyl 7 - aminomethyl - 1 - ethyl-4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3 - carboxylate, 7 - carbamyl - 1 - methyl-4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3 - carboxylic acid, diethyl 1 - ethyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine-3,7 - dicarboxylate, 1 - ethyl - 7 - hydroxymethyl - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylic acid, 1-ethyl - 7 - (2 - hydroxyethyl) - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, 7 - acetamidomethyl - 1 - ethyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine-3 - carboxylic acid, 6 - bromo - 1 - ethyl-4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3 - carboxylic acid and 1 - ethyl - 2-hydroxy - 7 - methyl - 4 - oxo - 1,4 - dihydro-1,8-naphthyridine-3-carboxylic acid.
- EXAMPLE 68.
- Ethyl 6,7 - dimethyl - 1 - ethyl - 4 - oxo-1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylate was prepared as follows: A mixture containing 12.3 g. of ethyl 6,7-dimethyl-4 - hydroxy - 1,8 - naphthyridine - 3-carboxylate, 15.4 g. of diethyl sulfate, 21.5 g. of anhydrous potassium carbonate and 100 cc. of dimethylformamide was stirred while heating on a steam bath for about 60 minutes.

The reaction mixture was poured into a mixture of ice and water (about 2 liters) and the aqueous mixture was stirred for 30 minutes. The precipitate was collected and dried at 80° C. to yield 12 g. of the product, ethyl 6,7-dimethyl - 1 - ethyl - 4 - oxo - 1,8 - naph-

thyridine-3-carboxylate. A 1 gram sample of this ethyl ester was recrystallized from isopropyl alcohol, using decolorizing charcoal, and dried at 80° C. to yield an analytically pure sample melting at 181.0—183.0° C. (corr.).

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21.
Found: C, 65.38; H, 6.77; N, 10.28.

The intermediate ethyl 6,7-dimethyl-4-hydroxy - 1,8 - naphthyridine - 3 - carboxylate was prepared in several steps starting with 2 - amino - 5,6 - dimethylpyridine as follows: A mixture containing 33 g. of 2-amino-5,6-dimethylpyridine and 58 g. of ethoxymethylene-malonic ester was heated for 2 hours on a steam bath, allowing the ethanol

to distil off during this reaction period. The reaction mixture was allowed to cool and the resulting solid was recrystallized from isopropyl alcohol using decolorizing charcoal to yield 56 g. (71% yield) of diethyl N-(5,6-dimethyl - 2 - pyridyl) - aminomethylene-malonate, m.p. 117.0—119.2° C. (corr.).

Anal. Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58.
Found: C, 61.41; H, 6.78; N, 9.85.

A solution containing 50 g. of diethyl N-(5,6 - dimethyl - 2 - pyridyl)aminomethylene-malonate in 50 cc. of diethylphthalate was heated to 150° C. and added, with stirring to 400 cc. of diethylphthalate heated to reflux (285° C.). The temperature was then brought back to 285° C. and held there for about 10 minutes. The heating source was removed and 100 cc. of ethanol was added slowly to cool the reaction mixture, the temperature dropping to about 150° C. The reaction mixture was

then allowed to cool to room temperature with stirring. The precipitate was collected, washed with ethyl acetate and dried overnight at 80° C. to yield 30 g. (72%) of ethyl 6,7-dimethyl-4 - hydroxy - 1,8 - naphthyridine - 3-carboxylate. For analysis a 3 gram sample was recrystallized from isopropyl alcohol using decolorizing charcoal and dried at 80° C. to yield 2.5 g. of the product, m.p. 267.0—268.0° C. (corr.) with decomposition.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38.
Found: C, 63.48; H, 5.87; N, 11.47.

The intermediate 2-amino-5,6-dimethylpyridine was prepared as follows: To a refluxing mixture containing sodamide (prepared from 85 g. of sodium and liquid ammonia) and 1500 cc. of xylene was added 321 g. of 2,3-dimethylpyridine during a 15 minute period. The reaction mixture was refluxed with stirring for 10 hours. To the reaction mixture was added 300 cc. of methanol with stirring to dissolve the separated solid. Two liters of water was then added slowly with stirring; the solution made acidic with concentrated hydrochloric acid; and ice added to cool the mixture. The xylene layer was separated and the aqueous layer then made basic with 35% aqueous sodium hydroxide solution, adding ice to cool the solution. The alkaline solution was then extracted with chloroform; and the chloroform extract was dried and evaporated *in vacuo* to remove the chloroform. The residual material was distilled *in vacuo* to yield a fraction distilling at 130—135° C. at 25 mm., $n_D^{25} = 1.5678$. This fraction was redistilled to yield a 29 g. fraction at 120—129° C. at 23 mm. and a

5 g. fraction at 129—150° C. at 23 mm. There was thus obtained 34 g. (9.2%) of 2-amino-5,6-dimethylpyridine, a solid when cold.

EXAMPLE 69.

6,7 - Dimethyl - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 9.5 g. of ethyl 6,7-dimethyl-1-ethyl-4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylate and 50 cc. of 10% aqueous potassium hydroxide solution was heated, with occasional stirring, on a steam bath for about 30 minutes. The reaction mixture was then treated with decolorizing charcoal, filtered, and the filtrate poured into an excess of dilute aqueous hydrochloric acid. The resulting precipitate was collected, washed with water, recrystallized once from acetonitrile and once from dioxane, and air-dried to yield 5.0 g. of the product, 6,7-dimethyl-1-ethyl-4-oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylic acid, m.p. 266.8—267.2° C. (corr.) with decomposition.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38.
Found: C, 63.56; H, 5.81; N, 11.29.

