APPLICATION FOR A STANDARD PATENT

I/We
Laboratoire Roger Bellon
of
159 Avenue Achille Peretti, Neuilly Sur Seine, 92200, France

hereby apply for the grant of a Standard Patent for an invention entitled:

New benzo[1,8]naphthyridine derivatives, their preparation and compositions containing them

which is described in the accompanying complete specification.

Details of basic application(s):

<table>
<thead>
<tr>
<th>Number</th>
<th>Convention Country</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>8900430</td>
<td>France</td>
<td>16 January 1989</td>
</tr>
<tr>
<td>8910219</td>
<td>France</td>
<td>28 July 1989</td>
</tr>
</tbody>
</table>

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this TWELFTH day of JANUARY 1990

To: THE COMMISSIONER OF PATENTS

[Signature]

Keith [Signature]
a member of the firm of DAVIES & COLLISON for and on behalf of the applicant(s)

Davies & Collison, Melbourne
COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952
DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT

In support of the Application made for a patent for an invention entitled: "New benzo[1,8]naphthyridine derivatives, their preparation and compositions containing them"

Jacques SAVINA, executive

of: LABORATOIRE ROGER BELLON, a French Body Corporate of: 159 Avenue Achille Peretti, 92200 Neuilly Sur Seine, France.

do solemnly and sincerely declare as follows:

(a) I am the applicant...for the patent to make this declaration on its behalf.

or (b) I am authorized by LABORATOIRE ROGER BELLON, the applicant for the patent to make this declaration on its behalf.

or (b) MICHEL ANTOINE; MICHEL BARREAU; JEAN-FRANCOIS DESCONCLOS; PHILIPPE GIRARD and GUY PICAUT, all citizens of France of: 184 Rue Nationale, 75013 PARIS, France; 24 Bis Avenue du Clos de Senart, 91230 MONTGERON, France; 12 Rue Beccaria, 75012 PARIS, France; 7 Rue du Bois-Gaudron, Allainville, 91290 ARPAJON, France and 30 Rue Henri Crette, 94550 CHEVILLY LARUE, France respectively.

State manner in which applicant(s) derive title from inventor(s)

"The applicants would, if a patent were granted upon an application made by the Inventors, be entitled to have the Patent assigned to it"

3. The basic application...as defined by Section 141 of the Act...were made in FRANCE NO. 8900430...on the...16th January...1989...by LABORATOIRE ROGER BELLON...
in FRANCE NO. 8910219...on the...28th July...1989...by LABORATOIRE ROGER BELLON...
in...on the...by...

4. The basic application...as referred to in paragraph 3 of this Declaration...were the first application...made in a Convention country in respect of the invention the subject of the application.

Declared at Antony this 3th day of January 1990.

Jacques SAVINA
Executive
The benzo[b][1,8]naphthyridine derivatives of formula (VII) and their pharmaceutically acceptable salts have antibacterial properties. They display a remarkable in vitro and in vivo activity against Gram-positive microorganisms and, in a general manner, on microorganisms responsible for the majority of the infections of the upper and lower air passages.

1. A benzo[b][1,8]naphthyridine derivative of the general formula:

![Chemical Structure](image)

in which R represents hydrogen, alkyl, fluoroalkyl,
cycloalkyl of 3 to 6 carbon atoms, alkoxy, alkylamino, or an amine protective radical, and either Hal represents fluorine, chlorine or bromine and R' represents hydrogen or Hal and R' both represent fluorine, the aforesaid alkyl radicals being straight-chain or branched and containing 1 to 4 carbon atoms each, its metal salts and its addition salts with nitrogenous bases.
COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952
COMPLETE SPECIFICATION

NAME & ADDRESS
OF APPLICANT:

Laboratoire Roger Bellon
159 Avenue Achille Peretti
Neuilly Sur Seine 92200
France

NAME(S) OF INVENTOR(S):

Michel ANTOINE
Michel BARREAU
Jean-François DESCONCLOIS
Philippe GIRARD
Guy PICAUT

ADDRESS FOR SERVICE:

DAVIES & COLLISON
Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

New benzo[1,8]naphthyridine derivatives, their preparation and compositions containing them

The following statement is a full description of this invention, including the best method of performing it known to me/us:—
The present invention relates to benzo[b][1,8]naphthyridine derivatives, their salts, their preparation and compositions which contain them.

Naphthyridine derivatives of formula:

\[
\begin{align*}
R_3 & \quad R_2 \\
R_4 & \quad R_1 \\
R_5 & \quad X \\
C_nH_{2n}NR_6R_7
\end{align*}
\]

in which \( X \) can be oxygen and two adjacent radicals of the radicals \( R_1 \) to \( R_5 \) can form a benzene ring, have been described in US Patents 4,229,456 and 4,133,885. These products are described as gastric acid secretion inhibitors.

German Patent Application 3,302,126 describes hypotensive agents of formula:

\[
\begin{align*}
Z & \quad \text{(CH}_2\text{)}^m \\
Y & \quad \text{(CH}_2\text{)}^n \\
N & \quad \text{-COCHR}_2 - \text{(CH}_2\text{)}^n - \text{SR}_1
\end{align*}
\]

in which the radicals \( X, Y \) and \( Z \) can be \( O \) or an \( NR_4 \) radical or a \( CR_5=CR_5 \) radical in which the \( R_5s \) can be joined to form a
benzene ring.

The present invention provides benzo[b][1,8]naphthyridin derivatives of formula:

![Formula Image]

in which

- either Hal represents fluorine, chlorine or bromine

and R' represents hydrogen,

- or Hal and R' both represent fluorine, the aforesaid alkyl radicals being straight-chain or branched and containing 1 to 4 carbon atoms each, and their metal salts and addition salts with nitrogenous bases.

When R represents a protective radical, this radical can be any group which is compatible with the remainder of the molecule and which can be introduced and removed without altering the remainder of the molecule, more especially, the groups described by T.W. GREENE, Protective Groups in Organic Synthesis, A. Wiley-Interscience Publication (1981),
or by McOMIE, Protective Groups in Organic Chemistry, Plenum Press (1973). By way of example, the protective group can be trimethylsilyl, trityl, benzhydryl, tetrahydropyrannyl, formyl, acetyl, chloroacetyl, trichloroacetyl, trifluoroacetyl, methoxycarbonyl, ethoxycarbonyl, t.butoxycarbonyl, trichloroethoxycarbonyl, ethoxymethyl or methoxymethyl.

According to a feature of the invention, the benzo[b][1,8]naphthyridine derivatives of formula (I) are obtained by converting the corresponding esters of general formula:

\[
\begin{align*}
\text{R} & \quad \text{Hal} \\
\text{N} & \quad \text{COOAlk}
\end{align*}
\]

in which R represents hydrogen, alkyl, fluoroalkyl, cycloalkyl of 3 to 6 carbon atoms, alkoxy, alkylamino or protected alkylamino (the aforesaid alkyl radicals containing 1 to 4 carbon atoms each in a straight or branched chain), Hal and R' are as defined above and Alk is a straight-chain or branched alkyl of 1 to 4 carbon atoms, by any method known for converting an ester into an acid without affecting the remainder of the molecule, followed, where
appropriate, by the introduction of the protective radical \( R \) in the 1-position or the removal of the protective group from the alkylamino radical, and optionally by the conversion of the product obtained into a metal salt or an addition salt with a nitrogenous base.

When \( R \) is a protected alkylamino radical, the protective radical can be any amino protective group compatible with the molecule and the operating conditions of the process. In particular, groups which can be removed simultaneously with the hydrolysis of the ester, for example the formyl radical, are advantageously used.

The preparation of the acid from the ester is generally carried out by acid hydrolysis. The reaction is advantageously carried out in an acetic acid/hydrochloric acid mixture, in sulphuric acid or in methanesulphonic acid, at a temperature of between 60 and 100°C. It is also possible to carry out the reaction by saponification in the presence of potassium hydroxide or sodium hydroxide, in an aqueous-alcoholic medium, at a temperature of between 20 and 80°C.

Where appropriate, the introduction of the protective radical in the 1-position is effected by the methods described in the above references.

The benzo[b][1,8]naphthyridine ester derivative of general formula (II) can be prepared by the action of 3-amino-1,2,4-triazine (to obtain a product for which \( R \) is a
hydrogen atom), or by the action of a compound of formula:

\[ R - \text{NH}_2 \]  \hspace{1cm} (III)

in which \( R \) is alkyl, fluoroalkyl, cycloalkyl, alkoxy, alkylamino or protected alkylamino, on a quinoline derivative of general formula:

\[
\begin{align*}
\text{F} & \quad \text{Hal} \\
\text{Hal} & \quad \text{Cl} \\
\text{R} & \quad \text{N(CH}_3)_2 \\
\text{R}' & \quad \text{COA} \text{lK}
\end{align*}
\]  \hspace{1cm} (IV)

in which \( \text{R}' \), \( \text{Hal} \) and \( \text{Alk} \) are defined as above, followed by cyclization by the action of an acid acceptor.

In general, the reaction of 3-amino-1,2,4-triazine or of the compound of formula (III) is carried out in an organic solvent such as an alcohol (ethanol or methanol for example) or a chlorinated solvent (trichloromethane for example) at a temperature of between 10 and 25°C.

The cyclization is carried out in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene or of a nitrogenous base, such as, for example, triethylamine, or an excess of the amine employed, in a straight-chain or branched alcohol containing 1 to 4 carbon atoms, at a temperature of between
20°C and the reflux temperature of the reaction mixture.

The quinoline derivative of general formula (IV) can be obtained from the keto-ester of general formula:

\[
\text{(IV)}
\]

in which \( R', \text{Hal} \) and \( \text{Alk} \) are defined as above, by the action of a \( N,N \)-dimethylformamide acetal of general formula:

\[
(\text{CH}_3)_2N - \text{CH(O}\text{Alk}_1)_{2}
\]

(\text{VI})

in which \( \text{Alk}_1 \) is a straight-chain or branched alkyl radical containing 1 to 4 carbon atoms.

The reaction is generally carried out in an organic solvent such as an ester (ethyl acetate for example) at a temperature of between 60 and 75°C.

The keto-ester of general formula (V) in which \( R' \) is a hydrogen atom and \( \text{Hal} \) is defined as above can be obtained from 2,7-dichloro-6-fluoroquinoline-3-carboxylic acid or 2-chloro-6,7-difluoroquinoline-3-carboxylic acid as described below in Examples 1 and 6 or from 7-bromo-2-chloro-6-fluoroquinoline-3-carboxylic acid by analogy with this
method. In this case, the 3-bromo-4-fluoroaniline used as starting material can be prepared by the method described by W.B. Austin et al., J. Org. Chem., 46 (11), 2280 (1981).

The keto-ester of general formula (V) in which R' and Hal are simultaneously fluorine atoms can be obtained from 2-chloro-6,7,8-trifluoroquinoline-3-carboxylic acid as described below in Example 9.

The compounds of formula I can be used as intermediates for the preparation of benzo[b][1,8]naphthyridine derivatives of general formula:

\[
\begin{align*}
\text{(VII)} & \\
R_1 & - N - N - R_3 & R_4 & R' & R_2 & F & COOH
\end{align*}
\]

in which:
- \( R_1 \) represents hydrogen, alkyl, or hydroxyalkyl,
- \( R_2 \) represents hydrogen, alkyl, fluoroalkyl, cycloalkyl of 3 to 6 carbon atoms, alkoxy or alkylamino,
- \( R_3 \) represents hydrogen or alkyl, and \( R_4 \) and \( R_5 \) are different and represent hydrogen or alkyl, or
- \( R_3 \) is hydrogen, alkyl, or cycloalkyl and \( R_4 \) and \( R_5 \) are both hydrogen, and
- \( R_1 \) represents hydrogen or fluorine, and their salts,
their hydrates and, where appropriate, their isomers.

The compounds of formula (VII) can be obtained by reaction of a piperazine of formula:

\[
\begin{array}{cccc}
& & R_5 \\
& R_1 - N - & & \text{NH} \\
& & R_3 & R_4 \\
\end{array}
\]  

(VIII)

in which R\(_1\), R\(_3\), R\(_4\) and R\(_5\) are as defined above, with a benzo[b][1,8]naphthyridine of formula (I), followed, if appropriate, if R\(_1\) is a hydrogen atom and if it is desired to obtain a benzo[b][1,8]naphthyridine derivative in which R\(_1\) is methyl, by the conversion of the product obtained to a 8-(4-methyl-1-piperazinyl)-benzo[b][1,8]naphthyridine and followed, if appropriate, by the removal of the protective radical in the 1-position.

