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(54) INTERMEDIATES FOR THE PRODUCTION OF NAPHTHYRIDINE-3-CARBOXYLIC ACID DERIVATIVES

ZWISCHENPRODUKTE FÜR DIE HERSTELLUNG VON NAPHTHYRIDIN-3-CARBONSÄURE-DERIVATEN

INTERMEDIAIRES DESTINES A LA PRODUCTION DE DERIVES DE QUINILONE D'ACIDE CARBOXYLIQUE

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(56) References cited:
EP-A- 0 688 772 **WO-A-98/42705**

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EP 1 212 321 B1

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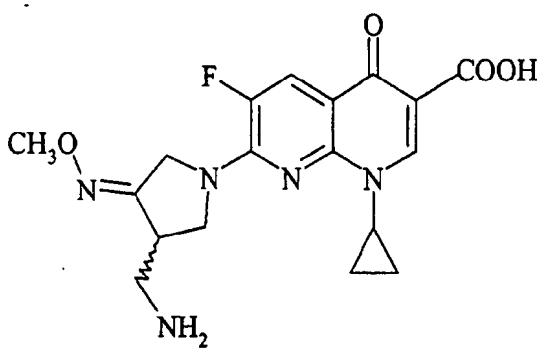
Description

[0001] The present invention relates to novel compounds which are of use in the production of pharmaceutically active compounds, for example, quinolone carboxylic acid derivatives having antibacterial activity.

[0002] EP 688772 discloses novel naphthyridine carboxylic acid derivatives having antibacterial activity, including anhydrous (R,S)-7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid of the formula:

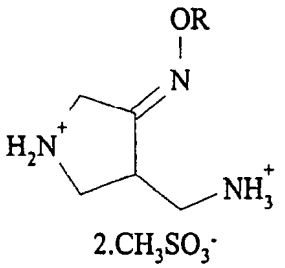


[0003] WO 98/42705 discloses (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate and hydrates thereof including the sesquihydrate.

[0004] PCT/KR99/00099 (published after the priority date of the present application) discloses a process for the production of 4-aminomethyl-3-alkoxyiminopyrrolidines and salts thereof from aminomethylpyrrolidin-3-one and the corresponding alkoxylamine. Suitable salts of the 4-aminomethyl-3-alkoxyiminopyrrolidines are described as the hydrochloride, trifluoroacetate and sulfate salts.

[0005] The present invention relates to novel 4-aminomethyl-3-alkoxyiminopyrrolidine salts which are of use in the synthesis of pharmaceutically active compounds.

[0006] According to the invention there is provided a compound of formula (I):

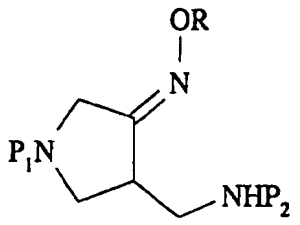


(I)

wherein R is C_{1-4} alkyl or C_{1-4} haloalkyl.

[0007] The compound of formula (I) is preferably 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate.

[0008] According to a further aspect of the invention there is provided a process for the production of a compound of formula (I) which comprises reaction of a compound of formula (II):



(II)

with methanesulfonic acid,

wherein R is as defined for formula **(I)** and P_1 and P_2, which may be the same or different, are suitable amino protecting groups which are removable by treatment with methanesulfonic acid.

[0009] The preferred protecting group for both P_1 and P_2 is t-butoxycarbonyl.

[0010] The reaction of the compound of formula (II) and methanesulfonic acid is suitably carried out at a temperature between 10°C and 50°C, more preferably at a temperature of 40-45°C.

