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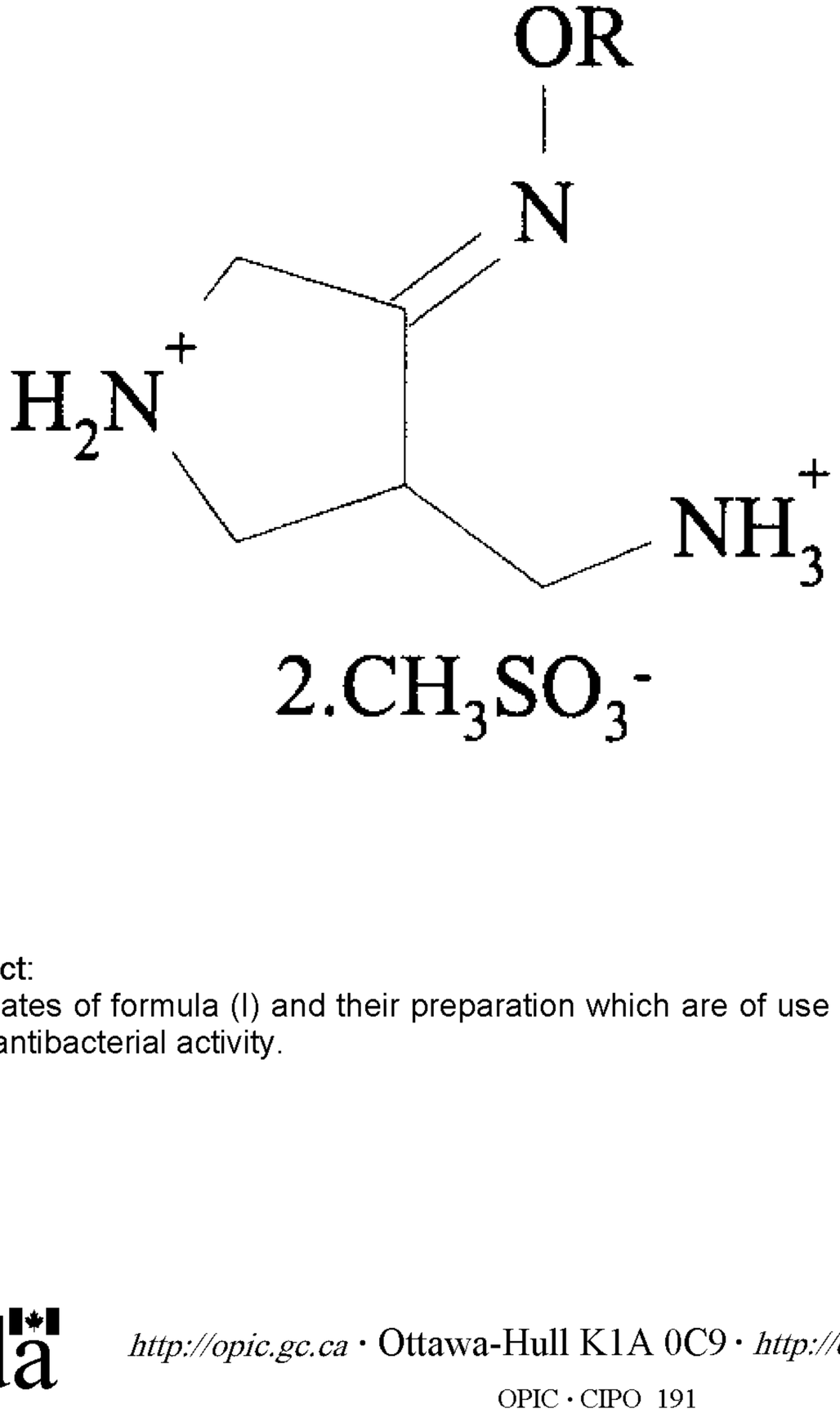
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(54) Titre : INTERMEDIAIRES DESTINES A LA PRODUCTION DE DERIVES D'ACIDE NAPHTHYRIDINE-3-CARBOXYLIQUE

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



(I)

$2.CH_3SO_3^-$

(57) Abrégé/Abstract:
Chemical intermediates of formula (I) and their preparation which are of use in the production of naphthyridine carboxylic acid derivatives having antibacterial activity.