The reaction of the piperazine derivative of formula (VIII) generally takes place in the presence of an excess of this derivative as an acid acceptor or in the presence of an organic or inorganic acid acceptor in a suitable organic solvent. It is possible to carry out the reaction with or without a solvent, at a temperature between 30 and 120°C. When it is carried out in the presence of a solvent, the reaction advantageously takes place in a solvent such as
pyridine, dimethylformamide, dimethyl sulfoxide or acetonitrile.

Where it is desired to obtain a product of formula III in which R₂ is a hydrogen atom it is preferable to carry out the reaction starting from a benzonaphthyridine derivative of formula I in which R is a protective radical. The protection, and the removal of the protective radical after the reaction, are carried out by customary methods.

Where appropriate, the subsequent operation for the methylation of the piperazinyl radical is advantageously carried out by the action of formaldehyde in the presence of formic acid. The reaction is generally carried out in an aqueous medium, at a temperature of between 90 and 100°C.

The products of formula I according to the present invention and the products of general formula (VII) can, if necessary, be purified by physical methods such as crystallization or chromatography.

The products of formula I according to the present invention and the products of general formula (VII) can be converted into metal salts or addition salts with nitrogenous bases by the methods known per se. These salts can be obtained by the action of a metal (for example alkali metal or alkaline earth metal)-containing base, ammonia or an amine on a product of formula I or VII in an appropriate solvent, such as an alcohol, an ether or water, or by an exchange reaction with a salt of an organic acid. The salt formed
precipitates, after concentration of its solution if necessary; it is separated by filtration, decanting or lyophilization.

The benzo[b][1,8]naphthyridine derivatives of formula (VII) and their pharmaceutically acceptable salts have antibacterial properties. They display a remarkable in vitro and in vivo activity against Gram-positive microorganisms and, in a general manner, on microorganisms responsible for the majority of the infections of the upper and lower air passages.

In vitro, the products of formula (VII) have been shown to be active at a concentration of between 0.12 and 50 μg/cm³ on Staphylococcus aureus IP 8203.

In vivo, the products of formula (VII) have been shown to be active against experimental infections of mice with Staphylococcus aureus IP 8203 at doses of between 2 and 150 mg/kg administered orally or subcutaneously.

Moreover, these products are of low toxicity. Their LD₅₀ is generally greater than 500 mg/kg when administered subcutaneously to mice.

The benzo[b]naphthyridine derivatives of formula (I) in which R is other than a protective radical, and their salts, are also of particular value because of their antibacterial properties in vitro and, because of this fact, they can be used in particular for local application in the case of cutaneous infections with staphylococci.
The benzo[b][1,8]naphthyridine derivatives of formula I have been shown to be active in vitro at concentrations of between 0.2 and 500 µg/cm³ on Staphylococcus aureus IP 8203.

Their LD₅₀ is likewise greater than 500 mg/kg when administered subcutaneously to mice.

The following may be mentioned as examples of pharmaceutically acceptable salts: the salts with the alkali metals (sodium, potassium, lithium) or with the alkaline earth metals (magnesium, calcium), the ammonium salt, the salts of nitrogenous bases (ethanolamine, diethanolamine, trimethylamine, triethylamine, methylamine, propylamine, diisopropylamine, N,N-dimethylethanolamine, benzylamine, dicyclohexylamine, N-benzyl-β-phenethylamine, N,N'-dibenzylethylenediamine, diphenylenediamine, benzhydrylamine, quinine, choline, arginine, lysine, leucine, dibenzylamine).

The compounds of formula (I) of particular interest are those in which R represents a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms or a fluoroethyl, cyclopropyl, methoxy or methylamino radical, and either Hal represents a fluorine or chlorine atom and R' represents a hydrogen atom, or Hal and R' simultaneously
in which R represents hydrogen, alkyl, fluoroalkyl,

\[ R^1, R^2 \]

represent fluorine atoms.

Amongst these products, the following are very particularly interesting:
- 7,8-difluoro-1-methyl-4-oxo-1,4-dihydro-
5 benzo[b][1,8]naphthyridine-3-carboxylic acid;
- 8-chloro-7-fluoro-1-methyl-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine-3-carboxylic acid;
- 1-methyl-4-oxo-7,8,9-trifluoro-1,4-dihydro-
benzo[b][1,8]naphthyridine-3-carboxylic acid;
10 - 7,8-difluoro-1-methoxy-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine-3-carboxylic acid;
- 1-cyclopropyl-7,8-difluoro-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine-3-carboxylic acid.

The following Examples illustrate the present invention.

**EXAMPLE 1**

A suspension of 15 g of 8-chloro-3-ethoxycarbonyl-7-
fluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine in 150 cm³ of acetic acid and 150 cm³ of hydrochloric acid as a 17.5 % aqueous solution is heated at a temperature close to 100°C, with stirring, for 4 hours. After cooling to a temperature close to 20°C, the product is drained and washed with twice 150 cm³ of ethanol and then twice 100 cm³ of diethyl ether. 12.7 g of 8-chloro-7-fluoro-1-methyl-4-oxo-
20 1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a beige solid which sublimes at 400-
The 8-chloro-3-ethoxycarbonyl-7-fluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine is prepared in the following manner:

Methylamine is bubbled into a stirred suspension of 19.3 g of ethyl 2-(2,7-dichloro-6-fluoro-quinoline-3-carbonyl)-3-dimethylaminoacrylate in 250 cm$^3$ of ethanol, kept at between 10 and 15°C, until 16 g of gas have been absorbed. The temperature is allowed to rise to about 20°C, 0.8 g of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is added and the mixture is heated at a temperature close to 75°C for 2 hours. After cooling to about 20°C, the product is drained and washed with twice 150 cm$^3$ of ethanol and twice with 100 cm$^3$ of diethyl ether. 15 g of 8-chloro-3-ethoxycarbonyl-7-fluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine are obtained in the form of a yellow solid melting at 360-362°C, which is used for the subsequent steps without further purification.

The ethyl 2-(2,7-dichloro-6-fluoro-quinoline-3-carbonyl)-3-dimethylaminoacrylate is prepared in the following manner:

A suspension of 16.5 g of ethyl 3-(2,7-dichloro-6-fluoro-3-quinolyl)-3-oxopropionate in 160 cm$^3$ of ethyl acetate and 19 cm$^3$ of N,N-dimethylformamide dimethyl acetal is heated at a temperature close to 75°C, with stirring, for 2 hours. The reaction mixture is concentrated to dryness
under reduced pressure (20 kPa) at 50°C. The dry extract is taken up in 50 cm³ of diisopropyl ether, drained and washed with twice 10 cm³ of diisopropyl ether. 16.57 g of ethyl 2-(2,7-dichloro-6-fluoro-quinoline-3-carbonyl)-3-dimethylaminoacrylate are obtained in the form of an orange solid melting at 122°C. This product is used for the subsequent steps without further purification.

The ethyl 3-(2,7-dichloro-6-fluoro-3-quinolyl)-3-oxopropionate is prepared in the following manner:

A suspension of 38.75 g of 2,7-dichloro-6-fluoro-quinoline-3-carboxylic acid in 410 cm³ of trichloromethane and 24 cm³ of thionyl chloride is heated at a temperature close to 60°C, with stirring, for 6 hours. The solution obtained is concentrated to dryness under reduced pressure (20 kPa) at 50°C. The dry extract is twice taken up in a total of 200 cm³ of toluene and again concentrated under reduced pressure under the same conditions as above. The yellow solid obtained, which melts at 124°C, is dissolved in 230 cm³ of anhydrous tetrahydrofuran. The solution obtained is introduced dropwise, with stirring, in the course of 30 minutes, at between 5 and 10°C, into 200 cm³ of a solution of magnesium chelate in tetrahydrofuran, the preparation of which is described below. The temperature is allowed to rise to 20°C and the mixture is stirred for 1 hour and a half at this temperature. The solution obtained is introduced dropwise, with vigorous stirring, at a temperature close to
5°C, into 1 litre of 0.5 N sulphuric acid. The temperature of the suspension obtained is allowed to rise to 20°C and the suspension is stirred for a further 2 hours at this temperature. The suspension is extracted with 1 litre of ethyl acetate and the organic and aqueous phases are filtered through diatomaceous silica for filtration, which enables a small amount of insoluble matter to be removed, and the aqueous phase is extracted twice more with 500 cm³ of ethyl acetate. The combined organic extracts are washed with twice 500 cm³ of water, dried over magnesium sulphate and filtered and the filtrate is concentrated to dryness under reduced pressure (20 kPa) at 40°C. The residue is taken up in 100 cm³ of diisopropyl ether at 20°C, drained and washed with twice 30 cm³ of diisopropyl ether. 40.55 g of ethyl 3-(2,7-dichloro-6-fluoro-3-quinolyl)-3-oxopropionate are obtained in the form of a beige solid melting at 112-114°C. This product is used for the subsequent steps without further purification.

Preparation of the magnesium chelate of ethyl monomalonate:

5 cm³ of absolute ethanol, 0.2 cm³ of tetrachloromethane and 2 g of ethyl monomalonate are added progressively to 6.9 g of magnesium turnings. After heating, a solution of 23.8 g of ethyl monomalonate in 450 cm³ of ethanol is added in the course of 15 minutes. The mixture is heated at a temperature close to 78°C for 20 hours and concentrated under
reduced pressure (20 kPa) at 50°C. The residue is taken up in twice 100 cm³ of toluene and concentrated under reduced pressure under the same conditions as above. The grey powder obtained is brought into solution by adding anhydrous tetrahydrofuran so as to obtain a total volume of 200 cm³.

The ethyl monomalonate was prepared by the method described by D.S. Breslow, E. Baumgarten, C.R. Hauser., J. Am. Chem. Soc., 66, 1287 (1944) and distilled under reduced pressure (boiling point = 132°C/2.7 kPa).

The 2,7-dichloro-6-fluoroquinoline-3-carboxylic acid is prepared in the following manner:

A solution of 89.3 g of potassium permanganate in 1.4 litres of water is added in the course of 1 hour and while keeping the temperature between 10 and 14°C to a stirred suspension, cooled to 10°C, of 69.5 g of 2,7-dichloro-6-fluoro-3-formyl-1,4-dihydroquinoline in 282 cm³ of 2 N aqueous potassium hydroxide solution and 282 cm³ of water. The temperature is allowed to rise to about 20°C and the mixture is stirred for a further 30 minutes at this temperature. 26 g of sodium dithionite are added, the mixture is stirred for 10 minutes at a temperature close to 20°C and filtered through diatomaceous silica for filtration and the filter cake is washed with twice 250 cm³ of water. The filtrate and the aqueous washing phases are combined and 90 cm³ of a 35 % aqueous solution of hydrochloric acid are added. The precipitate formed is extracted with 4 times 500
cm$^3$ of ethyl acetate. The combined organic extracts are washed with 3 times 500 cm$^3$ of water, dried over magnesium sulphate, filtered and the filtrate is concentrated under reduced pressure (20 kPa) at 50°C. The residue is taken up in 5 350 cm$^3$ of diethyl ether, drained and washed with twice 200 cm$^3$ of diethyl ether. 45 g of 2,7-dichloro-6-fluorquinoline-3-carboxylic acid are obtained in the form of a beige solid melting at 230°C which is used for the subsequent steps without further purification.