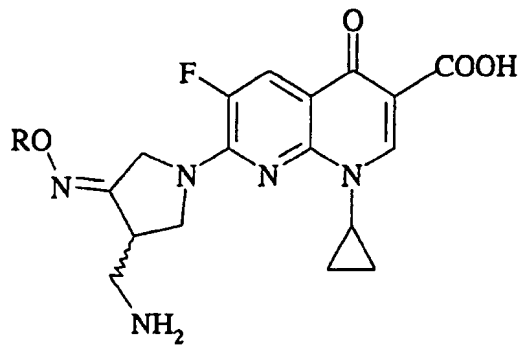
[0011] The amount of methanesulfonic acid used to effect the deprotection of the compound of formula (II) is suitably 2 to 4 equivalents. For example, 2.4 equivalents, suitably used at a temperature of between 35°C and 40°C; or 3 equivalents, suitably used at ambient temperature. More preferably 2.5 equivalents used at a temperature of 40-45°C.

[0012] The reaction is suitably carried out in a solvent, for example, an alcohol such as methanol, ethanol, isopropanol, or n-propanol, dichloromethane, acetonitrile, acetone, methyl iso-butyl ketone, DME, THF, tert-butylmethyl ether, dioxane or ethyl acetate or a mixture of any of these. The solvent is preferably methanol. Suitably, up to 10 equivalents by volume of solvent may be used, e.g. about 4 equivalents.

[0013] The compounds of formula (II) may be prepared by the processes described in US 5,633,262, EP 688772 and PCT/KR99/00099.

[0014] The compounds of formula (I) are useful as an intermediates for preparing quinolone antibacterials particularly those described in US 5,633,262 and EP 688772.

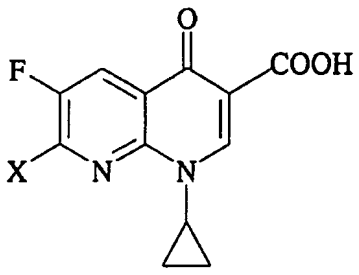
[0015] Thus according to a further aspect of the invention there is provided a process for the production of a compound of formula (III), or a pharmaceutically acceptable salt and/or hydrate thereof:



(III)

wherein R is as defined for formula (I), which process comprises:

reaction of a compound of formula (I) with a compound of formula (IV):



(IV)

wherein X is a suitable leaving group, e.g. a halogen atom, preferably chlorine; and wherein the reaction of the compounds of formulae (I) and (IV) is conducted in the presence of a base;

and optionally forming a pharmaceutically acceptable salt and/or hydrate of the compound of formula (III).

[0016] Other suitable leaving groups X will be apparent to those skilled in the art.

[0017] The reaction of the compounds of formulae (I) and (IV) is conducted in the presence of a base e.g. triethylamine. The reaction of the compounds of formulae (I) and (IV) is preferably conducted in a solvent, e.g. acetonitrile, an aqueous solvent such as aqueous acetonitrile or an aqueous alcohol and more preferably water. When water is used as solvent for this process the resulting compound of formula (III) is of superior quality to that obtained using other solvents. This leads to an improvement in the quality of the resulting drug substance as well as a process that may offer environmental advantages. Further details regarding the reaction of the compounds of formula (I) and (IV) can be found in US 5,633,262 and EP 688772. The compounds of formula (IV) may be synthesisied as described in US 5,633,262 and EP 688772.

[0018] The compound of formula (III) produced according to this aspect of the invention is preferably (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof, preferably the sesquihydrate, as disclosed in WO 98/42705. The methanesulfonate and hydrates thereof may be synthesised from the free acid as described in WO 98/42705 and WO 00/17199.

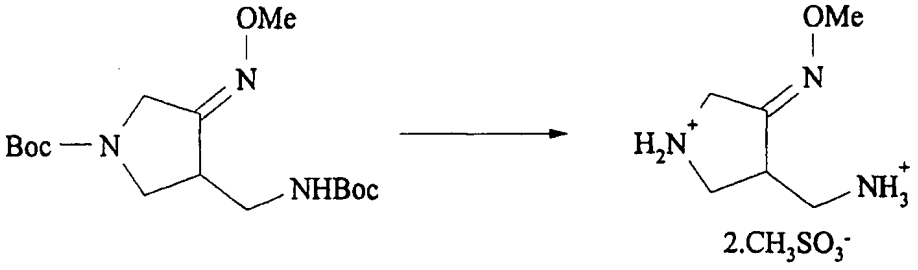
[0019] The compounds of the invention have the advantage that they are stable, i.e. not hygroscopic. They can be isolated from the reaction in higher yield and purity than the corresponding dihydrochloride or free base. The dimesylate salts can be recrystallised if necessary, whereas the corresponding dihydrochloride or free base has not been successfully recrystallised. The dimesylate salts can be used to produce quinolone antibacterials of high purity and several advantages result from using this intermediate. For example, when the resulting drug substance is (R,S)-7-(3-aminomethyl-4-syn-methoxyimino-pyrrolidin- 1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof, it has improved colour and significantly lower levels of high molecular weight impurites compared to the drug substance produced using the corresponding dihydrochloride or free base as intermediate.