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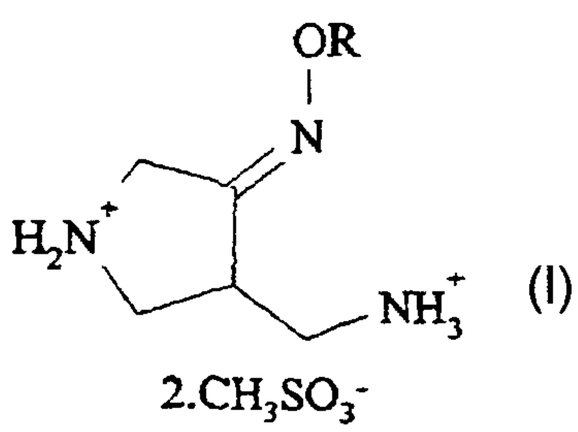
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(54) Title: INTERMEDIATES FOR THE PRODUCTION OF NAPHTHYRIDINE-3-CARBOXYLIC ACID DERIVATIVES



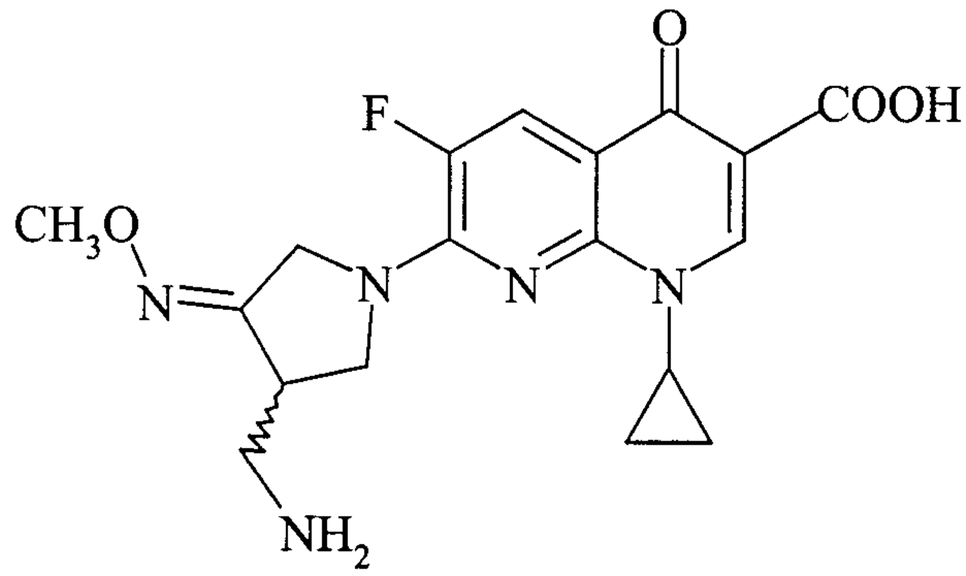
(I)

(57) Abstract: Chemical intermediates of formula (I) and their preparation which are of use in the production of naphthyridine carboxylic acid derivatives having antibacterial activity.

INTERMEDIATES FOR THE PRODUCTION OF QUINOLONE CARBOXYLIC ACID DERIVATIVES

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.