The 2,7-dichloro-6-fluoro-3-formyl-1,4-dihydroquinoline was prepared in the following manner:

55.6 cm$^3$ of phosphoryl chloride are added in the course of 30 minutes, with stirring, at between 10 and 15°C, to a mixture of 250 cm$^3$ of trichloromethane and 54 cm$^3$ of dimethylformamide and the mixture is stirred for 1 hour at a temperature close to 20°C. 52 g of 7-chloro-6-fluoro-3,4-dihydrocarbostyril are added progressively, with vigorous stirring, in the course of 10 minutes, at about 20°C to the solution obtained. The suspension obtained is heated to a temperature close to 60°C and is kept at this temperature for a further 2 hours, with stirring. The reaction mixture is concentrated under reduced pressure (20 kPa) at 50°C until a pasty mixture is obtained. A mixture of 250 cm$^3$ of water and 250 g of crushed ice is added, with vigorous stirring. The solid obtained is drained at about 5°C and washed with 4 times 125 cm$^3$ of water at 5°C. The moist product obtained and
58 g of sodium acetate are added simultaneously, in the course of 1 hour, to 500 cm$^3$ of water at 90°C in such a way as to maintain the pH at about 6. The mixture is stirred for a further 15 minutes at 90°C, the temperature is allowed to fall to about 50°C and the product is drained at this temperature and washed with 3 times 250 cm$^3$ of water at about 20°C. 54.3 g of 2,7-dichloro-6-fluoro-3-formyl-1,4-dihydroquinoline are obtained in the form of a yellow solid melting at 260°C which is used in this form for the subsequent steps.

The 7-chloro-6-fluoro-3,4-dihydrocarbostyril is prepared in the following manner:

350 g of aluminium chloride are added in the course of 5 minutes, with vigorous stirring, to 174.4 g of 3'-chloro-4'-fluoro-3-(N-chloro)-propionanilide. The solid mixture is heated to about 60°C in the course of 30 minutes. The temperature rises on its own to about 80°C and the reaction mixture becomes liquid. It is then heated to 110°C in the course of 15 minutes and kept at between 110 and 120°C for 3 hours. The reaction mixture (at about 110°C) is poured, in the course of 10 minutes, with vigorous stirring, into a mixture of 550 cm$^3$ of 35% hydrochloric acid and 500 g of crushed ice. The temperature is allowed to rise to 20°C and the product is drained and washed with 6 times 500 cm$^3$ of water.

The moist product is recrystallized from 1.2 litres
of ethanol. 108 g of 7-chloro-6-fluoro-3,4-
dihydrocarbostyril are obtained in the form of a beige solid melting at 215°C.

The 3'-chloro-4'-fluoro-3-(N-chloro)-propionanilide was prepared in the following manner:

A solution of 127 g of 3-chloropropionyl chloride in 200 cm³ of acetone is added, with stirring, in the course of 35 minutes, to a solution, at a temperature close to 55°C, of 291 g of 3-chloro-4-fluoroaniline in 500 cm³ of acetone and the mixture is kept at this temperature for 2 hours. After cooling to about 20°C, the insoluble matter is removed by filtration and washed with twice 200 cm³ of acetone. The filtrate and the combined washings are poured into 2 litres of water and 1 kg of ice, with stirring. The temperature is allowed to rise to about 20°C and the mixture is extracted with 4 times 500 cm³ of dichloromethane. The combined organic extracts are washed with 3 times 500 cm³ of water, dried over magnesium sulphate, stirred for 15 minutes with 6 g of Norit vegetable charcoal, filtered through diatomaceous silica for filtration and concentrated under reduced pressure (20 kPa) at 50°C. The solid obtained is recrystallized from a mixture of 133 cm³ of cyclohexane and 67 cm³ of diisopropyl ether. 176 g of 3'-chloro-4'-fluoro-3-(N-chloro)-propionanilide are obtained in the form of a beige solid melting at 94°C, which is used in this form for the subsequent steps.
EXAMPLE 2

Carrying out the reaction under the conditions described in Example 1 but starting from 10.5 g of 8-chloro-7-fluoro-3-ethoxycarbonyl-1-ethyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine. 9.3 g of 8-chloro-1-ethyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a beige solid melting at 380°C.

The 8-chloro-3-ethoxycarbonyl-1-ethyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine is prepared in the following manner:

16 g of ethylamine are added, in the course of 5 minutes, at between 10 and 15°C, to a stirred suspension of 13.5 g of ethyl 2-(2,7-dichloro-6-fluoroquinoline-3-carbonyl)-3-dimethylaminoacrylate in 135 cm³ of ethanol, the temperature is allowed to rise to about 20°C, 0.5 g of DBU is added and the mixture is heated, with stirring, for 2 hours at a temperature close to 75°C. After cooling to a temperature close to 20°C, the precipitate is drained and washed with twice 100 cm³ of ethanol and twice 100 cm³ of diethyl ether. 10.4 g of 8-chloro-3-ethoxycarbonyl-1-ethyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine are obtained in the form of a yellow solid melting at 300-301°C, which is used for the subsequent steps without further purification.
EXAMPLE 3

A suspension of 16.4 g of 8-chloro-3-ethoxycarbonyl-7-fluoro-1-(N-formyl-N-methylamino)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine in 164 cm$^3$ of acetic acid and 164 cm$^3$ of an aqueous 17.5 % hydrochloric acid solution is heated at a temperature close to 100°C, with stirring, for 4 hours. After cooling to a temperature close to 10°C, 165 cm$^3$ of 30 % slaked lime is added at between 10 and 20°C. The product is drained and washed with 3 times 150 cm$^3$ of water, 3 times 150 cm$^3$ of ethanol and 3 times 150 cm$^3$ of diethyl ether. 13.64 g of 8-chloro-7-fluoro-1-methylamino-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 354-356°C.

The 8-chloro-3-ethoxycarbonyl-7-fluoro-1-(N-formyl-N-methylamino)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine is prepared under the conditions of Example 1 but starting from 19.25 g of ethyl 2-(2,7-dichloro-6-fluoroquinoline-3-carbonyl)-3-dimethylaminoacrylate, 4.05 g of N-formyl-N-methylhydrazine and 1.6 g of DBU in 200 cm$^3$ of ethanol. 16.4 g of 8-chloro-3-ethoxycarbonyl-7-fluoro-1-(N-formyl-N-methylamino)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine are obtained in the form of a colourless solid melting at 296-298°C, which can be used for the subsequent steps without further purification.

The N-formyl-N-methylhydrazine can be prepared by the method described by Carl Th. Pedersen, Acta Chem. Scand.,
EXAMPLE 4

Carrying out the reaction under the conditions of Example 1 but starting from 6.1 g of 8-chloro-1-cyclopropyl-3-ethoxycarbonyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine, 4.85 g of 8-chloro-1-cyclopropyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 330°C.

The 8-chloro-1-cyclopropyl-3-ethoxycarbonyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine is prepared under the following conditions:

A solution of 20.6 g of ethyl 2-(2,7-dichloro-6-fluoroquinoline-3-carbonyl)-3-dimethylaminoacrylate and 6 g of cyclopropylamine in 100 cm³ of trichloromethane is stirred at a temperature close to 20°C for 24 hours. The reaction mixture is concentrated under reduced pressure (20 kPa) at 50°C. The residue is taken up in 180 cm³ of ethanol and 10 g of DBU and the solution obtained is heated at a temperature close to 78°C for 4 hours. After cooling to a temperature close to 20°C, the precipitate obtained is drained and washed with twice 60 cm³ of ethanol. 13.65 g of 8-chloro-1-cyclopropyl-3-ethoxycarbonyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine are obtained in the form of a pale yellow solid melting at 256°C, which is used for the subsequent steps without further purification.
EXAMPLE 5

A suspension of 1.88 g of 8-chloro-3-ethoxycarbonyl-7-fluoro-4-oxo-1-tert.-butyl-1,4-dihydro-benzo[b][1,8]naphthyridine in 10 cm³ of ethanol, 5 cm³ of water and 15 cm³ of 2 N aqueous potassium hydroxide solution is heated at a temperature close to 75°C, with stirring, for one hour. 2 cm³ of acetic acid are added to the solution obtained. The precipitate formed is drained and washed with 3 times 10 cm³ of water and 3 times 10 cm³ of ethanol. After recrystallizing once from 50 cm³ of dimethylformamide, 1.7 g of 8-chloro-7-fluoro-4-oxo-1-tert.-butyl-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 398°C.

The 8-chloro-3-ethoxycarbonyl-7-fluoro-4-oxo-1-tert.-butyl-1,4-dihydro-benzo[b][1,8]naphthyridine is prepared under the conditions of Example 4 but starting from 8.86 g of ethyl 2-(2,7-dichloro-6-fluorquinoline-3-carbonyl)-3-dimethylaminoacrylate and 4.03 g of tert.-butylamine in 45 cm³ of trichloromethane and then in 4.53 g of DBU and 45 cm³ of ethanol. 5 g of 8-chloro-3-ethoxycarbonyl-7-fluoro-4-oxo-1-tert.-butyl-1,4-dihydro-benzo[b][1,8]naphthyridine are obtained in the form of a yellow solid melting at 239°C.

EXAMPLE 6

A suspension of 1.95 g of 1-cyclopropyl-3-ethoxycarbonyl-7,8-difluoro-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine in 20 cm$^3$ of 17.5 % hydrochloric acid and 20 cm$^3$ of acetic acid is heated at a temperature close to 100°C for 1 hour 30 minutes. After cooling to about 20°C, the reaction mixture is poured into 100 cm$^3$ of water. The precipitate is drained and washed with 3 times 20 cm$^3$ of water. After recrystallizing once from a mixture of 30 cm$^3$ of dimethylformamide and 30 cm$^3$ of ethanol, 1.31 g of 1-cyclopropyl-7,8-difluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 284-285°C.

The 1-cyclopropyl-3-ethoxycarbonyl-7,8-difluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine is prepared in the following manner:

A stirred suspension of 5.27 g of ethyl 2-(2-chloro-6,7-difluoroquinoline-3-carbonyl)-3-cyclopropylaminoacrylate in 2.22 g of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 120 cm$^3$ of ethanol is heated at a temperature close to 75°C for 35 minutes. After cooling to about 20°C, the reaction mixture is taken up in 100 cm$^3$ of water and extracted once with 100 cm$^3$ and twice with 50 cm$^3$ of trichloromethane. The combined organic extracts are washed with 3 times 50 cm$^3$ of water, dried over magnesium sulphate, filtered and concentrated under reduced pressure (20 kPa) at a temperature close to 20°C. The dry extract obtained is taken up in 30 cm$^3$ of diisopropyl ether, drained and recrystallized from a mixture
of 75 cm$^3$ of ethanol and 75 cm$^3$ of dimethylformamide. 3.57 g of 1-cyclopropyl-3-ethoxycarbonyl-7,8-difluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine are obtained in the form of a yellow solid melting at 229-230°C.

The ethyl 2-(2-chloro-6,7-difluoroquinoline-3-carbonyl)-3-cyclopropylaminoacrylate is prepared in the following manner:

A solution of 6.25 g of ethyl 2-(2-chloro-6,7-difluoroquinoline-3-carbonyl)-3-dimethylaminoacrylate in 2.91 g of cyclopropylamine and 25 cm$^3$ of trichloromethane is stirred for 3 hours at a temperature close to 20°C. The reaction mixture is concentrated under reduced pressure (20 kPa) at a temperature close to 50°C. The dry extract is taken up in 50 cm$^3$ of diisopropyl ether, drained and then washed with 20 cm$^3$ of the same solvent.

5.27 g of ethyl 2-(2-chloro-6,7-difluoroquinoline-3-carbonyl)-3-cyclopropylaminoacrylate are obtained in the form of an orange solid melting at 116-117°C. This product is used for the subsequent steps without further purification.

The ethyl 2-(2-chloro-6,7-difluoroquinoline-3-carbonyl)-3-dimethylaminoacrylate is prepared in the following manner:

A suspension of 6.17 g of ethyl 3-(2-chloro-6,7-difluoro-3-quinolyl)-3-oxopropionate in 7.15 g of N,N-dimethylformamide dimethyl acetal and 60 cm$^3$ of ethyl acetate is heated at a temperature close to 75°C for 1 hour.
minutes. The reaction mixture is concentrated to dryness under reduced pressure (20 kPa) at about 50°C. The residue is taken up in 50 cm³ of diisopropyl ether, drained and washed with 3 times 25 cm³ of the same solvent. 6.65 g of ethyl 2-(2-chloro-6,7-difluoroquinoline-3-carbonyl)-3-dimethylaminoacrylate are obtained in the form of an orange solid melting at 140°C.