[0020] The invention is illustrated by the following examples.

Example 1

Synthesis of 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate

[0021]



[0022] A solution of 1-(N-t-butoxycarbonyl)-4-(t-butoxycarbonylaminomethyl) pyrrolidin-3-methoxime (100g) in meth-

anol (660mL) at 15-20°C under nitrogen was treated with methanesulfonic acid (56.4mL) over 5 min keeping the temperature below 30°C. The solution was stirred at 20-25°C for 16-20hrs. During this time the product precipitated forming a thick suspension. The product was isolated by filtration, washed with methanol (165ml) and dried under vacuo at 25°C to give the title compound 84g (86%).

m.p. 189-193°C;

m/z: 144 $(M+H)^+$;

^1H NMR (400MHz, d_6-DMSO) δ: 9.27, (2H, brs), 7.95 (3H, brs), 4.01 (1H, d), 3.92 (1H, d), 3.87 (3H, s), 3.69 (1H, m), 3.26 (2H, m), 3.26 (2H, m), 3.15 (1H, m), 3.08 (1H, m), 2.39 (6H, s);

Analysis: C, 28.64%, H, 6.25%, N, 12.46%; $C_8H_{21}N_3O_7S_2$ requires C, 28.65%, H, 6.31%, N, 12.53%.

Example 2

Synthesis of 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate

[0023] A solution of 1-(N-t-butoxycarbonyl)-4-(t-butoxycarbonylaminomethyl) pyrrolidin-3-methoxime (100g) in methanol (400mL) at 20°C under nitrogen was treated with methanesulfonic acid (47mL, 70g, 2.5 equiv) over 15 min keeping the temperature below 25°C. The solution was heated to 40-45°C over 30 mins and maintained at this temperature for 4-5 hrs. During this time the product precipitated forming a thick suspension. The crude product was isolated by filtration under nitrogen and washed with methanol (200mL). The crude product was suspended in methanol (4 volumes, approx. 360mL) and heated to reflux for 1 hr. After cooling to 20°C the suspension was stirred for 1 hour. The product was filtered, washed with methanol (2 volumes, approx. 180ml) and dried under vacuum at 40°C to give the title compound 73.8g (78%).

Characterising data were consistent with a standard sample of the title compound.

Example 3

Synthesis of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

[0024] Triethylamine (5.1ml) was added to 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (3.05g) in water (25ml) at 15-20°C and the mixture stirred for 20 min. 4-Aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate (3.86g) was added, followed by water (5ml), and the mixture stirred at 20-25°C for 17¾ hours. The resulting product was filtered and the cake washed with water (30ml) followed by ethanol (30ml) and dried under vacuum at 50°C to give the title compound as a white solid (4.23g). (102% as is, 86% on assay). Characterising data were consistent with a standard sample of the title compound.

Example 4

Synthesis of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate

[0025] A solution of methanesulfonic acid (0.33 g, 3.43 mmol) in dichloromethane (1 ml) was added to a suspension of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1 -yl)-1 -cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (1.5 g at 89.9% purity, 3.46 mmol) in a mixture of dichloromethane (23.2 ml) and ethanol (2.7 ml) at 30°C. The mixture was stirred at 30°C for 3 hours then cooled to 20°C and filtered. The cake was washed with dichloromethane (20 ml) and dried at 50°C under vacuum to give the title compound (1.71 g) (102% as is, 91 % on assay). Characterising data were consistent with a standard sample of the title compound.