EXAMPLE 70.

1,6,7 - Trimethyl - 4 - oxo - 1,4 - dihydro-
1,8 - naphthyridine - 3 - carboxylic acid
was prepared as follows: A mixture contain-
5 ing 4.9 g. of ethyl 6,7-dimethyl-4-hydroxy-
1,8 - naphthyridine - 3 - carboxylate, 5.0
g. of dimethyl sulfate, 8.3 g. of anhydrous
potassium carbonate and 50 cc. of dimethyl-
formamide was heated with stirring on a steam
10 bath for about 2 hours. The reaction mixture
was then poured into a mixture of ice and
water and the resulting aqueous mixture was
allowed to warm up to room temperature. The
resulting precipitate was collected, warmed

on a steam bath with 50 cc. of 10% aqueous 15
potassium hydroxide solution with occasional
stirring. The alkaline solution was treated with
decolorizing charcoal, filtered and the filtrate
acidified with concentrated hydrochloric acid. 20
The resulting precipitate was collected, re-
crystallized from acetonitrile, using de-
colorizing charcoal, and then dried at 80° C.
to yield 3.5 g. (76%) of the product, 1,6,7-
trimethyl - 4 - oxo - 1,4 - dihydro - 1,8-
naphthyridine - 3 - carboxylic acid, m.p. 25
297.6—299.0° C. (corr.) with decomposi-
tion.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06.
Found: C, 61.83; H, 5.04; N, 11.92.

EXAMPLE 71.

6,7 - Dimethyl - 1 - n - propyl - 4 - oxo-
1,4 - dihydro - 1,8 - naphthyridine - 3-
carboxylic acid was prepared as follows: A
mixture containing 7.0 g. of ethyl 6,7-di-
35 methyl - 4 - hydroxy - 1,8 - naphthyridine-
3-carboxylate, 6.9 g. of n-propyl bromide,
11.5 g. of anhydrous potassium carbonate and
75 cc. of dimethylformamide was heated with
stirring on a steam bath for 2 hours. The
40 mixture was poured into about 700 cc. of ice
and water, the resulting aqueous mixture
stirred a few minutes, and the precipitate
collected. The precipitate was warmed on a

steam bath with about 75 cc. of 45
10% aqueous potassium hydroxide solu-
tion for about 30 minutes with
occasional stirring. The alkaline solution was
treated with decolorizing charcoal, filtered,
and the filtrate acidified with concentrated 50
hydrochloric acid. The resulting precipitate
was collected and recrystallized from isopropyl
alcohol, using decolorizing charcoal, and dried
at 80° C. to yield 4.0 g. (55%) of the pro-
duct, 6,7 - dimethyl - 1 - n - propyl - 4-
55 oxo - 1,4 - dihydro - 1,8 - naphthyridine-
3-carboxylic acid, m.p. 215.6—218.0° C.
(corr.).

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.70.
Found: C, 64.81; H, 6.18; N, 10.71.

EXAMPLE 72.

1,7 - Diethyl - 4 - oxo - 1,4 - dihydro-
1,8 - naphthyridine - 3 - carboxylic acid
was prepared as follows: A mixture contain-
ing 12.3 g. of ethyl 7-ethyl-4-hydroxy-1,8-
65 naphthyridine - 3 - carboxylate, 15.4 g. of
diethyl sulfate, 20.5 g. of anhydrous potassium
carbonate and 300 cc. of isobutyl methyl
ketone was refluxed with stirring for 24 hours.
The reaction mixture was evaporated to dry-
70 ness and the residual material taken up with
200 cc. of water and 100 cc. of 10% aqueous

potassium hydroxide solution. The resulting
mixture was refluxed for about 3 hours,
treated with decolorizing charcoal, filtered
while hot, allowed to cool, washed with 75
chloroform and acidified with dilute aqueous
hydrochloric acid. The resulting precipitate
was collected, recrystallized from isopropyl
alcohol, using decolorizing charcoal, and
80 dried overnight at 70° C. to yield 6.5 g.
(53%) of the product, 1,7-diethyl-4-oxo-1,4-
dihydro - 1,8 - naphthyridine - 3 - carboxylic
acid, m.p. 174.2—176.0° C. (corr.).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38.
Found: C, 63.61; H, 5.41; N, 11.28.

The intermediate ethyl 7-ethyl-4-hydroxy-
1,8 - naphthyridine - 3 - carboxylate was
prepared in several steps starting with 2-
amino-6-ethylpyridine following the procedure
described above in Example 68. There was
90 first obtained 112 g. (84% yield) of diethyl
N - (6 - ethyl - 2 - pyridyl)aminomethylene-
malonate, m.p. 64—66° C., recrystallized
from n-hexane using decolorizing charcoal,
95 from 55 g. of 2-amino-6-ethylpyridine and 98
g. of ethoxymethylenemalonate ester. About 35

g. of ethyl 7-ethyl-4-hydroxy-1,8-naph-
thyridine - 3 - carboxylate was obtained
using 96 g. of diethyl N-(6-ethyl-2-pyridyl)-
aminomethylenemalonate and 800 cc. of di- 100
ethylphthalate, this amount being obtained
after one recrystallization from dimethyl-
formamide using decolorizing charcoal. A 6
gram portion was recrystallized from dioxane,
washed with n-hexane and air-dried to yield 105
6 g. of an analytically pure sample m.p.
254.4—256.2° C. (corr.) with decomposition.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38.
Found: C, 63.70; H, 5.46; N, 11.34.