The ethyl 3-(2-chloro-6,7-difluoro-3-quinolyl)-3-oxopropionate is prepared in the following manner:

A suspension of 14.13 g of 2-chloro-6,7-difluoroquinoline-3-carboxylic acid in 29 cm³ of thionyl chloride and 220 cm³ of trichloromethane is heated at a temperature close to 60°C for 4 hours. The solution obtained is concentrated to dryness under reduced pressure (20 kPa) at about 60°C. The residue obtained is taken up in 75 cm³ of n-hexane, drained and washed with twice 60 cm³ of the same solvent. The 14.4 g of yellow solid obtained are poured into solution in 115 cm³ of tetrahydrofuran. This solution is introduced dropwise, with stirring, in the course of 35 minutes, at between 5 and 10°C, into 70 cm³ of a solution of magnesium chelate of ethyl monomalonate in tetrahydrofuran, prepared under the conditions described below. The temperature is allowed to rise to about 20°C and the mixture is stirred for a further 2 hours under these conditions. The solution obtained is introduced dropwise, with stirring, in the course of 30 minutes, at a temperature close to 5°C, into
560 cm³ of 0.5 N sulphuric acid. The temperature of the suspension obtained is allowed to rise to 20°C and the suspension is then stirred for a further 1 hour and a half at this temperature. It is extracted with 3 times 250 cm³ of ethyl acetate. The combined organic extracts are washed with twice 250 cm³ of water, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (20 kPa) at 50°C. The residue obtained is taken up in 50 cm³ of n-hexane containing 20 % of diisopropyl ether, drained, washed with 10 cm³ of the same mixture and recrystallized from 60 cm³ of isopropanol containing 30 % of n-hexane. 11.84 g of ethyl 3-(2-chloro-6,7-difluoro-3-quinolyl)-3-oxopropionate are obtained in the form of a cream solid melting at 107°C.

Preparation of the magnesium chelate of ethyl monomalonate:

2 cm³ of absolute ethanol, 0.1 cm³ of tetrachloromethane and 1 g of ethyl monomalonate are added progressively to 2.78 g of magnesium turnings. After heating, a solution of 9 g of ethyl monomalonate in 180 cm³ of ethanol is added in the course of 15 minutes. The mixture is heated for 20 hours at a temperature close to 75°C and concentrated under reduced pressure (20 kPa) at 50°C. The residue is taken up in twice 100 cm³ of toluene and the mixture is concentrated under reduced pressure under the same conditions as above. The grey powder obtained is brought into solution
by adding anhydrous tetrahydrofuran so as to obtain a total volume of 70 cm³.

The 2-chloro-6,7-difluoroquinoline-3-carboxylic acid was prepared in the following manner:

A solution of 115 g of potassium permanganate in 1.215 litres of water is added in the course of 1 hour, while keeping the temperature between 10 and 14°C, to a stirred suspension, cooled to 10°C, of 70.18 g of 2-chloro-6,7-difluoro-3-formyl-1,4-dihydroquinoline in 970 cm³ of N aqueous potassium hydroxide solution. The temperature is allowed to rise to about 20°C and the mixture is stirred for a further 30 minutes at this temperature. 38.5 g of sodium dithionite are added, the mixture is stirred for 10 minutes at a temperature close to 20°C and filtered through diatomaceous silica and the filter cake is washed with 3 times 200 cm³ of water. The filtrate and the aqueous washing phases are combined and 140 cm³ of 35 % aqueous hydrochloric acid solution are added. The precipitate formed is extracted with 4 times 800 cm³ of ethyl acetate. The combined organic extracts are washed with twice 500 cm³ of water, dried over magnesium sulphate, filtered and concentrated under reduced pressure (20 kPa) at 50°C. The residue is taken up in 400 cm³ of diethyl ether, drained and washed with twice 200 cm³ of the same solvent. 49.2 g of 2-chloro-6,7-difluoroquinoline-3-carboxylic acid are obtained in the form of a beige solid melting at 232°C, which is used for the subsequent steps.
without further purification.

The 2-chloro-6,7-difluoro-3-formyl-1,4-
dihydroquinoline was prepared in the following manner:

76.9 cm$^3$ of phosphoryl chloride are added in the

5 course of 30 minutes, with stirring, at between 10 and 15°C,
to a mixture of 800 cm$^3$ of trichloromethane and 74.35 cm$^3$ of
dimethylformamide and the mixture is stirred for 1 hour at a
temperature close to 20°C. 65.8 g of 6,7-difluoro-3,4-
dihydrocarbostyril are added in the course of 10 minutes, at

10 about 20°C, with vigorous stirring, to the solution obtained.
The solution obtained is heated to a temperature close to

60°C and kept at this temperature for 2 hours. The reaction
mixture is concentrated under reduced pressure (20 kPa) at

50°C until a pasty mixture is obtained. A mixture of 500 g of

15 ice and 500 cm$^3$ of water is added, with vigorous stirring.
The solid obtained is drained at about 5°C and washed with 3
times 300 cm$^3$ of water at 5°C. The moist product obtained and

60 g of sodium acetate are added simultaneously, in the

course of 1 hour, to 1.5 litres of water at 90°C, in such a

20 way as to maintain the pH at about 6. The mixture is stirred

for a further 30 minutes at 90°C, the temperature is allowed
to fall to about 50°C and the product is drained at this
temperature and washed with 3 times 300 cm$^3$ of water at about

20°C. 70.18 g of 2-chloro-6,7-difluoro-3-formyl-1,4-
dihydroquinoline are obtained in the form of a yellow solid

25 melting at 260°C, which is used in this form for the
The 6,7-difluoro-3,4-dihydrocarbostyril is obtained in the following manner:

134 g of aluminium chloride are added to 67 g of 3',4'-difluoro-3-(N-chloro)-propionanilide with vigorous stirring and then, after about 2 minutes, a further 135.9 g of 3',4'-difluoro-3-(N-chloro)-propionanilide and 272 g of aluminium chloride are added in small fractions in the course of 15 minutes. The temperature rises on its own to about 60°C and the reaction mixture becomes liquid. It is then heated to 110°C in the course of 20 minutes and kept at between 110 and 120°C for 2 hours. The reaction mixture (at about 110°C) is poured in the course of 10 minutes, with vigorous stirring, into a mixture of 840 cm³ of 35% hydrochloric acid and 1 kg of crushed ice. The temperature is allowed to rise to about 20°C and the product is drained and washed with 600 cm³ of water, twice 300 cm³ of ethanol at 5°C and twice 400 cm³ of diethyl ether at about 20°C. 131.58 g of 6,7-difluoro-3,4-dihydrocarbostyril are obtained in the form of a beige solid melting at 216°C, which is used in this form for the subsequent steps.

The 3',4'-difluoro-3-(N-chloro)-propionanilide is prepared in the following manner:

139.16 g of 3-chloro-propionyl chloride are added, with stirring, in the course of 1 hour and a half to a solution of 125 g of 3,4-difluoroaniline in 80 cm³ of
pyridine and 1.5 litres of acetone heated to a temperature close to 55°C and the mixture is kept at this temperature for 1 hour and a half. After cooling to about 20°C, the solution is poured, with stirring, into a mixture of 1 litre of water and 500 g of crushed ice. The temperature is allowed to rise to about 20°C and the mixture is extracted with 3 times 500 cm³ of dichloromethane. The combined organic extracts are washed with 500 cm³ of N hydrochloric acid and 5 times 500 cm³ of water, dried over magnesium sulphate, filtered and concentrated under reduced pressure (20 kPa) at about 50°C. The solid obtained is taken up in 500 cm³ of n-hexane, drained and washed with twice 100 cm³ of the same solvent. 202.9 g of 3',4'-difluoro-3-(N-chloro)-propionanilide are obtained in the form of a beige solid melting at 76°C, which is used for the subsequent steps without further purification.

EXAMPLE 7

A suspension of 2.78 g of 3-ethoxycarbonyl-7,8-difluoro-1-methoxy-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine in 30 cm³ of 17.5 % of hydrochloric acid and 30 cm³ of acetic acid is heated at a temperature close to 100°C for 1 hour. After cooling to about 20°C, the reaction mixture is poured into 100 cm³ of water. The precipitate formed is drained and washed with 3 times 30 cm³ of water and twice 5 cm³ of ethanol. After recrystallizing from 100 cm³ of dimethylformamide containing
20 % of ethanol, 2.03 g of 7,8-difluoro-1-methoxy-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 325-327°C.

The 3-ethoxycarbonyl-7,8-difluoro-1-methoxy-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine is prepared under the following conditions:

2.13 g of triethylamine are added to a suspension of 1.7 g of methoxylamine hydrochloride in 40 cm³ of trichloromethane. After stirring for 15 minutes at a temperature close to 20°C, 3.69 g of ethyl 2-(2-chloro-6,7-difluoroquinoline-3-carbonyl)-3-dimethylaminoacrylate are added to the solution obtained and the mixture is stirred for 4 hours and a half at about 20°C. The reaction mixture is concentrated to dryness under reduced pressure (20 kPa) at a temperature close to 50°C. The residue is taken up in 70 cm³ of ethanol and 3.6 g of triethylamine and the mixture is heated for 30 minutes at a temperature close to 75°C. After cooling to about 20°C, the precipitate obtained is drained and washed with 3 times 30 cm³ of ethanol. 2.67 g of 3-ethoxycarbonyl-7,8-difluoro-1-methoxy-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine are obtained in the form of a pale yellow solid melting at 266-268°C.

EXAMPLE 8

A suspension of 8 g of 3-ethoxycarbonyl-7,8-difluoro-1-methyl-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine in 80 cm³ of a 17.5 % aqueous solution of hydrochloric acid and 80 cm³ of acetic acid is heated, with stirring, at a temperature close to 100°C for one hour and a half. After cooling to about 20°C, the solid is drained and washed with 6 times 100 cm³ of water. After recrystallizing once from 160 cm³ of dimethylformamide, 6.44 g of 7,8-difluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid which decomposes at 360°C.

The 3-ethoxycarbonyl-7,8-difluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine is prepared in the following manner:

A solution, at about 0°C, of 11.3 g of methylamine in 50 cm³ of ethanol is added in the course of 10 minutes, at between 0 and 5°C to a stirred suspension of 22.3 g of ethyl 2-(2-chloro-6,7-difluoroquinoline-3-carbonyl)-3-dimethylamino acrylate in 480 cm³ of ethanol, kept at a temperature close to 0°C, the mixture is stirred for 1 hour at between 0 and 5°C, the temperature is allowed to rise to about 25°C and the mixture is stirred for a further 16 hours at this temperature. The insoluble matter is drained and washed with 3 times 100 cm³ of ethanol and twice 100 cm³ of diethyl ether. After recrystallizing once from 250 cm³ of dimethylformamide, 16 g of 3-ethoxycarbonyl-7,8-difluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine are obtained in the form of a yellow solid melting at 323-324°C.
EXAMPLE 9

A suspension of 4 g of 3-ethoxycarbonyl-7,8,9-trifluoro-1-methyl-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine in 30 cm$^3$ of acetic acid and 30 cm$^3$ of 50 % hydrochloric acid is heated at a temperature close to 100°C for 2 hours. After cooling to about 20°C, 100 cm$^3$ of water are added. The precipitate formed is drained, washed with 3 times 50 cm$^3$ of water and recrystallized from 80 cm$^3$ of dimethylformamide. 3.4 g of 7,8,9-trifluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a colourless solid melting at 350-352°C.

The 3-ethoxycarbonyl-7,8,9-trifluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine is prepared in the following manner:

A solution, at about 5°C, of 10 g of methylamine in 50 cm$^3$ of ethanol is added in the course of 10 minutes, at between 5 and 10°C, to a stirred suspension of 19.3 g of ethyl 2-(2-chloro-6,7,8-trifluoro-quinoline-3-carbonyl)-3-dimethylaminoacrylate in 150 cm$^3$ of ethanol kept at a temperature close to 5°C, the mixture is stirred for 1 hour at between 5 and 10°C and the temperature is allowed to rise to about 20°C. 7.6 g of DBU are added to the solution obtained and the mixture is heated at about 30°C for 1 hour. After cooling to a temperature close to 20°C, the product is drained and washed with twice 100 cm$^3$ of ethanol and twice
100 cm$^3$ of diisopropyl ether. 13.4 g of 3-ethoxycarbonyl-7,8,9-trifluoro-1-methyl-4-oxo-1,4-dihydrobenzo[b][1,8]napthyridine are obtained in the form of a yellow solid melting at 320°C, which is used for the subsequent steps without further purification.