Example 5

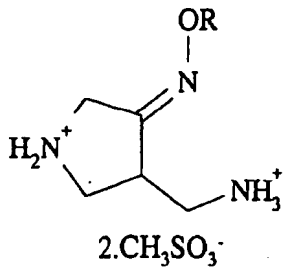
Synthesis of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate

[0026] (R,S)-7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate (27.5 g at 91% purity, 51.4 mmol) was stirred in a mixture of isopropanol (150 ml) and water (75 ml) and heated until a clear solution was obtained (52°C). The solution was cooled to 34°C and seed crystals of (R,S)-7-(3-aminomethyl-4-syn-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate added. The resulting suspension

was allowed to cool to 25°C over 1 hour and stirred for 18 hours. The slurry was cooled to 0 - 4°C, stirred for 2 hours, then filtered and the cake washed with isopropanol (30 ml). The product was sucked dry for 2 hours and then further dried at 50°C under vacuum. The dried product was exposed to the atmosphere to give the sesquihydrate, 22.9 g (92%). Characterising data were consistent with a standard sample of the title compound.

Claims

1. A compound of formula (I):

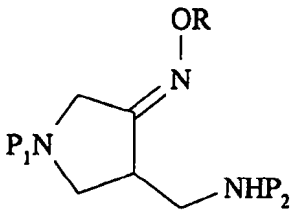


(I)

wherein R is C_{1-4} alkyl or C_{1-4} haloalkyl.

2. A compound of formula (I) as claimed in claim 1, which is 4-Aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate.

3. A process for the production of a compound of formula (I) as defined in claim 1 or 2 which comprises reaction of a compound of formula (II):



(II)

with methanesulfonic acid,
wherein R is as defined for formula (I) as defined in claim 1 or 2; and P_1 and P_2, which may be the same or different, are suitable amino protecting groups which are removable by treatment with methanesulfonic acid.

4. The process according to claim 3 wherein P_1 and P_2 are both t-butyloxycarbonyl.

5. The process according to claim 3 or 4 wherein the amount of methanesulfonic acid used to effect the deprotection of the compound of formula (II) is 2 to 4 equivalents.

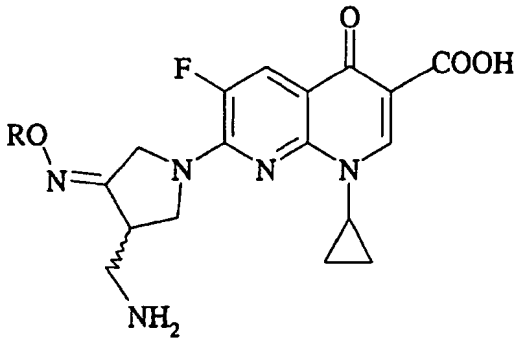
6. The process according to any one of claims 3 to 5 wherein the reaction is carried out at a temperature between 10°C and 50°C.

7. The process according to any one of claims 3 to 6 wherein the reaction is carried out in a solvent being methanol, ethanol, isopropanol, n-propanol, dichloromethane, acetonitrile, acetone, methyl iso-butyl ketone, DME, THF, tert-butylmethyl ether, dioxane, ethyl acetate, or a mixture of any of these.

8. The process according to any one of claims 3 to 6 wherein the reaction is carried out in a solvent being methanol.

9. The process according to any one of claims 3 to 8 wherein the reaction is carried out in a solvent, and wherein from about 4 equivalents to 10 equivalents by volume of the solvent are used.

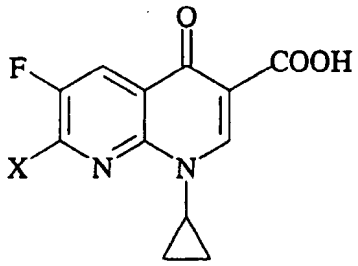
10. A process for the production of a compound of formula (III), or a pharmaceutically acceptable salt and/or hydrate thereof:



(III)

wherein R is as defined for formula (I) in claim 1 or 2, which process comprises:

reaction of a compound of formula (I), as defined in claim 1 or 2, with a compound of formula (IV):



(IV)

wherein X is a suitable leaving group, and wherein the reaction of the compounds of formulae (I) and (IV) is conducted in the presence of a base;

and optionally forming a pharmaceutically acceptable salt and/or hydrate of the compound of formula (III).