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:

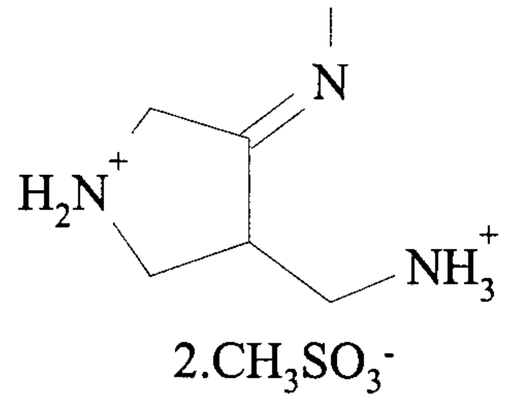


WO 98/42705 discloses (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate and hydrates thereof including the sesquihydrate.

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.

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

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

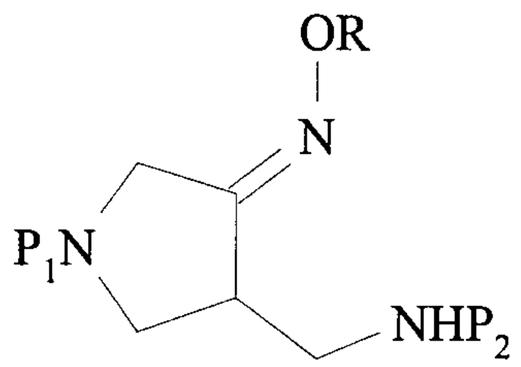


(I)

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

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

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)

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

Suitable protecting groups P_1 and P_2 include any suitable amino protecting groups which are removable by treatment with methanesulfonic acid. The preferred protecting group for both P_1 and P_2 is t-butoxycarbonyl.

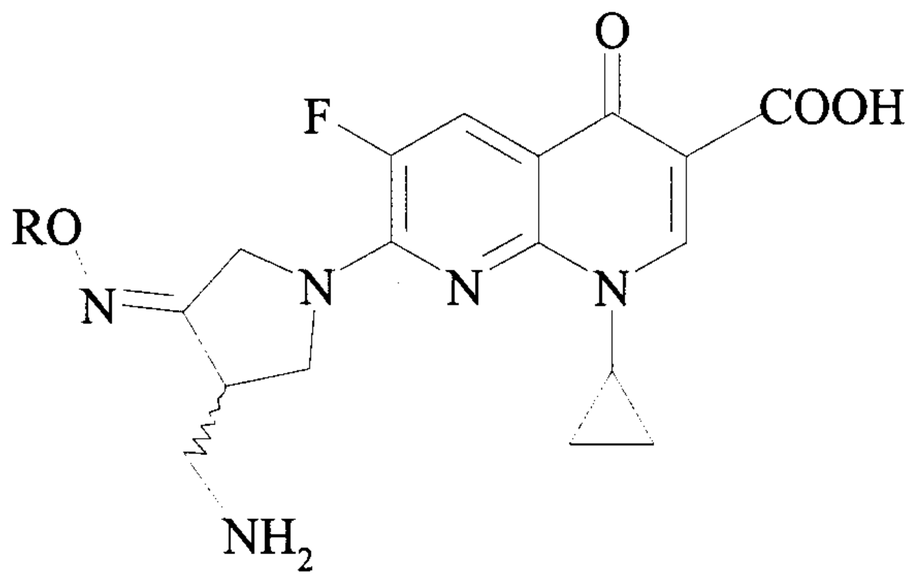
The reaction of the compound of formula (II) and methanesulfonic acid is suitably carried out at a temperature between about 10°C and about 50°C, more preferably at a temperature of 40-45°C.

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.

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.