- 2 - Amino - 6 - ethylpyridine was prepared by reacting 2-ethylpyridine with sodamide following the procedure described in Example 68. From 107 g. of 2-ethylpyridine there was obtained 25 g. of a fraction distilling at 120—125° C. at 0.05 mm., $n_D^{25} = 1.5992$, which solidified on cooling. This solid 2-amino-6-ethylpyridine was converted into its picrate which was recrystallized from ethanol and found to melt at 191—193° C.

Anal. Calcd. for $C_{20}H_{20}N_6O_7$: C, 52.63; H, 4.42; N, 18.42.
Found: C, 52.66; H, 4.18; N, 18.45.

15 EXAMPLE 73.

- 7 - Ethyl - 1 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid was prepared as follows: A mixture containing 12.3 g. of ethyl 7-ethyl-4-hydroxy-1,8-naphthyridine - 3 - carboxylate and 300 cc. of 10% aqueous potassium hydroxide solution was stirred on a steam bath for 1 hour after which time the naphthyridine had dissolved. To this solution was added 300 cc. of ethanol and 10 cc. of methyl iodide and the resulting reaction mixture was refluxed with stirring. Ten cc. portions of methyl iodide were added after 1, 5 and 6 hours of refluxing. The reaction mixture was then refluxed overnight with stirring. The reaction mixture was treated with decolorizing charcoal, filtered, and the filtrate evaporated to dryness. The residue was taken up in water and acidified with excess concentrated hydrochloric acid to yield a yellow precipitate. The precipitate was collected, washed with acetone, recrystallized from acetonitrile using decolorizing charcoal and dried *in vacuo* at 70° C. for 5 hours to yield 5 g. of the product, 7-ethyl-1-methyl - 4 - oxo - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylic acid, m.p. 243.4—244.2° C. (corr.).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06.
Found: C, 62.30; H, 5.54; N, 12.05.

45 EXAMPLE 74.

- 1 - (2 - Benzyloxy)ethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acid was prepared following the procedure described in Example 1 using 59.6 g. of 4 - hydroxy - 7 - methyl - 1,8-naphthyridine - 3 - carboxylic acid, 62.2 g. of potassium hydroxide, 1230 cc. of ethanol, 480 cc. of water, 108.7 g. of 2-benzyloxyethyl chloride, 10 g. of potassium iodide, and a reflux period of 5 days. After recrystallizing from acetonitrile and drying in a vacuum oven at 70° C., there was obtained 42.3 g. of 1-(2 - benzyloxy)ethyl - 7 - methyl - 4 - oxo-1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 161.4—162.2° C. (corr.).

Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.38; N, 8.28.
Found: C, 67.31; H, 5.43; N, 8.15.

EXAMPLE 75.

- 1 - (2 - Hydroxyethyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acid was prepared following the procedure described in Example 1 using 20.4 g. of 4 - hydroxy - 7 - methyl - 1,8-naphthyridine - 3 - carboxylic acid, 39 g. of potassium hydroxide, 385 cc. of ethanol, 150 cc. of water, 42.8 g. of vinyl 2-chloroethyl ether, 3 g. of potassium iodide, and a reflux period of 5 days. The reaction mixture which contained 7 - methyl - 4 - oxo - 1-(2 - vinyloxyethyl) - 1,4 - dihydro - 1,8-naphthyridine - 3 - carboxylic acid was heated to reflux and acidified with concentrated hydrochloric acid to cleave the vinyl ether and produce the corresponding 1-(2-hydroxyethyl) compound. The reaction mixture was cooled in an ice bath and the separated product was collected, washed with water, recrystallized once from acetonitrile and twice from methanol, and dried in a vacuum oven at 70° C. for 6 hours to yield 3.4 g. of the product, 1-(2-hydroxyethyl)-7-methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid, m.p. 230.8—234.2° C. (corr.) with decomposition.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.04; H, 4.88; N, 11.29.
Found: C, 57.95; H, 4.65; N, 11.15.

- 1 - (2 - Hydroxyethyl) - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxylic acid was also prepared by catalytically reducing the corresponding 1-(2-benzyloxy)ethyl compound of Example 74 using 3.5 g. of the 1-(2-benzyloxy)ethyl compound, 150 cc. of acetic acid, 0.5 g. of 10% palladium on charcoal and an initial pressure of hydrogen of 49 lbs. per sq. inch. A mixed melting point with the above product obtained from the vinyl ether was not depressed.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: N, 11.29; N.E., 248.
Found: N, 11.62; N.E., 256.5.

N.E. = neutral equivalent.

EXAMPLE 76.

Cupric di(1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate) was prepared as follows: To a solution containing 11.6 g. of 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and 3.0 g. of sodium methoxide dissolved in 400 cc. of hot methanol was added with stirring a solution containing 5.0 g. of cupric acetate

monohydrate in 300 cc. of hot methanol. The reaction mixture was stirred at room temperature for 2 hours and the precipitated blue solid was collected and dried in a vacuum oven at 70° C. overnight. There was thus obtained 10 g. of the product, cupric di(1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate), m.p. 278.0—279.0° C. (corr.) with decomposition

Anal. Calcd. for $C_{24}H_{22}N_4O_6Cu$: N, 10.64; Cu, 12.08.

Found: N, 10.60; Cu, 11.75.

EXAMPLE 77.