11. The process according to claim 10 wherein X is a halogen atom.

12. The process according to claim 10 wherein X is chlorine.

13. The process according to claim 10, 11, or 12 wherein the reaction of the compound of formula (I) and the compound of formula (IV) is conducted in a solvent.

14. The process according to claim 13, wherein the solvent is acetonitrile or an aqueous solvent.

15. The process according to claim 14, wherein the solvent is an aqueous solvent.

16. The process according to any of claims 10 to 15, wherein R is C_1alkyl.

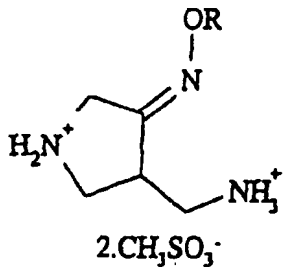
17. The process according to any of claims 10 to 15 wherein the compound of formula (III) is (R,S)-7-(3-aminomethyl-

4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof.

18. The process according to any of claims 10 to 17 comprising producing the compound of formula (I) by a process according to any of claims 3 to 9.

Patentansprüche

1. Verbindung der Formel (I):

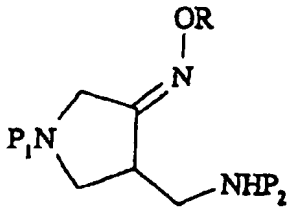


(I)

worin R für C_{1-4}-Alkyl oder C_{1-4}-Haloalkyl steht.

2. Verbindung der Formel (I) nach Anspruch 1, die 4-Aminomethyl-3-methoxyiminopyrrolidinium-dimethansulfonat darstellt.

3. Verfahren zur Herstellung einer Verbindung der Formel (I) wie nach Anspruch 1 oder 2 definiert, das die Reaktion einer Verbindung der Formel (II)



(II)

mit Methansulfonsäure umfasst,
worin R wie für die Formel (I) nach Anspruch 1 oder 2 definiert ist; und P_1 und P_2, die gleich oder unterschiedlich sein können, geeignete Aminoschutzgruppen darstellen, die durch Behandlung mit Methansulfonsäure entfernbar sind.

4. Verfahren nach Anspruch 3, worin P_1 und P_2 beide t-Butyloxycarbonyl darstellen.

5. Verfahren nach Anspruch 3 oder 4, worin die zur Bewirkung der Entschützung der Verbindung der Formel (II) verwendete Methansulfonsäuremenge 2 bis 4 Äquivalente beträgt.

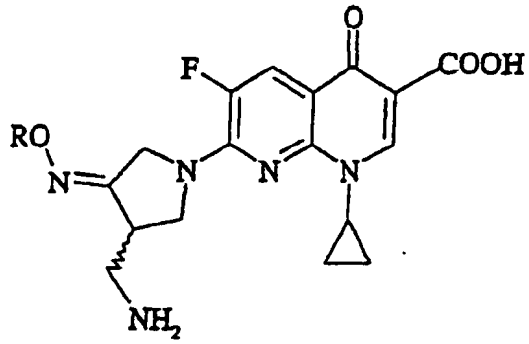
6. Verfahren nach einem der Ansprüche 3 bis 5, worin die Reaktion bei einer Temperatur zwischen 10 °C und 50 °C durchgeführt wird.

7. Verfahren nach einem der Ansprüche 3 bis 6, worin die Reaktion in einem Lösungsmittel durchgeführt wird, das Methanol, Ethanol, Isopropanol, n-Propanol, Dichlormethan, Acetonitril, Aceton, Methyl-iso-butylketon, DME, THF, tert-Butylmethylether, Dioxan, Ethylacetat oder ein Gemisch von jedwedem von diesen darstellt.