The ethyl 2-(2-chloro-6,7,8-trifluoroquinoline-3-carbonyl)-3-dimethylaminoacrylate can be prepared in the following manner:

A suspension of 26.7 g of ethyl 3-(2-chloro-6,7,8-trifluoro-3-quinolyl)-3-oxopropionate in 270 cm$^3$ of ethyl acetate and 32 cm$^3$ of N,N-dimethylformamide dimethyl acetal is heated at a temperature close to 75°C, with stirring, for 2 hours. The reaction mixture is concentrated to dryness under reduced pressure (20 kPa) at about 50°C. The dry extract is taken up in 175 cm$^3$ of diisopropyl ether, drained and washed with twice 85 cm$^3$ of the same solvent. 19.32 g of ethyl 2-(2-chloro-6,7,8-trifluoroquinoline-3-carbonyl)-3-dimethylaminoacrylate are obtained in the form of an orange solid melting at 118°C, which is used for the subsequent steps without further purification.

The ethyl 3-(2-chloro-6,7,8-trifluoro-3-quinolyl)-3-oxopropionate is prepared in the following manner:

A suspension of 46.3 g of 2-chloro-6,7,8-trifluoroquinoline-3-carboxylic acid in 640 cm$^3$ of trichloromethane and 84 cm$^3$ of thionyl chloride is heated, with stirring, at a temperature close to 60°C for 6 hours.
The solution obtained is concentrated to dryness under reduced pressure (20 kPa) at about 50°C. The dry extract obtained is taken up in 140 cm³ of petroleum ether (40-60), drained and washed with twice 60 cm³ of the same solvent. The 47.61 g of yellow solid obtained are brought into solution in 400 cm³ of tetrahydrofuran. This solution is introduced dropwise, with stirring, in the course of 1 hour and a half, at between 5 and 10°C, into 250 cm³ of a solution of the magnesium chelate of ethyl monomalonate in tetrahydrofuran prepared under the conditions of Example 6. The temperature is allowed to rise to about 20°C and the mixture is stirred for a further 2 hours under these conditions. The solution obtained is introduced dropwise, with vigorous stirring, in the course of 1 hour, at a temperature close to 5°C, into 1750 cm³ of 0.5 N sulphuric acid. The mixture is stirred for a further 2 hours at this temperature and extracted at about 5°C with 3 times 600 cm³ of diethyl ether. The combined organic phases are washed with 3 times 500 cm³ of water, dried over magnesium sulphate and concentrated under reduced pressure (20 kPa) at a temperature close to 30°C. The dry extract is taken up in a mixture of 135 cm³ of diisopropyl ether and 15 cm³ of n-hexane, drained at about 5°C and washed with twice 115 cm³ of the same mixture at the same temperature. 47.4 g of ethyl 3-[(2-chloro-6,7,8-trifluoro-3-quinolyl)-3-oxopropionate are obtained in the form of a beige solid melting at 78-80°C, which is used for the subsequent
steps without further purification.

The 2-chloro-6,7,8-trifluoroquinoline-3-carboxylic acid is prepared in the following manner:

A solution of 69.65 g of potassium permanganate in 730 cm$^3$ of water is added in the course of 1 hour, while keeping the temperature between 10 and 14°C, to a stirred suspension, cooled to about 10°C, of 45.7 g of 2-chloro-6,7,8-trifluoro-3-formyl-1,4-dihydroquinoline in 585 cm$^3$ of N potassium hydroxide solution. The mixture is stirred for a further 30 minutes at about 10°C. 12 g of sodium dithionite are added and the mixture is stirred for 10 minutes at a temperature close to 10°C and filtered through diatomaceous silica and the filter cake is washed with 3 times 400 cm$^3$ of water. The filtrate and the washings are combined and 70 cm$^3$ of a 35% aqueous solution of hydrochloric acid are added. The precipitate formed is extracted with 3 times 500 cm$^3$ of ethyl acetate. The combined organic extracts are dried over magnesium sulphate, filtered and concentrated under reduced pressure (20 kPa) at 50°C. The residue is taken up in a mixture of 100 cm$^3$ of diethyl ether and 100 cm$^3$ of diisopropyl ether, drained and washed with 100 cm$^3$ of the same mixture. 46.43 g of 2-chloro-6,7,8-trifluoroquinoline-3-carboxylic acid are obtained in the form of a colourless solid which decomposes at 225-230°C and which is used for the subsequent steps without further purification.

The 2-chloro-6,7,8-trifluoro-3-formyl-1,4-
dihydroquinoline is prepared in the following manner:

50 cm³ of phosphoryl chloride are added in the course of 40 minutes, with stirring, at between 5 and 10°C, to a mixture of 525 cm³ of trichloromethane and 49 cm³ of dimethylformamide, the mixture is stirred for 15 minutes at this temperature and the temperature is allowed to rise to about 20°C. 46.8 g of 6,7,8-trifluoro-3,4-dihydrocarbostyril are added progressively in the course of 20 minutes, at about 20°C, with vigorous stirring, to the solution obtained. The mixture is stirred for 30 minutes at a temperature close to 20°C, heated to about 60°C and kept at this temperature for 2 hours and a half. The reaction mixture is concentrated under reduced pressure (20 kPa) at about 50°C. The oily residue is poured into 500 g of ice, with vigorous stirring. 100 g of sodium acetate are added in small fractions in the course of 30 minutes. The suspension obtained is poured in the course of 15 minutes, with vigorous stirring, into 1 litre of water which has previously been heated to about 90°C and the mixture is stirred for a further 15 minutes at this temperature. The insoluble matter is drained at about 90°C and washed with 3 times 250 cm³ of water. 47.7 g of 2-chloro-6,7,8-trifluoro-3-formyl-1,4-dihydroquinoline are obtained in the form of a colourless solid which decomposes at 220°C.

The 6,7,8-trifluoro-3,4-dihydrocarbostyril is prepared in the following manner:
24.35 g of 6,7,8-trifluorocarbostyril in suspension in a mixture of 450 cm$^3$ of ethanol and 150 cm$^3$ of dimethylformamide are hydrogenated, with stirring, at about 50°C, in the presence of 5 g of Raney nickel under a pressure of 1 atmosphere until the absorption of hydrogen has ceased. The W-2 grade Raney nickel used is washed beforehand with 50 cm$^3$ of an aqueous 2% acetic acid solution, twice 50 cm$^3$ of water and 3 times 50 cm$^3$ of ethanol. 250 cm$^3$ of dimethylformamide are added to the reaction mixture and the mixture is filtered at about 50°C through diatomaceous silica. The filtrate is concentrated under reduced pressure (20 kPa) at about 70°C. The dry extract is taken up in 150 cm$^3$ of water, drained and washed with twice 50 cm$^3$ of water. 23.6 g of 6,7,8-trifluoro-3,4-dihydrocarbostyril are obtained in the form of a light beige solid melting at 217°C, which is used for the subsequent steps without further purification.

The 6,7,8-trifluorocarbostyril is prepared in the following manner:

60.83 g of 4-chloro-6,7,8-trifluorocarbostyril in suspension in 520 cm$^3$ of acetic acid and 38.15 cm$^3$ of triethylamine are hydrogenated under a pressure of 1 atmosphere in the presence of 5.25 g of 10% palladium-on-charcoal until the absorption of hydrogen has ceased, at a temperature close to 25°C. The reaction mixture is then heated to about 40°C and filtered at this temperature through diatomaceous silica for filtration. The filtrate is
concentrated under reduced pressure (20 kPa) at a temperature close to 50°C. The dry extract is taken up in 400 cm$^3$ of water; the insoluble matter is drained and washed with 4 times 170 cm$^3$ of water, twice 110 cm$^3$ of ethanol and twice 100 cm$^3$ of diisopropyl ether. 48.35 g of 6,7,8-trifluorocarbostyril are obtained in the form of a colourless solid which sublimes at 288°C and which is used for the subsequent steps without further purification.

The 4-chloro-6,7,8-trifluorocarbostyril is prepared in the following manner:

A suspension of 70.4 g of 4-chloro-2-ethoxy-6,7,8-trifluoroquinoline in 170 cm$^3$ of a 35 % aqueous solution of hydrochloric acid, 420 cm$^3$ of acetic acid and 250 cm$^3$ of water is heated, with stirring, at a temperature close to 100°C for 2 hours and a half. After cooling to about 20°C, the reaction mixture is poured into 1,100 cm$^3$ of water at about 5°C, the mixture is stirred for 15 minutes at this temperature and the insoluble matter is then drained and washed with 3 times 220 cm$^3$ of water. 61 g of 4-chloro-6,7,8-trifluorocarbostyril are obtained in the form of a cream solid melting at 213°C, which is used for the subsequent steps without further purification.

The 4-chloro-2-ethoxy-6,7,8-trifluoroquinoline is prepared in the following manner:

A suspension of 69.5 g of 2-ethoxy-6,7,8-trifluoro-4-hydroxyquinoline in 430 cm$^3$ of phosphoryl chloride is heated,
with stirring, at a temperature close to 100°C for 30 minutes. The solution obtained is concentrated under reduced pressure (20 kPa) at about 60°C until the volume is 100 cm³. The residue is taken up in 750 cm³ of ethyl acetate; the solution obtained is poured, with stirring, in the course of 10 minutes into a mixture of 400 cm³ of water and 200 g of ice and the mixture is stirred under these conditions for 30 minutes. After separating off the organic extract, the aqueous phase is extracted again with twice 250 cm³ of ethyl acetate. The combined organic extracts are washed with 3 times 250 cm³ of water, dried over magnesium sulphate and concentrated under reduced pressure (20 kPa) at about 40°C. The oily residue obtained is taken up in 370 cm³ of petroleum ether (40-60). After filtering through diatomaceous silica, the filtrate is concentrated to dryness under reduced pressure (20 kPa) at about 30°C. 70.7 g of 4-chloro-2-ethoxy-6,7,8-trifluoroquinoline are obtained in the form of a beige solid melting at 45°C, which is used for the subsequent steps without further purification.

The 2-ethoxy-6,7,8-trifluoro-4-hydroxyquinoline can be prepared in the following manner:

A solution of 122 g of 2,3,4-trifluoro-N-[(1'-ethoxy-2'-ethoxycarbonyl)ethyldene]-aniline in 120 cm³ of phenyl oxide is introduced dropwise, in the course of 25 minutes, with stirring, into 600 cm³ of phenyl oxide at a temperature close to 250°C while removing the ethanol formed
by distillation. After stirring for 15 minutes at this temperature, the solution is cooled to about 20°C and 750 cm³ of n-hexane are added. The precipitate formed is drained and washed 3 times with 200 cm³ of n-hexane. 69.5 g of 2-ethoxy-6,7,8-trifluoro-4-hydroxyquinoline are obtained in the form of a beige solid melting at 171°C, which is used for the subsequent steps without further purification.

The 2,3,4-trifluoro-N-[(1'-ethoxy-2'-ethoxycarbonyl)ethylidene]-aniline can be prepared in the following manner:

58.8 g of 2,3,4-trifluoroaniline are added in a single amount, with stirring, to a solution of 90 g of 2-ethoxycarbonyl-1-ethoxy-ethylideneamine hydrochloride in 820 cm³ of ethanol. After stirring for 48 hours at a temperature close to 20°C, the suspension obtained is filtered; the filtrate is concentrated under reduced pressure (20 kPa) at a temperature close to 50°C. The oily residue is taken up in 250 cm³ of water. The mixture obtained is extracted with 3 times 200 cm³ of diethyl ether. The combined organic extracts are washed with 4 times 150 cm³ of water, dried over magnesium sulphate and concentrated under reduced pressure (20 kPa) at about 30°C. 122 g of 2,3,4-trifluoro-N-[(1'-ethoxy-2'-ethoxycarbonyl)ethylidene]-aniline are obtained in the form of a yellow oil which is used for the subsequent steps without further purification.