7-Amino-1-(2,4-dichlorobenzyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid was prepared following the procedure described in Example 48 using 33 g. of ethyl 7-acetamido-4-hydroxy-1,8-naphthyridine-3-carboxylate, 20.2 g. of potassium hydroxide, 500 cc. of ethanol, 150 cc. of water, 39 g. of 2,4-dichlorobenzyl chloride,

and a reflux period of 3 hours. The product was isolated as its potassium salt, converted into the acid, recrystallized from dimethylformamide-ethanol and dried at 60° C. *in vacuo* to yield 12.6 g. of the product, 7-amino-1-(2,4-dichlorobenzyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, m.p. 288.2—289.2° C. (corr.).

Anal. Calcd. for $C_{18}H_{11}Cl_2N_3O_3$: C, 52.75; H, 3.05; N, 11.54.

Found: C, 52.91; H, 3.97; N, 11.66.

EXAMPLE 78.

The N-methylglucamine salt of 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid was prepared by adding a hot solution of 61.0 g. of the amine dissolved in 600 cc. of hot ethanol to a hot suspension of 69.6 g. of the acid in 600 cc. of ethanol, heating the mixture to effect dissolution, filtering the hot solution, allowing the filtrate to cool to about 40° C., and allowing it to stand for several hours at that temperature. The salt was recrystallized

by dissolving it in 2400 cc. of hot absolute ethanol and 100 cc. of hot water, concentrating the resulting volume to about 2 liters and then allowing the solution to cool. The resulting precipitate was collected, washed first with absolute ethanol and then n-hexane, and dried *in vacuo* at 65° C. for 8 hours to yield 9 g. of the product, the N-methylglucamine salt of 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, m.p. 202.4—207.0° C. (corr.).

Anal. Calcd. for $C_{12}H_{12}N_2O_3 \cdot C_6H_{17}NO_5$: C, 53.30; H, 6.84; N, 9.83.

Found: C, 53.61; H, 6.54; N, 9.80.

EXAMPLE 79.

1,2-Ethylene-bis(1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate) was prepared following the procedure described in Example 17 using 16 g. of ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate, 1.75 g. of ethylene glycol, 0.3 g. of sodium methoxide and a reaction temperature of 123—129° C. for 16 hours. The reaction mixture which solidified on cooling was dissolved in ethylene dichloride; this solution

washed with water, dried over anhydrous sodium sulfate, treated with decolorizing charcoal, filtered, and concentrated *in vacuo* to remove the solvent. The remaining solid was triturated with warm ethyl acetate and then recrystallized once from acetonitrile and twice from dimethylformamide to yield 2.0 g. of the product, 1,2-ethylene-bis(1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate), m.p. 244.2—246.0° C. (corr.).

Anal. Calcd. for $C_{26}H_{26}N_4O_6$: C, 63.67; H, 5.35; N, 11.43.

Found: C, 63.96; H, 5.45; N, 11.63.

EXAMPLE 80.

N-(3-diethylaminopropyl)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide was prepared as follows: A mixture of 13 g. of ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxy-

late and 13 g. of 3-diethylaminopropylamine was heated in an oil bath kept at 123—129° C. for 16 hours. The excess 3-diethylaminopropylamine was removed by distilling *in vacuo*. The remaining material was triturated with acetone, filtered, and recrystallized once from n-heptane and once from acetone to

yield 1.5 g. of the product, N-(3-diethylaminopropyl) - 1 - ethyl - 7 - methyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine-3-carboxamide, m.p. 119.4—120.8° C. (corr.).

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Anal. Calcd. for $C_{19}H_{28}N_4O_2$: C, 66.24; H, 8.19; N, 16.27.
Found: C, 66.54; H, 8.32; N, 16.19.

EXAMPLE 81.

Ethyl 7 - carboxy - 1 - ethyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylate was prepared as follows: A 60 gram portion of ethyl 1-ethyl-4-oxo-7-styryl-1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylate was suspended in a mixture of 15 380 cc. of pyridine and 66 cc. of water. The mixture was cooled to 10° C. and to it was added with stirring in small portions over a period of 90 minutes 85.5 g. of potassium permanganate. The temperature of the reaction mixture was kept at 10—15° C. using 20 an ice bath. At 30 minute intervals 110 cc. portions of water were added to facilitate stirring. Stirring was continued for an additional hour after all of the potassium permanganate had been added. The reaction 25 mixture was then allowed to stand overnight allowing the temperature to rise to room temperature. The precipitated manganese dioxide was filtered off and washed with water. The 30 filtrate and washings were combined and acidified with concentrated hydrochloric acid to yield a pale yellow precipitate. The mixture was cooled overnight in a cold room; 35 and the precipitate was then collected, washed with a little water, washed with acetone, and air-dried to yield 33.9 g. (68% yield) of the product, ethyl 7 - carboxy - 1 - ethyl - 4-

oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylate, m.p. 241—243° C.

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EXAMPLE 82.

Ethyl 7 - ethylmercaptocarbonyl - 1-ethyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate was prepared as follows: To a suspension of 10.0 g. of ethyl 7 - carboxy - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylate in 200 cc. of chloroform was added 4.8 g. of oxalyl chloride and the resulting mixture was refluxed on a steam bath. An additional 2.2 g. portion of oxalyl chloride was added after 15 minutes and again after 10 more minutes for a total of 9.2 g. of this reactant. Refluxing was continued for 5 minutes more, the reaction mixture cooled slightly, and 20 g. of ethyl mercaptan added. The mixture was stirred and allowed to stand at room temperature overnight. A small amount of insoluble material was filtered off and the filtrate was evaporated to dryness on steam bath to yield a brown solid residue which was washed well with ether, dried, and recrystallized from ethyl acetate (about 200 cc.) using decolorizing charcoal and dried at 80° C. for 2 hours to yield 6.3 g. of the product, ethyl 7 - ethylmercaptocarbonyl - 1-ethyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate, m.p. 189.2—190.8° C. (corr.).