8. Verfahren nach einem der Ansprüche 3 bis 6, worin die Reaktion in einem Lösungsmittel durchgeführt wird, bei dem es sich um Methanol handelt.

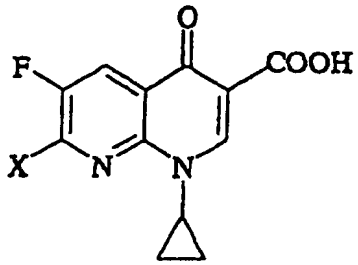
9. Verfahren nach einem der Ansprüche 3 bis 8, worin die Reaktion in einem Lösungsmittel durchgeführt wird und worin von ca. 4 Volumenäquivalente bis 10 Volumenäquivalente des Lösungsmittels verwendet werden.

10. Verfahren zur Herstellung einer Verbindung der Formel (III) oder eines pharmazeutisch verwendbaren Salzes und/oder Hydrates davon:



(III)

worin R wie für die Formel (I) nach Anspruch 1 oder 2 definiert ist, welches Verfahren Folgendes umfasst: Reaktion einer Verbindung der Formel (I), wie nach Anspruch 1 oder 2 definiert, mit einer Verbindung der Formel (IV):



(IV)

worin X eine geeignete Austrittsgruppe darstellt und worin die Reaktion der Verbindungen der Formeln (I) und (IV) in Gegenwart einer Base durchgeführt wird;
und gegebenenfalls Bilden eines pharmazeutisch verwendbaren Salzes und/oder Hydrates der Verbindung der Formel (III).

11. Verfahren nach Anspruch 10, worin X ein Halogenatom darstellt.

12. Verfahren nach Anspruch 10, worin X Chlor darstellt.

13. Verfahren nach Anspruch 10, 11 oder 12, worin die Reaktion der Verbindung der Formel (I) und der Verbindung der Formel (IV) in einem Lösungsmittel durchgeführt wird.

14. Verfahren nach Anspruch 13, worin das Lösungsmittel Acetonitril oder ein wässriges Lösungsmittel darstellt.

15. Verfahren nach Anspruch 14, worin das Lösungsmittel ein wässriges Lösungsmittel darstellt.

16. Verfahren nach einem der Ansprüche 10 bis 15, worin R für C_1-Alkyl steht.

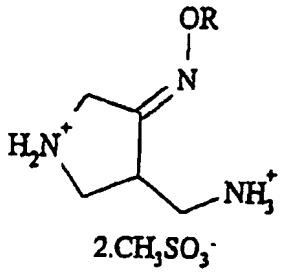
17. Verfahren nach einem der Ansprüche 10 bis 15, worin die Verbindung der Formel (III) (R,S)-7-(3-Aminomethyl-

4-syn-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridin-3-carbonsäure-methansulfonat oder ein Hydrat davon darstellt.

18. Verfahren nach einem der Ansprüche 10 bis 17, umfassend die Herstellung der Verbindung der Formel (I) durch ein Verfahren nach einem der Ansprüche 3 bis 9.

Revendications

1. Composé de formule (I) :

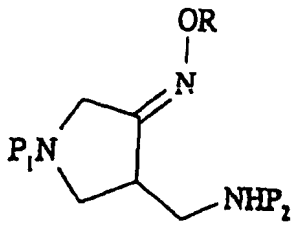


(I)

dans lequel R est un alkyle en C_{1-4} ou un haloalkyle en C_{1-4}.

2. Composé de formule (I) comme revendiqué dans la revendication 1, qui est le diméthanesulfonate de 4-amino-méthyl-3-méthoxyiminopyrrolidinium.

3. Procédé pour la production d'un composé de formule (I) tel que défini dans la revendication 1 ou 2 qui comprend la réaction d'un composé de formule (II):



(II)

avec l'acide méthanesulfonique,
dans lequel R est tel que défini pour la formule (I) telle que définie dans la revendication 1 ou 2; et P_1 et P_2, qui peuvent être les mêmes ou différents, sont des groupements aminoprotecteurs appropriés qui peuvent être enlevés par traitement avec l'acide méthanesulfonique.