The 2-ethoxycarbonyl-1-ethoxy-ethylideneamine

**EXAMPLE 10**

The 6,7,8-trifluoro-1-methoxy-4-oxo-1,4-dihydro-5'-benzo[b][1,8]naphthyridine-3-carboxylic acid was prepared under the conditions of Example 9 but starting from 9 g of 3-ethoxycarbonyl-6,7,8-trifluoro-1-methoxy-4-oxo-1,4-dihydrobenzo[b][1,8]naphthyridine. 7.7 g of 6,7,8-trifluoro-1-methoxy-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a beige solid melting at 322°C.

The 3-ethoxycarbonyl-6,7,8-trifluoro-1-methoxy-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine was prepared under the following conditions:

8.7 cm$^3$ of triethylamine are added to a suspension of 5.1 g of methylhydroxylamine hydrochloride in 120 cm$^3$ of trichloromethane. 7.8 g of ethyl 2-(2-chloro-6,7,8-trifluoroquinoline-3-carbonyl)-3-dimethylaminoacrylate are added, at about 20°C, to the solution obtained. After stirring for 2 hours at this temperature, the solution is concentrated to dryness under reduced pressure (20 kPa) at about 50°C. The residue obtained is taken up in 150 cm$^3$ of ethanol and 10 cm$^3$ of triethylamine and the mixture is heated, with stirring, for 30 minutes. After cooling to about 20°C, the insoluble matter is drained and washed with 3 times 50 cm$^3$ of ethanol and twice 50 cm$^3$ of diisopropyl ether.
After recrystallizing from 120 cm$^3$ of dimethylformamide, 9 g of 3-ethoxycarbonyl-6,7,8-trifluoro-1-methoxy-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine are obtained in the form of a yellow solid melting at 298-300°C.

EXAMPLE 11

Carrying out the reaction under the conditions of Example 9, but starting from 1.8 g of 1-cyclopropyl-3-ethoxycarbonyl-7,8,9-trifluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine, 1.1 g of 1-cyclopropyl-7,8,9-trifluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 304°C.

The 1-cyclopropyl-3-ethoxycarbonyl-7,8,9-trifluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine can be prepared in the following manner:

4.12 g of cyclopropylamine are added in the course of 5 minutes to a solution of 7 g of ethyl 2-(2-chloro-6,7,8-trifluoroquinoline-3-carbonyl)-3-dimethylamino acrylate in 100 cm$^3$ of trichloromethane kept at a temperature close to 20°C and the mixture is stirred for a further 4 hours at this temperature. The reaction mixture is concentrated under reduced pressure (20 kPa) at about 50°C. The oily residue obtained is taken up in 100 cm$^3$ of ethanol and 3 g of DBU. The mixture is heated to 80°C and kept at this temperature, with stirring, for 1 hour and a half. After cooling to about 20°C, the insoluble matter is drained and washed with twice
30 cm$^3$ of ethanol and twice 30 cm$^3$ of diisopropyl ether. 4.5 g of 1-cyclopropyl-3-ethoxycarbonyl-7,8,9-trifluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine are obtained in the form of a colourless solid melting at 260°C.

**EXAMPLE 12**

A suspension of 6 g of 8-chloro-3-ethoxycarbonyl-1-ethoxymethyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine in 120 cm$^3$ of water, 120 cm$^3$ of ethanol and 47.5 cm$^3$ of 2 N aqueous potassium hydroxide solution is heated, with stirring, at a temperature close to 75°C for 2 hours and a half. A small amount of insoluble matter is removed by filtering at the same temperature. After cooling to about 20°C, 6 cm$^3$ of acetic acid are added to the filtrate. The precipitate obtained is drained, washed with 3 times 20 cm$^3$ of water and recrystallized from 60 cm$^3$ of dimethylformamide. 4 g of 8-chloro-1-ethoxymethyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid which decomposes at 285°C.

The 8-chloro-3-ethoxycarbonyl-1-ethoxymethyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine is prepared in the following manner:

A suspension of 6 g of 8-chloro-3-ethoxycarbonyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine and 5.16 g of potassium carbonate in 120 cm$^3$ of dimethylformamide is heated at a temperature close to 110°C for 1 hour. After
cooling to about 15°C, 5.44 cm³ of chloromethyl ethyl ether are added and the mixture is stirred for 5 hours at between 15 and 20°C. The reaction mixture is concentrated to dryness under reduced pressure (20 kPa) at about 60°C. The residue is taken up in 3 times 150 cm³ of trichloromethane. The combined organic extracts are filtered in order to remove the insoluble matter. The filtrate is dried over magnesium sulphate and concentrated under reduced pressure (20 kPa) at about 40°C. The residue is recrystallized from 55 cm³ of dimethylformamide. 5.6 g of 8-chloro-3-ethoxycarbonyl-1-ethoxymethyl-7-fluoro-4-oxo-1,4-dihydrobenzo[b][1,8]naphthyridine are obtained in the form of a beige solid melting at 261°C.

The 8-chloro-3-ethoxycarbonyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine was prepared in the following manner:

A mixture of 11.3 g of ethyl 2-(2,7-dichloro-6-fluoroquinoline-3-carbonyl)-3-dimethylaminoacrylate and 5.65 g of 3-amino-1,2,4-triazine in 60 cm³ of trichloromethane is stirred for 16 hours at a temperature close to 20°C. The reaction mixture is concentrated to dryness under reduced pressure (20 kPa) at a temperature close to 30°C. The residue is taken up in 60 cm³ of ethanol and 5.6 g of DBU and the mixture is heated at a temperature close to 75°C for 20 hours. After cooling to 20°C, the insoluble matter is drained and washed with twice 40 cm³ of ethanol. 6.1 g of 8-chloro-3-
ethoxycarbonyl-7-fluoro-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine are obtained in the form of a
brown solid which decomposes at 378-380°C and is used for the
subsequent steps without further purification.

EXAMPLE 13

A suspension of 5.75 g of 8-chloro-3-ethoxycarbonyl-
7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine in 60
cm³ of 17.5 % hydrochloric acid is heated, with stirring, at
a temperature close to 100°C for 30 minutes. After cooling to
about 20°C, the insoluble matter is drained and washed with 3
times 20 cm³ of ethanol and 3 times 20 cm³ of diethyl ether.
3.05 g of 8-chloro-7-fluoro-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in
the form of a beige solid which decomposes at 416°C.

EXAMPLE 14

A suspension of 8 g of 3-ethoxycarbonyl-1-ethyl-7,8-
difluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine in 80
cm³ of 17.5 % hydrochloric acid and 80 cm³ of acetic acid is
heated, with stirring, at a temperature close to 100°C for 1
hour and 30 minutes. After cooling to about 20°C, the
insoluble matter is drained, washed with 3 times 20 cm³ of
water and recrystallized from 50 cm³ of dimethylformamide.
6.3 g of 1-ethyl-7,8-difluoro-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in
the form of a yellow solid melting at 330°C.

The 3-ethoxycarbonyl-1-ethyl-7,8-difluoro-4-oxo-1,4-
dihydro-benzo[b][1,8]naphthyridine was prepared under the following conditions:

A solution, at about 2°C, of 14.6 g of ethylamine in 200 cm³ of ethanol is added, in the course of 10 minutes, at between 2 and 5°C, with stirring, to a suspension of 20 g of ethyl 2-(2-chloro-6,7-difluoroquinoline-3-carbonyl)-3-dimethylamino acrylate in 200 cm³ of ethanol at about 2°C, the mixture is stirred for a further 40 minutes at between 2 and 5°C and the temperature is then allowed to rise to about 20°C in the course of 2 hours. After 24 hours at about 20°C, the insoluble matter is drained and washed with twice 30 cm³ of ethanol and twice 50 cm³ of diisopropyl ether. 16.35 g of 3-ethoxycarbonyl-1-ethyl-7,8-difluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine are obtained in the form of a beige solid melting at 290°C.

EXAMPLE 15

8-Chloro-7-fluoro-1-(2-fluoroethyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Example 9 but starting from 2.2 g of 8-chloro-3-ethoxycarbonyl-7-fluoro-1-(2-fluoroethyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine. After recrystallizing twice from 10 cm³ of dimethylformamide each time, 1.4 g of 8-chloro-7-fluoro-1-(2-fluoroethyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 310°C.

8-Chloro-3-ethoxycarbonyl-7-fluoro-1-(2-fluoroethyl)-
4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine is prepared in the following manner:

2.7 cm$^3$ of triethylamine are added to a suspension of 1.9 g of 2-fluoroethylamine hydrochloride in 25 cm$^3$ of trichloromethane. 3.5 g of ethyl 2-(2,7-dichloro-6-fluoroquinoline-3-carbonyl)-3-dimethylaminoacrylate are added to the solution obtained at about 20°C. After stirring at this temperature for 16 hours, the solution is concentrated to dryness under reduced pressure (20 kPa) at about 50°C. The residue is taken up in 20 cm$^3$ of ethanol and 3 cm$^3$ of triethylamine and heated at about 75°C, with stirring, for 2 hours. After cooling to about 20°C the insoluble matter is drained and washed with twice 10 cm$^3$ of ethanol and twice 10 cm$^3$ of diisopropyl ether. 1.9 g of 8-chloro-3-ethoxycarbonyl-7-fluoro-1-(2-fluoroethyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine are obtained in the form of a yellow solid melting at 268°C, which is used for the subsequent step without further purification.

The products according to the invention can be used under the conditions described below by way of example:

**REFERENCE EXAMPLE 1**

A suspension of 3.5 g of 8-chloro-7-fluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 4.6 g of 2-methylpiperazine in 40 cm$^3$ of pyridine is heated at a temperature close to 115°C, with stirring, for 13 hours. The reaction mixture is concentrated to dryness under
reduced pressure (20 kPa) at 60°C. The residue is twice taken up with 30 cm³ of ethanol and concentrated under reduced pressure under the above conditions. The solid obtained is taken up in 60 cm³ of water and 10 cm³ of 30% aqueous potassium hydroxide solution. The aqueous phase is washed with twice 100 cm³ of trichloromethane, 10.28 g of methanesulphonic acid are added and the aqueous phase is again washed with twice 100 cm³ of trichloromethane. 10 cm³ of 30% aqueous potassium hydroxide solution are added. The precipitate formed is drained and washed with 3 times 10 cm³ of water and twice 10 cm³ of ethanol. 2.7 g of 7-fluoro-1-methyl-8-((3-methyl-1-piperazinyl)-4-oxo-1,4-dihydrobenzo[b][1,8]napthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 360-363°C.

REFERENCE EXAMPLE 2

7-Fluoro-1-methyl-4-oxo-8-((1-piperazinyl)-1,4-dihydrobenzo[b][1,8]napthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 1 but starting from 10 g of 8-chloro-7-fluoro-1-methyl-4-oxo-1,4-dihydrobenzo[b][1,8]napthyridine-3-carboxylic acid and 28 g of piperazine in 100 cm³ of pyridine. 5.5 g of 7-fluoro-1-methyl-4-oxo-8-((1-piperazinyl)-1,4-dihydrobenzo[b][1,8]napthyridine-3-carboxylic acid hemihydrate are obtained in the form of a yellow solid melting at 370-375°C.

REFERENCE EXAMPLE 3

7-Fluoro-1-methyl-8-((4-methyl-1-piperazinyl)-4-oxo-1,4-
dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under conditions analogous to Reference Example 1 but starting from 5 g of 8-chloro-7-fluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 16 g of 1-methylpiperazine in 50 cm$^3$ of pyridine. After concentrating the reaction mixture under reduced pressure, 25 cm$^3$ of acetic acid are added to the residue, which is suspended in 100 cm$^3$ of water. A very small amount of insoluble matter is removed by filtration through diatomaceous silica for filtration. 200 cm$^3$ of 3 N aqueous potassium hydroxide solution are added to the filtrate and a very small amount of insoluble matter is again removed by filtration through diatomaceous silica for filtration. 5 cm$^3$ of acetic acid are added to the filtrate. The precipitate formed is drained and washed with 3 times 50 cm$^3$ of water. After recrystallizing twice from 17 cm$^3$ of dimethylformamide each time, 3.2 g of 7-fluoro-1-methyl-8-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 356°C.

REFERENCE EXAMPLE 4

8-(4-Ethyl-1-piperazinyl)-7-fluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions described below in Reference Example 5 but starting from 1.85 g of 8-chloro-7-fluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]-
naphthyridine-3-carboxylic acid and 2.75 g of 1-ethyl-piperazine in 20 cm³ of pyridine. 1.3 g of 8-(4-ethyl-1-piperazinyl)-7-fluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 285-286°C.