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70 *Anal.* Calcd. for $C_{19}H_{18}N_2O_3S$: N, 8.38; S, 9.59.
Found: N, 8.49; S, 9.71.

EXAMPLE 83.

Ethyl 1 - ethyl - 7 - hydroxymethyl - 4-oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylate was prepared as follows: A mixture containing 3.3 g. of ethyl 7-ethylmercaptocarbonyl - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylate, 20 g. of Raney nickel and 100 cc. of ethanol was refluxed on a steam bath with stirring for 3 days. The reaction mixture was filtered through a sintered glass funnel to remove the nickel catalyst; the catalyst rinsed with fresh ethanol; and the combined ethanol 85 washings and filtrate from the reaction mixture were evaporated to dryness on a steam bath. The remaining residue was triturated with a small amount of ethyl acetate and the solid that formed was collected, washed with cold ethyl acetate and air-dried. This solid material was then boiled with ethyl acetate and the hot mixture filtered; most of the solid did not dissolve. The filtrate on cooling yielded a crystalline product which was recrystallized again from ethyl acetate to yield a small quantity of the desired product, ethyl 1 - ethyl - 7 - hydroxymethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylate, m.p. 173.5—174.0° C.

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100 *Anal.* Calcd. for $C_{14}H_{16}N_2O_3$: N, 10.14; C, 60.86; H, 5.84.
Found: N, 10.19; C, 61.14; H, 5.52.

EXAMPLE 84.

1 - Ethyl - 7 - hydroxymethyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylic acid was prepared by hydrolyzing its ethyl ester as follows: A mixture of a small portion of the ethyl ester and 5% aqueous potassium hydroxide was boiled for

2 to 3 minutes, after which time the ester had dissolved; boiling was continued for another 2 minutes and the reaction mixture was allowed to cool slowly. The cooled solution was made slightly acidic with 6N hydrochloric acid. The white precipitate was collected, washed successively with water and

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acetone, recrystallized from absolute ethanol, and air-dried to yield the desired product, 1-ethyl-7-hydroxymethyl-4-oxo-1,4-

dihydro-1,8-naphthyridine-3-carboxylic acid, m.p. 258—260° C.

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Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29.
Found: C, 57.98; H, 4.94; N, 11.33.

EXAMPLE 85.

- 10 7-Acetoxymethyl-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid was prepared by acylating the corresponding 7-hydroxymethyl compound as follows: A mixture containing 10.0 g. of 1-ethyl-7-hydroxymethyl-4-oxo-1,4-
- 15 dihydro-1,8-naphthyridine-3-carboxylic acid, 8.2 g. of acetic anhydride and 50 cc. of pyridine was warmed on a steam bath for 1

hour. The reaction mixture was then poured into a mixture of ice and water with stirring, followed by addition of 20 cc. of acetic acid. The mixture was stirred; and the precipitate was collected, recrystallized twice from isopropyl alcohol and dried *in vacuo* at 70° C. for 7 hours to yield 8.0 g. of the product, 7-acetoxymethyl-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, m.p. 169.8—171.6° C. (corr.).

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Anal. Calcd. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65.
Found: C, 57.63; H, 4.84; N, 9.79.

- 30 **EXAMPLE 86.**

- Ethyl 7-carbamyl-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate was prepared as follows: A mixture of 36.0 g. of ethyl 7-carboxy-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate and 100 cc. of thionyl chloride was stirred for 15 minutes at room temperature, then warmed slightly on a steam bath for about 5 minutes until a clear, pale yellow solution resulted. Stirring was continued for an additional 5 minutes and the mixture was then evaporated on a steam bath to remove most of the excess liquid. The remaining

material was suspended in 200 cc. of warm dioxane and the suspension poured into 300 cc. of 28% ammonium hydroxide containing about 40—50 g. of ice; and the resulting mixture was stirred overnight. The yellow precipitate was collected, recrystallized once from dimethylformamide using decolorizing charcoal and a second time from dimethylformamide, washed well with acetone, and dried in a vacuum oven to yield 14.0 g. (39%) of the product, ethyl 7-carbamyl-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate, m.p. 280.2—294.2° C. (corr.) with decomposition.

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Anal. Calcd. for $C_{14}H_{13}N_3O_4$: C, 58.12; H, 5.22; N, 14.53.
Found: C, 58.03; H, 5.02; N, 14.38.

- 60 **EXAMPLE 87.**

- 1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-hydroxamic acid was prepared as follows: A solution of 13.9 g. of hydroxylamine hydrochloride in 75 cc. of methanol was cooled and mixed, with shaking and cooling in an ice bath, with a cold solution containing 16.2 g. of sodium methoxide dissolved in 75 cc. of methanol. After allowing the mixture to stand in an ice bath for 5 minutes to ensure precipitation of the sodium chloride, a solution containing 26.0 g. of ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate in 150 cc. of methanol was added, the mixture shaken vigorously and filtered immediately through a sintered glass funnel. The white residue was rinsed with 50 cc of methanol and the combined filtrates were allowed to stand at room temperature in a stoppered flask for about 4

days. The crystals that separated were collected, washed with absolute ethanol and air-dried to yield 26.1 g. (97%) of yellow crystalline sodium 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-hydroxamate.