4. Procédé selon la revendication 3 dans lequel P_1 et P_2 sont tous deux un t-butyloxycarbonyle.

5. Procédé selon la revendication 3 ou 4 dans lequel la quantité d'acide méthanesulfonique utilisé pour effectuer la déprotection du composé de la formule (II) est de 2 à 4 équivalents.

6. Procédé selon n'importe laquelle des revendications 3 à 5 dans lequel la réaction est effectuée à une température comprise entre 10 et 50°C.

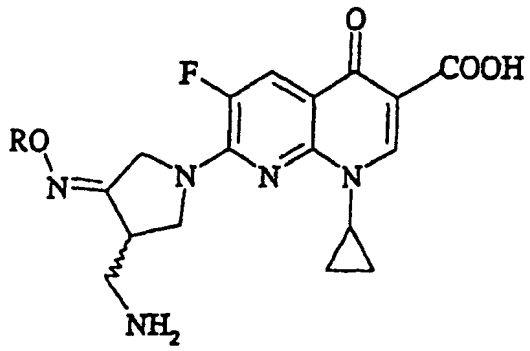
7. Procédé selon n'importe laquelle des revendications 3 à 6 dans lequel la réaction est effectuée dans un solvant

qui est le méthanol, l'éthanol, l'isopropanol, le n-propanol, le dichlorométhane, l'acétonitrile, l'acétone, la méthylisobutylcétone, le DME, le THF, l'éther tert-butylméthylique, le dioxane, l'acétate d'éthyle ou un mélange de n'importe lesquels de ces solvants.

8. Procédé selon n'importe laquelle des revendications 3 à 6 dans lequel la réaction est effectuée dans un solvant qui est le méthanol.

9. Procédé selon n'importe laquelle des revendications 3 à 8 dans lequel la réaction est effectuée dans un solvant, et dans lequel environ de 4 équivalents à 10 équivalents en volume du solvant sont utilisés

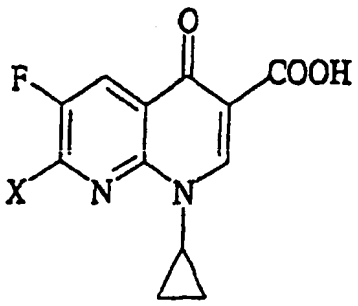
10. Procédé pour la production d'un composé de formule (III), ou d'un sel et/ou hydrate pharmaceutiquement acceptable de celui-ci :



(III)

dans lequel R est tel que défini pour la formule (I) dans la revendication 1 ou 2, lequel procédé comprend :

la réaction d'un composé ayant la formule (I) tel que défini dans la revendication 1 ou 2 avec un composé ayant la formule (IV) :



(IV)

X étant un groupement se détachant approprié, et dans lequel la réaction des substances de formules (I) et (IV) est effectuée en présence d'une base ;
et formant de manière optionnelle un sel et/ou hydrate du composé ayant la formule (III) pharmaceutiquement acceptable.

11. Procédé selon la revendication 10 dans lequel X est un atome d'halogène.

12. Procédé selon la revendication 10 dans lequel X est du chlore.

13. Procédé selon la revendication 10, 11 ou 12 dans lequel la réaction du composé de formule (I) avec le composé de formule (IV) est effectuée dans un solvant.

14. Procédé selon la revendication 13, le solvant étant de l'acétonitrile ou un solvant aqueux.

15. Procédé selon la revendication 14, le solvant étant un solvant aqueux.

16. Procédé selon n'importe laquelle des revendications 10 à 15, R étant un alkyle C_1.

17. Procédé selon n'importe laquelle des revendications 10 à 15, le composé ayant la formule (III) étant le (R,S)-7-(3-aminométhyl-4-syn-méthoxyimino-pyrrolidine-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-acide carboxylique méthanesulfonate ou un hydrate de celui-ci.

18. Procédé selon n'importe laquelle des revendications 10 à 17 comprenant la production du composé de la formule (I) par un procédé selon n'importe laquelle des revendications 3 à 9.