REFERENCE EXAMPLE 5

7-Fluoro-8-[4-(2-hydroxyethyl)-1-piperazinyl]-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 1 but starting from 1.6 g of 8-chloro-7-fluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 6.8 g of 1-(2-hydroxyethyl)-piperazine in 16 cm³ of pyridine. After concentrating the reaction mixture to dryness under reduced pressure, the residue is taken up in 50 cm³ of water. The mixture is brought to pH 6.9 by adding 0.4 cm³ of acetic acid. The precipitate obtained is drained, washed with twice 10 cm³ of water and recrystallized twice from 10 cm³ of dimethylformamide. 1.1 g of 7-fluoro-8-[4-(2-hydroxyethyl)-1-piperazinyl]-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 275-276°C.

REFERENCE EXAMPLE 6

8-(3,5-Dimethyl-1-piperazinyl)-7-fluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 3 but
starting from 1.7 g of 8-chloro-7-fluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 2.5 g of 2,6-dimethylpiperazine in 20 cm³ of pyridine. 1.1 g of 8-(3,5-dimethyl-1-piperazinyl)-7-fluoro-1-methyl-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid hemihydrate are obtained in the form of a yellow solid melting at 294-295°C.

REFERENCE EXAMPLE 7

1-Ethyl-7-fluoro-8-(1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 5, but starting from 1.6 g of 8-chloro-1-ethyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 4.3 g of piperazine in 20 cm³ of pyridine. After recrystallizing 3 times from, in total, 300 cm³ of dimethylformamide, 0.94 g of 1-ethyl-7-fluoro-8-(1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid trihydrate is obtained in the form of a yellow solid melting at 320-322°C.

REFERENCE EXAMPLE 8

1-Ethyl-7-fluoro-8-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 5, but starting from 1.6 g of 8-chloro-1-ethyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 4.5 g of 4-methylpiperazine in 16 cm³ of pyridine. After recrystallizing 4 times from, in total, 120 cm³ of
dimethylformamide, 1.2 g of 1-ethyl-7-fluoro-8-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 285-286°C solvated by 1% of water.

REFERENCE EXAMPLE 9

1-Ethyl-7-fluoro-8-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 1 but starting from 2.1 g of 8-chloro-1-ethyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid, 20 cm³ of pyridine and 2.4 g of 2-methylpiperazine.

After taking up in ethanol and concentrating to dryness under reduced pressure (20 kPa at 50°C), the solid residue is taken up in 20 cm³ of water and 10 cm³ of 2 N potassium hydroxide solution. The aqueous solution obtained is washed with twice 20 cm³ of trichloromethane, 10 cm³ of acetic acid are added and the mixture is again washed with twice 40 cm³ of trichloromethane. 23 cm³ of 4.5 N potassium hydroxide solution are added and the suspension obtained is heated to a temperature close to 90°C. After cooling to a temperature close to 20°C, the precipitate is drained and washed with 3 times 10 cm³ of water and twice 10 cm³ of ethanol. After recrystallizing twice from 120 cm³ of dimethylformamide each time, 1.7 g of 1-ethyl-7-fluoro-8-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in
the form of a yellow solid melting at 310-312°C.

REFERENCE EXAMPLE 10

1-Ethyl-8-(4-ethyl-1-piperazinyl)-7-fluoro-4-oxo-1,4-
dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is

prepared under the conditions of Reference Example 5 but
starting from 1.6 g of 8-chloro-1-ethyl-7-fluoro-4-oxo-1,4-
dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 2.3
g of 1-ethylpiperazine in 16 cm³ of pyridine. 1.4 g of
1-ethyl-8-(4-ethyl-1-piperazinyl)-7-fluoro-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in
the form of a yellow solid melting at 287-288°C, solvated by
1.6 % of water.

REFERENCE EXAMPLE 11

1-Ethyl-7-fluoro-8-[4-(2-hydroxyethyl)-1-
piperazinyl]-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-
carboxylic acid is prepared under the conditions of Reference
Example 5 but starting from 1.6 g of 8-chloro-1-ethyl-7-
fluoro-4-oxo-1,4-dihydro-benzo[b][1,8] naphthyridine-3-
carboxylic acid and 2.6 g of 1-(2-hydroxyethyl)-piperazine in
16 cm³ of pyridine. 1.3 g of 1-ethyl-7-fluoro-8-[4-(2-
hydroxyethyl)-1-piperazinyl]-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in
the form of a yellow solid melting at 264-265°C.

REFERENCE EXAMPLE 12

7-Fluoro-1-methylamino-4-oxo-8-(1-piperazinyl)-1,4-
dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is
prepared under the conditions of Reference Example 5 but starting from 2.25 g of 8-chloro-7-fluoro-1-methylamino-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 2.4 g of piperazine in 30 cm$^3$ of pyridine. After recrystallizing 3 times from, in total, 400 cm$^3$ of dimethylformamide, 0.82 g of 7-fluoro-1-methylamino-4-oxo-8-(1-piperazinyl)-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is obtained in the form of a deep yellow solid melting at 322-324°C, solvated by 13.6 % of dimethylformamide.

**REFERENCE EXAMPLE 13**

7-Fluoro-1-methylamino-8-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under conditions analogous to Reference Example 1 but starting from 1.93 g of 8-chloro-7-fluoro-1-methylamino-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid, 2.4 g of 1-methylpiperazine and 20 cm$^3$ of pyridine. After recrystallizing twice from 15 cm$^3$ of dimethylformamide each time, 0.9 g of 7-fluoro-1-methylamino-8-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is obtained in the form of a yellow solid melting at 263-264°C.

**REFERENCE EXAMPLE 14**

7-Fluoro-1-methylamino-8-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 5 but
starting from 3.2 g of 8-chloro-7-fluoro-1-methylamino-4-oxo-1,4-dihydro-benzo[b][1,8] naphthyridine-3-carboxylic acid and 4 g of 2-methylpiperazine in 40 cm³ of pyridine. The crude product obtained is taken up in 30 cm³ of water and 7 cm³ of 2 N aqueous potassium hydroxide solution. A very small amount of insoluble matter is removed by filtration through diatomaceous silica. The filtrate is washed with twice 20 cm³ of diethyl ether and the product is then precipitated by adding 3.5 cm³ of 4 N methanesulphonic acid. The precipitate obtained is drained and washed with 3 times 20 cm³ of water and 3 times 20 cm³ of ethanol. 2.2 g of 7-fluoro-1-methylamino-8-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a deep yellow solid melting at 343-345°C, solvated by 3.7 of water.

REFERENCE EXAMPLE 15
1-Cyclopropyl-7-fluoro-4-oxo-8-(1-piperazinyl)-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 5 but starting from 1 g of 8-chloro-1-cyclopropyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 2.6 g of piperazine in 10 cm³ of pyridine. 0.6 g of 1-cyclopropyl-7-fluoro-4-oxo-8-(1-piperazinyl)-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid dihydrate is obtained in the form of a yellow solid melting at 342-343°C.
REFERENCE EXAMPLE 16

1-Cyclopropyl-7-fluoro-8-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 5 but starting from 1 g of 8-chloro-1-cyclopropyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 3 g of 1-methylpiperazine in 10 cm$^3$ of pyridine. After recrystallizing from 10 cm$^3$ of dimethylformamide, 0.63 g of 1-cyclopropyl-7-fluoro-8-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is obtained in the form of a yellow solid melting at 250°C.

REFERENCE EXAMPLE 17

1-Cyclopropyl-7-fluoro-8-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 1 but starting from 1 g of 8-chloro-1-cyclopropyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 3 g of 2-methylpiperazine in 10 cm$^3$ of pyridine. The pure product is obtained after a supplementary purification by recrystallization from 200 cm$^3$ of dimethylformamide. 0.5 g of 1-cyclopropyl-7-fluoro-8-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid hemihydrate is obtained in the form of a yellow solid melting at 343°C.

REFERENCE EXAMPLE 18

1-Cyclopropyl-8-(4-ethyl-1-piperazinyl)-7-fluoro-4-
oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 5 but starting from 2 g of 8-chloro-1-cyclopropyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 2.74 g of 1-ethyl-piperazine in 20 cm³ of pyridine. The pure product is isolated after a first recrystallization from 105 cm³ of ethanol containing 25 % of dimethylformamide followed by a second recrystallization from 75 cm³ of ethanol containing 50 % of dimethylformamide. 0.67 g of 1-cyclopropyl-8-(4-ethyl-1-piperazinyl)-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is obtained in the form of a yellow-green solid melting at 254°C.

REFERENCE EXAMPLE 19

1-Cyclopropyl-7-fluoro-8-[4-(2-hydroxyethyl)-1-piperazinyl]-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under conditions analogous to Reference Example 5 but starting from 4 g of 8-chloro-1-cyclopropyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 6.2 g of 1-(2-hydroxyethyl)-piperazine in 40 cm³ of pyridine. The reaction mixture is heated for 22 hours at a temperature close to 115°C. The pure product is isolated after recrystallizing 3 times from 3 times 200 cm³ of ethanol containing 10 % of dimethylformamide each time. 0.94 g of 1-cyclopropyl-7-fluoro-8-[4-(2-hydroxyethyl)-1-piperazinyl]-4-
oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is obtained in the form of a yellow solid melting at 255°C.

**REFERENCE EXAMPLE 20**

7-Fluoro-4-oxo-8-(1-piperazinyl)-1-tert.-butyl-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 5 but starting from 1.7 g of 8-chloro-7-fluoro-4-oxo-1-tert.-butyl-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 4.3 g of piperazine in 20 cm³ of pyridine. The pure product is obtained after a single recrystallization from 20 cm³ of dimethylformamide. 1.25 g of 7-fluoro-4-oxo-8-(1-piperazinyl)-1-tert.-butyl-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are isolated in the form of a yellow solid melting at 290°C, solvated by 4.5% of water.

**REFERENCE EXAMPLE 21**

A solution of 1.15 g of 7-fluoro-1-methyl-8-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid in 1.35 cm³ of 98% formic acid and 3.25 cm³ of a 30% aqueous solution of formaldehyde is heated at a temperature close to 100°C for 2 hours. The reaction mixture is concentrated under reduced pressure (20 kPa) at 50°C and 5 cm³ of water are then added, the solution obtained is brought to pH 7 by adding 0.5 cm³ of 2 N aqueous potassium hydroxide solution and heated at a
temperature close to 100°C for 2 minutes. The product, which crystallizes, is drained at 20°C and washed with twice 10 cm³ of water. The crude product obtained is recrystallized twice from 10 cm³ of dimethylformamide each time. 0.55 g of 8-(3,4-dimethyl-1-piperazinyl)-7-fluoro-1-methyl-4-oxo-1,4-dihydrobenzo[b][1,8]naphthyridine-3-carboxylic acid is obtained in the form of a yellow solid melting at 306-308°C.

REFERENCE EXAMPLE 22

8-(3,4-Dimethyl-1-piperazinyl)-1-ethyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 21 but starting from 2.3 g of 1-ethyl-7-fluoro-8-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid, 2.26 cm³ of 98 % formic acid and 5.6 cm³ of a 30 % aqueous solution of formaldehyde. 1.75 g of 8-(3,4-dimethyl-1-piperazinyl)-1-ethyl-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 293-294°C.

REFERENCE EXAMPLE 23

1-Cyclopropyl-8-(3,4-dimethyl-1-piperazinyl)-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is prepared under the conditions of Reference Example 21 but starting from 1.9 g of 1-cyclopropyl-7-fluoro-8-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid, 1.38 cm³ of formic acid and 3.30 cm³ of a 30 % aqueous solution of
formaldehyde. After recrystallizing the crude product from 50 cm$^3$ of ethanol, 1.3 g of 1-cyclopropyl-8-(3,4-dimethyl-1-piperazinyl)-7-fluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 219°C.