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A mixture containing 13.5 g. of sodium 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-hydroxamate, 2.9 cc. of acetic acid and 40 cc. of water was stirred and warmed on a steam bath for about 2 hours. The reaction mixture was then cooled in an ice bath and the separated product was collected, recrystallized from acetic acid using decolorizing charcoal, washed with acetone and dried for 1 hour in an oven at 70° C. to yield 6.8 g. (55%) of the product, 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-hydroxamic acid, m.p. 234.0—234.6° C. (corr.) with decomposition.

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Anal. Calcd. for $C_{12}H_{12}N_3O_3$: C, 58.29; H, 5.30; N, 17.00.
Found: C, 58.36; H, 5.33; N, 16.88.

EXAMPLE 88.

- 105 1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-(N-acetoxy)-carboxamide was prepared as follows:

To a solution containing 9.0 g. of sodium 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-hydroxamate in 200 cc. of water was added 10 cc. of acetic

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- anhydride. A copious, pale yellow solid separated and the mixture was stirred at room temperature for about 5 minutes. The solid was collected, washed with a small quantity of water, recrystallized from ethanol and dried overnight in a vacuum desiccator to yield 6.3 g. of the product, 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-(N-acetoxy)-carboxamide, m.p. 195.0—195.6° C. (corr.) with decomposition. 10

Anal. Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.12; H, 5.23; N, 14.53.
Found: C, 58.32; H, 5.34; N, 14.75.

EXAMPLE 89.

- Trans-2-[7-(3-carbethoxy-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridinyl)]-1-chloro-1-phenylethylene was prepared as follows: A mixture containing 48.0 g. of 1-ethyl-4-oxo-7-styryl-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and 175 cc. of thionyl chloride was stirred on a steam bath for about 40 minutes. The reaction mixture was evaporated to dryness by heating on a steam bath. To the syrupy residue was added 240 cc. of absolute ethanol and the resulting mixture was refluxed for 1 hour and then allowed to stand overnight at room temperature. The resulting yellow crystalline precipitate was collected, recrystallized several times from acetonitrile, and air-dried to yield 23.3 g. (39%) of the product, trans-2-[7-(3-carbethoxy-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridinyl)]-1-chloro-1-phenylethylene, m.p. 178.0—179.6° C. (corr.). 25 30

- Anal.* Calcd. for $C_{21}H_{19}ClN_2O_3$: Cl, 9.26; N, 7.31.
Found: Cl, 9.38; N, 7.23.

- The corresponding acid was obtained by refluxing a mixture of 1.9 g. of the above ethyl ester and 25 cc. of 10% aqueous potassium hydroxide solution for 90 minutes. The reaction mixture was cooled and the supernatant liquid was decanted from a solid cake which was broken up and triturated well with ether. There resulted a dispersion which was separated by filtering several times through a sintered glass funnel. The solid was dissolved in boiling water containing a little potassium hydroxide. The solution was acidified with hydrochloric acid and the resulting white precipitate was collected, recrystallized from acetic acid, washed with acetone and dried in a vacuum oven at 70° C. to yield trans-2-[7-(3-carboxy-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridinyl)]-1-chloro-1-phenylethylene, m.p. 245—247° C., which was used in the following preparation without further purification. 40 45 50 55

EXAMPLE 90.

- 1-Ethyl-4-oxo-7-phenylethinyl-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid was prepared as follows: Sodium (1.5 g.) was dissolved with magnetic stirring in 100 cc. of liquid ammonia containing a trace of ferric nitrate. After the blue color had disappeared, 5.5 g. of trans-2-[7-(3-carboxy-1-ethyl-4-oxo-1,4-dihydro-1,8-naphthyridinyl)]-1-chloro-1-phenylethylene was added cautiously. The reaction mixture was stirred for about 30 minutes, 100 cc. of benzene was added, and the resulting mixture allowed to stand overnight. About 300 cc. of water was added and the resulting mixture was heated until the solids dissolved and most of the benzene had distilled off. The solution was filtered through infusorial earth. The filtrate was extracted twice with chloroform; the combined chloroform extracts were dried over anhydrous calcium sulfate and evaporated to dryness on a steam bath to yield a solid. The solid was triturated with water, recrystallized from acetic acid using decolorizing charcoal, washed with acetone and air-dried to yield the product, 1-ethyl-4-oxo-7-phenylethinyl-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, m.p. 237.4—240.0° C. (corr.). 65 70 75 80 85

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 71.69; H, 4.43; N, 8.80.
Found: C, 71.38; H, 4.46; N, 9.06.

EXAMPLE 91.

- Ethyl 1-ethyl-4-oxo-7-tribromomethyl-1,4-dihydro-1,8-naphthyridine-3-carboxylate was prepared according to the procedure described in Example 68 using 7.0 g. of ethyl 4-hydroxy-7-tribromomethyl-1,8-naphthyridine-3-carboxylate, 4.6 g. of diethyl sulfate, 6.2 g. of anhydrous potassium carbonate and 40 cc. of dimethylformamide. There was obtained 1.25 g. of the product, ethyl 1-ethyl-4-oxo-7-tribromomethyl-1,4-dihydro-1,8-naphthyridine-3-carboxylate, m.p. 146—147° C., after one recrystallization from ethanol and air-drying. 90 95 100

Anal. Calcd. for $C_{14}H_{13}Br_3N_2O_3$: C, 33.83; H, 2.64; Br, 48.24; N, 5.64.
Found: C, 34.12; H, 2.82; Br, 50.94; N, 5.66.

- The intermediate ethyl 4-hydroxy-7-tribromomethyl-1,8-naphthyridine-3-carboxylate was prepared as follows: A solution of 86 g. of bromine in 100 cc. of acetic acid was added slowly with stirring to a heated mixture containing 42 g. of ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate, 89 g. of anhydrous sodium 110

acetate and 900 cc. of acetic acid, keeping the temperature of the reaction mixture at 60° C. After addition had been completed, the reaction mixture was heated on a steam bath for 2 hours and allowed to stand at room temperature overnight. The mixture was then refluxed for 90 minutes, allowed to cool to room temperature and cooled further to 18°

Anal. Calcd. for $C_{12}H_9Br_3N_2O_3$: Br, 51.08; N, 5.98.
Found: Br, 50.67; N, 5.90.

WHAT WE CLAIM IS:—

20 1. A process for the preparation of a 3—X—4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine having a molecular structure in which an organic radical having the formula —YZ as defined herein is attached through
25 a saturated carbon atom to the 1-nitrogen atom of the naphthyridine nucleus, where X stands for hydroxycarbamyl, acyloxycarbamyl, carboxy or a salt thereof, carbalkoxy having from two to eleven carbon atoms inclusive, carbo - [(lower - tertiary - amino)-
30 (polycarbon - lower - alkoxy)], cyano, carbamyl, aminocarbamyl, carbophenoxy, carbo-[(lower - secondary - amino) - (polycarbon-lower - alkoxy)], carbo(hydrocarbon mercapto), $C(=NH)O$ - (lower - alkyl), $C(=NH)NH_2$, $C(=NH)NH$ (lower - alkyl), $C(=S)OH$, or $C(=S)SH$, which comprises reacting the corresponding 3—X—4-hydroxy-
35 1,8-naphthyridine with an organic ester of a strong acid providing the desired 1-substituent, and, if desired, obtaining a salt of a free product obtained.

2. A process according to claim 1, in which a 3-carboxy compound obtained is converted to the corresponding alkyl 3-carboxylate or vice versa.

3. A process according to claim 1, in which a 7-acylated amino compound obtained is hydrolyzed to produce the 7-amino compound which, if desired, is converted via its
50 diazonium salt to the corresponding 7-hydroxy compound which, if desired, is halogenated to the corresponding 7-halo compound.

4. A process according to claim 1, in which a 7 - [2 - (lower - aromatic)ethenyl] compound obtained is reduced or oxidized to obtain the corresponding 7-[2-(lower-aromatic)-ethyl] or 7-carboxy compound
60 respectively.

5. A process according to any one of the preceding claims, in which the organic ester of a strong acid is bifunctional and a corresponding bis-naphthyridine derivative is produced.
65

6. A process according to any one of the preceding claims, in which the X functions of a compound obtained are condensed with a diol to form a bis-ester.

70 7. A process according to any one of the preceding claims, in which the compound prepared has the formula I as defined herein, the

C. The resulting precipitate was collected, washed with acetone and air-dried. This solid was recrystallized from 2-ethoxyethanol, washed with methanol and air-dried to yield 7.0 g. of the product, ethyl 4-hydroxy-7-tri-bromomethyl - 1,8 - naphthyridine - 3-carboxylate, m.p. 250.0—250.4° C. (corr.) with decomposition. 10 15

ester of a strong acid having the formula $Z-Y-An$ or $An-Y-An$, where Z and Y have the meanings already given and An is an anion of a strong inorganic acid or an organic sulphonic acid. 75

8. A process according to claim 7, in which Q is 7-methyl.

9. 3—X—4 - oxo - 1,4 - dihydro - 1,8-naphthyridine having a molecular structure in which an organic radical having the formula —YZ as defined herein is attached through a saturated carbon atom thereof to the 1-nitrogen atom of the naphthyridine nucleus where X is hydroxycarbamyl, acyloxycarbamyl, carboxy or a salt thereof, carbalkoxy having from two to eleven carbon atoms inclusive, carbo - [(lower - tertiary - amino)-
80 (polycarbon - lower - alkoxy)], cyano, carbamyl, aminocarbamyl, carbophenoxy, carbo-[(lower - secondary - amino) - (polycarbon-lower - alkoxy)], carbo - (hydrocarbon mercapto), $C(=NH)O$ - (lower - alkyl), $C(=NH)NH_2$, $C(=NH)NH$ (lower - alkyl), $C(=S)OH$, or $C(=S)SH$; or a bis-ester of said compound wherein X is carboxy with an aliphatic diol having 2—10 carbon atoms. 85 90 95

10. A compound having the formula I as defined herein. 100

11. A compound according to claim 10, in which X is carboxy or alkyl carboxylate, Y—Z is alkyl and Q is 7-methyl or 7-styryl, said alkyl groups having 1 to 10 carbon atoms.

12. 1 - Ethyl - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid. 105

13. Ethyl 1 - ethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylate. 110

14. 7 - Methyl - 1 - n - propyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3 - carboxylic acid.

15. 1 - Allyl - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid. 115

16. Ethyl 1 - ethyl - 4 - oxo - 1,4 - dihydro - 7 - styryl - 1,8 - naphthyridine - 3 - carboxylate.

17. 7 - Amino - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid. 120

18. 1 - Ethyl - 7 - hydroxy - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid. 125

19. 7 - Chloro - 1 - ethyl - 4 - oxo - 1,4-

- acetate and 900 cc. of acetic acid, keeping the temperature of the reaction mixture at 60° C. After addition had been completed, the reaction mixture was heated on a steam bath for 2 hours and allowed to stand at room temperature overnight. The mixture was then re-fluxed for 90 minutes, allowed to cool to room temperature and cooled further to 18° C. The resulting precipitate was collected, washed with acetone and air-dried. This solid was recrystallized from 2-ethoxyethanol, washed with methanol and air-dried to yield 7.0 g. of the product, ethyl 4-hydroxy-7-tri-bromomethyl - 1,8 - naphthyridine - 3-carboxylate, m.p. 250.0—250.4° C. (corr.) with decomposition.