REFERENCE EXAMPLE 24

A suspension of 0.47 g of 1-cyclopropyl-7,8-difluoro-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid and 0.6 g of 1-methylpiperazine in 7 cm$^3$ of dimethyl sulphoxide is heated at a temperature close to 80°C for 15 minutes. The reaction mixture is poured into 25 cm$^3$ of water and 9 cm$^3$ of N hydrochloric acid are added. The solid obtained is drained and washed with 3 times 5 cm$^3$ of water. After recrystallizing once from a mixture of 4.5 cm$^3$ of ethanol and 4.5 cm$^3$ of dimethylformamide, 0.29 g of 1-cyclopropyl-7-fluoro-8-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid is obtained in the form of a yellow solid melting at 250°C.

REFERENCE EXAMPLE 25

A suspension of 2 g of 7,8-difluoro-1-methoxy-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid in 2.8 g of piperazine and 40 cm$^3$ of dimethyl sulphoxide is stirred for 15 minutes at a temperature close to 40°C. After cooling to about 20°C, the reaction mixture is poured into 150 cm$^3$ of water and 27.75 cm$^3$ of 2 N methanesulphonic acid are added. A very small amount of insoluble matter is removed.
by filtration through diatomaceous silica. 15 cm³ of 2 N aqueous potassium hydroxide solution are added to the solution obtained. The precipitate formed is drained, washed with 3 times 15 cm³ of water and taken up in 100 cm³ of 5 dimethylformamide and the mixture is heated, with stirring, for 10 minutes at a temperature close to 150°C. The suspension is cooled to about 100°C; the insoluble matter is drained and taken up in 100 cm³ of ethanol and the mixture is heated at a temperature close to 75°C for 1 hour. The insoluble matter is drained at about 50°C and washed with 40 cm³ of the same solvent at the same temperature as above. 1.8 g of 7-fluoro-1-methoxy-4-oxo-8-(1-piperazinyl)-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid are obtained in the form of a brown solid melting at 298-300°C, solvated by 2.4 % of water.

REFERENCE EXAMPLE 26

A suspension of 0.93 g of 7,8-difluoro-1-methoxy-4-oxo-1,4-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid in 0.6 g of 1-methylpiperazine and 20 cm³ of dimethyl sulphoxide is heated at a temperature close to 80°C for 5 minutes. After cooling to about 20°C, the reaction mixture is poured into 30 cm³ of water, 1.5 cm³ of 2 N methanesulphonic acid are added and the product is drained and washed with 3 times 5 cm³ of water. After recrystallizing from 30 cm³ of dimethylformamide containing 30 % of ethanol, 0.55 g of 7-fluoro-1-methoxy-8-(4-methyl-1-piperazinyl)-4-oxo-1,4-
dihydro-benzob[1,8]naphthyridine-3-carboxylic acid is obtained in the form of a brown solid melting at 270°C.

**REFERENCE EXAMPLE 27**

A suspension of 2 g of 8-chloro-7-fluoro-1-methyl-4-oxo-1,4-dihydro-benzob[1,8]naphthyridine-3-carboxylic acid in 7.44 g of 2,2-dimethylpiperazine and 20 cm$^3$ of pyridine is heated at a temperature close to 115°C for 44 hours. Carrying out the reaction as described above in Reference Example 1, 1.6 g of 8-(3,3-dimethyl-1-piperazinyl)-7-fluoro-4-oxo-1,4-dihydro-benzob[1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid, solvated by 4.9 % of water, melting at 362-365°C.

**REFERENCE EXAMPLE 28**

A suspension of 4 g of 7,8,9-trifluoro-1-methyl-4-oxo-1,4-dihydro-benzob[1,8]naphthyridine-3-carboxylic acid in 60 cm$^3$ of dimethyl sulphoxide and 3 g of 1-methylpiperazine is heated at 80°C for 1 hour and a half. After cooling to about 20°C, 150 cm$^3$ of water are added. 18 cm$^3$ of 10 % acetic acid are added to the solution obtained. The precipitate formed is drained, washed with 3 times 50 cm$^3$ of water and recrystallized from 50 cm$^3$ of dimethylformamide. 4 g of 7,9-difluoro-1-methyl-8-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-benzob[1,8]naphthyridine-3-carboxylic acid are obtained in the form of a yellow solid melting at 316°C.
REFERENCE EXAMPLE 29

A suspension of 2 g of 6, 7, 8-trifluoro-1-methoxy-4-
6 o xo-1, 4-dihydro-benzo[b][1, 8]naphthyridine-3-carboxylic acid
and 2.8 g of piperazine in 40 cm³ of dimethyl sulphoxide is
heated, with stirring, at about 50°C for 45 minutes. After
cooling to a temperature close to 20°C, the suspension
obtained is poured into 100 cm³ of water to which 9.22 g of
methanesulphonic acid has been added. A small amount of
insoluble matter is removed by filtration through
diatomaceous silica. 32 cm³ of 2 N aqueous potassium
hydroxide solution are added to the filtrate. The precipitate
obtained is drained, washed with 3 times 50 cm³ of water and
recrystallized from 80 cm³ of dimethylformamide. 1.4 g of
7, 9-difluoro-1-methoxy-4-oxo-8-(1-piperazinyl)-1, 4-dihydro-
benzo[b][1, 8]naphthyridine-3-carboxylic acid are obtained in
the form of a yellow solid melting at 305-308°C.

REFERENCE EXAMPLE 30

A suspension of 1.2 g of 8-chloro-7-fluoro-1-
(2-fluoroethyl)-4-oxo-1, 4-dihydro-
benzo[b][1, 8]naphthyridine-3-carboxylic acid in 12 cm³ of
pyridine and 3.52 g of 1-methylpiperazine is heated, with
stirring, at a temperature close to 110°C for 6 hours. After
treatment under the conditions described in Reference Example
3, 0.6 g of 7-fluoro-1-(2-fluoroethyl)-8-(4-methyl-1-
piperazinyl)-4-oxo-1, 4-dihydro-benzo[b][1, 8]naphthyridine-3-
carboxylic acid is obtained in the form of a yellow solid
melting at 306-308°C.

The present invention also provides pharmaceutical compositions for topical use in human and veterinary medicine and which contain, as active product, at least one product of formula (I), in which R is other than a protective radical, in the pure form (in the free form or in the form of a salt) or in combination with one or more compatible and pharmaceutically acceptable diluents or adjuvants.

Solid compositions for topical application which can be used include powders, creams, pommades or gels. In these compositions the active product of general formula (I) is mixed with one or more inert diluents or adjuvants, such as lactose, cellulose derivatives or talc for example. These compositions can also contain other substances, such as, for example, fatty acids and their derivatives or fatty substances of animal, vegetable or synthetic origin.

Liquid compositions which can be used include emulsions, solutions and suspensions which are pharmaceutically acceptable for topical application, containing inert diluents such as water, oils (e.g. paraffin oil, white petroleum jelly oil or olive oil) or organic esters. These compositions can also contain adjuvants such as wetting agents, emulsifiers, dispersants or stabilizers.

The compositions can also be prepared in the form of solid compositions which can be dissolved at the time of use.

The compositions containing a product of general
formula (I) are particularly useful for the treatment of cutaneous infections by staphylococci.

In general, the compositions contain concentrations of from 0.01 % to 1 %.

The following Example illustrates a composition for topical application containing a product of formula (I).

EXAMPLE

- 1-cyclopropyl-7,8-difluoro-4-oxo-
- 1,4-dihydro-benzo[b][1,8]naphthyridine-
- 3-carboxylic acid ....................... 1 g
- zinc oxide .............................. 1.5 g
- talc .................................... q.s. 100 g

The products of formula (I) can also be used as preservatives or disinfectants for organic or inorganic materials. In particular in the dyestuffs, fatty matter, paper, wood and polymer industries or in the textile industry, the foodstuffs industry or water treatment. The compositions intended for preservation or as disinfectants and containing a compound of general formula (I) in the pure form or in the form of a combination with compatible diluents or adjuvants, also fall within the scope of the present invention.
The claims defining the invention are as follows:

1. A benzo[b][1,8]naphthyridine derivative of the general formula:

\[
\begin{array}{c}
\text{F} \\
\text{Hal} \\
\text{R'} \\
\text{R}
\end{array}
\]

in which R represents hydrogen, alkyl, fluoroalkyl, cycloalkyl of 3 to 6 carbon atoms, alkoxy, alkylamino, or an amine protective radical, and either Hal represents fluorine, chlorine or bromine and R' represents hydrogen or Hal and R' both represent fluorine, the aforesaid alkyl radicals being straight-chain or branched and containing 1 to 4 carbon atoms each, its metal salts and its addition salts with nitrogenous bases.

2. A benzo[b][1,8]naphthyridine derivative according to Claim 1, in which

- R represents hydrogen, alkyl of 1 to 4 carbon atoms, fluoroethyl, cyclopropyl, methoxy or methylamino, and either Hal represents fluorine or chlorine and R' represents hydrogen, or Hal and R' both represent fluorine, its metal salts and its addition salts with nitrogenous bases.

3. A benzo[b][1,8]naphthyridine derivative according to
Claim 1, which is 7,8-difluoro-1-methyl-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine-3-carboxylic acid, its metal salts
and its addition salts with nitrogenous bases.

4. A benzo[b][1,8]naphthyridine derivative according to
Claim 1, which is 8-chloro-7-fluoro-1-methyl-4-oxo-1,4-
dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid, its
metal salts and its addition salts with nitrogenous bases.

5. A benzo[b][1,8]naphthyridine derivative according to
Claim 1, which is 1-methyl-4-oxo-7,8,9-trifluoro-1,4-dihydro-
benzo[b][1,8]naphthyridine-3-carboxylic acid, its metal salts
and its addition salts with nitrogenous bases.

6. A benzo[b][1,8]naphthyridine derivative according to
Claim 1, which is 7,8-difluoro-1-methoxy-4-oxo-1,4-dihydro-
benzo[b][1,8]naphthyridine-3-carboxylic acid, its metal salts
and its addition salts with nitrogenous bases.

7. A benzo[b][1,8]naphthyridine derivative according to
Claim 1, which is 1-cyclopropyl-7,8-difluoro-4-oxo-1,4-
dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid, its
metal salts and its addition salts with nitrogenous bases.

8. Process for the preparation of a
benzo[b][1,8]naphthyridine derivative of the general formula:
in which \( R \) represents hydrogen, alkyl, fluoroalkyl, cycloalkyl of 3 to 6 carbon atoms, alkoxy, alkylamino, or an amine protective radical, and either \( \text{Hal} \) represents fluorine, chlorine or bromine and \( R' \) represents hydrogen or 5 Hal and \( R' \) both represent fluorine, the aforesaid alkyl radicals being straight-chain or branched and containing 1 to 4 carbon atoms each, its metal salts and its addition salts with nitrogenous bases, which comprises converting an ester of formula:

\[
\begin{align*}
\text{Hal} & \\
R' & \\
R & \\
\text{COOAlk} & \\
\end{align*}
\]

10 in which \( \text{Hal} \) and \( R' \) are as hereinbefore defined, \( R \) represents hydrogen, alkyl, fluoroalkyl, cycloalkyl of 3 to 6 carbon atoms, alkoxy, alkylamino or protected alkylamino (the aforesaid alkyl radicals containing 1 to 4 carbon atoms each in a straight or branched chain), and \( \text{Alk} \) is alkyl of 1 to 4 carbon atoms in a straight or branched chain, by any method known for converting an ester into an acid without affecting the remainder of the molecule and then, if appropriate, introducing an amine-protective radical when it is desired to obtain a benzo[b][1,8]naphthyridine derivative in which \( R \) is such a radical, or the removal of the protective group from
the alkylamino radical, and optionally converting the product
obtained into a metal salt or an addition salt with a
nitrogenous base.

9. Process according to Claim 8 substantially as
described in any one of Examples 1 to 15.

10. A benzo[b][1,8]naphthyridine according to Claim 1
when produced by the process claimed in Claim 8 or 9.

11. A pharmaceutical composition for topical application,
preservative or disinfectant which comprises at least one
benzo[b][1,8]naphthyridine according to any one of Claims 1
to 7 or 10, in which R is not an amine-protective radical, in
combination with one or more compatible and pharmaceutically
acceptable diluents or adjuvants.
12. The steps, features, compositions and compounds disclosed herein or referred to or indicated in the specification and/or claims of this application, individually or collectively, and any and all combinations of any two or more of said steps or features.

DATED this TWELFTH day of JANUARY 1990

Laboratoire Roger Bellon

by DAVIES & COLLISON
Patent Attorneys for the applicant(s)