Anal. Calcd. for $C_{12}H_3Br_3N_2O_3$: Br, 51.08; N, 5.98.

Found: Br, 50.67; N, 5.90.

WHAT WE CLAIM IS:—

1. A process for the preparation of a 3—X—4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine having a molecular structure in which an organic radical having the formula —YZ as defined herein is attached through a saturated carbon atom to the 1-nitrogen atom of the naphthyridine nucleus, where X stands for hydroxycarbamyl, acyloxycarbamyl, carboxy or a salt thereof, carbalkoxy having from two to eleven carbon atoms inclusive, carbo - [(lower - tertiary - amino) - (polycarbon - lower - alkoxy)], cyano, carbamyl, aminocarbamyl, carbophenoxy, carbo-[(lower - secondary - amino) - (polycarbon - lower - alkoxy)], carbo(hydrocarbon mercapto), $C(=NH)O$ - (lower - alkyl), $C(=NH)NH_2$, $C(=NH)NH$ (lower - alkyl), $C(=S)OH$, or $C(=S)SH$, which comprises reacting the corresponding 3—X—4-hydroxy-1,8-naphthyridine with an organic ester of a strong acid providing the desired 1-substituent, and, if desired, obtaining a salt of a free product obtained.
2. A process according to claim 1, in which a 3-carboxy compound obtained is converted to the corresponding alkyl 3-carboxylate or vice versa.
3. A process according to claim 1, in which a 7-acylated amino compound obtained is hydrolyzed to produce the 7-amino compound which, if desired, is converted via its diazonium salt to the corresponding 7-hydroxy compound which, if desired, is halogenated to the corresponding 7-halo compound.
4. A process according to claim 1, in which a 7 - [2 - (lower - aromatic)ethenyl] compound obtained is reduced or oxidized to obtain the corresponding 7-[2-(lower-aromatic)-ethyl] or 7-carboxy compound respectively.
5. A process according to any one of the preceding claims, in which the organic ester of a strong acid is bifunctional and a corresponding bis-naphthyridine derivative is produced.
6. A process according to any one of the preceding claims, in which the X functions of a compound obtained are condensed with a diol to form a bis-ester.
7. A process according to any one of the preceding claims, in which the compound prepared has the formula I as defined herein, the ester of a strong acid having the formula $Z-Y-An$ or $An-Y-An$, where Z and Y have the meanings already given and An is an anion of a strong inorganic acid or an organic sulphonic acid.
8. A process according to claim 7, in which Q is 7-methyl.
9. 3—X—4 - oxo - 1,4 - dihydro - 1,8-naphthyridine having a molecular structure in which an organic radical having the formula —YZ as defined herein is attached through a saturated carbon atom thereof to the 1-nitrogen atom of the naphthyridine nucleus where X is hydroxycarbamyl, acyloxycarbamyl, carboxy or a salt thereof, carbalkoxy having from two to eleven carbon atoms inclusive, carbo - [(lower - tertiary - amino) - (polycarbon - lower - alkoxy)], cyano, carbamyl, aminocarbamyl, carbophenoxy, carbo-[(lower - secondary - amino) - (polycarbon - lower - alkoxy)], carbo - (hydrocarbon mercapto), $C(=NH)O$ - (lower - alkyl), $C(=NH)NH_2$, $C(=NH)NH$ (lower - alkyl), $C(=S)OH$, or $C(=S)SH$; or a bis-ester of said compound wherein X is carboxy with an aliphatic diol having 2—10 carbon atoms.
10. A compound having the formula I as defined herein.
11. A compound according to claim 10, in which X is carboxy or alkyl carboxylate, Y—Z is alkyl and Q is 7-methyl or 7-styryl, said alkyl groups having 1 to 10 carbon atoms.
12. 1 - Ethyl - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid.
13. Ethyl 1 - ethyl - 7 - methyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylate.
14. 7 - Methyl - 1 - n - propyl - 4 - oxo - 1,4 - dihydro - 1,8 - naphthyridine - 3-carboxylic acid.
15. 1 - Allyl - 7 - methyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid.
16. Ethyl 1 - ethyl - 4 - oxo - 1,4 - dihydro - 7 - styryl - 1,8 - naphthyridine - 3-carboxylate.
17. 7 - Amino - 1 - ethyl - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid.
18. 1 - Ethyl - 7 - hydroxy - 4 - oxo - 1,4-dihydro - 1,8 - naphthyridine - 3 - carboxylic acid.
19. 7 - Chloro - 1 - ethyl - 4 - oxo - 1,4-



dihydro - 1,8 - naphthyridine - 3 - carboxylic acid.

- 5 20. 1 - Ethyl - 7 - hydroxymethyl - 4 - oxo-
1,4 - dihydro - 1,8 - naphthyridine - 3-
carboxylic acid.

21. A salt of the compounds according to
any one of claims 11, 12, 14, 15 and 17 to
20.

- 10 22. A process for the preparation of a
3—X—4-oxo-1,8-naphthyridine or a salt

thereof substantially as herein described with
reference to the Examples.

23. A compound produced by the process
according to any one of claims 1 to 7 and 22.

24. A compound according to claim 9 or 15
21 as herein described.

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