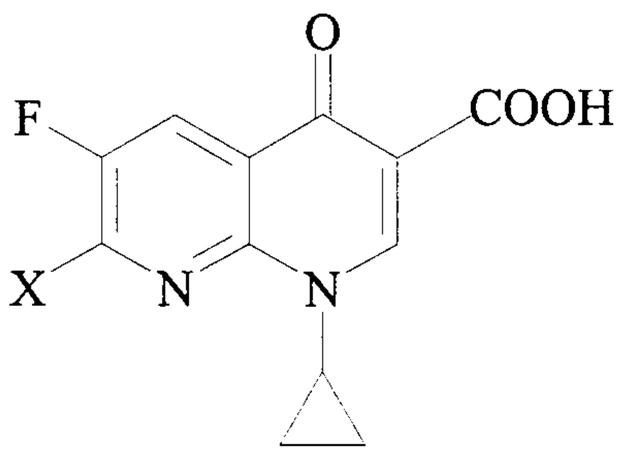
The compounds of formula (II) may be prepared by the processes described in US 5,633,262, EP 688772 and PCT/KR99/00099.

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. 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 comprises reaction of a compound of formula (I), with a compound of formula (IV):



(IV)

wherein X is a leaving group, e.g. a halogen atom, preferably chlorine; and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

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

The reaction of the compounds of formulae (I) and (IV) is preferably 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.

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.

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

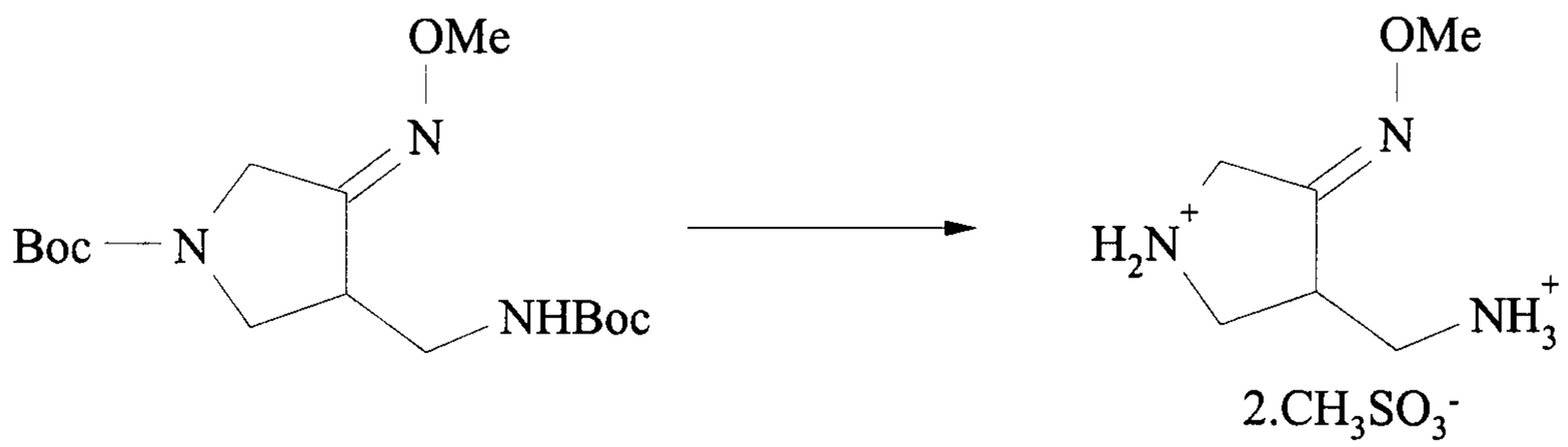
recrystallised if necessary, whereas the corresponding dihydrochloride or free base has not been successfully recrystallised. The dimesylate salts can be used to produce quinolone antibacterials of high purity and several advantages result from using this intermediate. For example, when the resulting 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.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The invention is illustrated by the following examples. However, it should be understood that the examples are intended to illustrate but not in any manner limit the scope of the invention.

Example 1

Synthesis of 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate



A solution of 1-(N-t-butoxycarbonyl)-4-(t-butoxycarbonylaminomethyl) pyrrolidin-3-methoxime (100g) in methanol (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 $(M+H)^+$;

^{1}H 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

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

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-methoxyimino-pyrrolidinium 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

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.

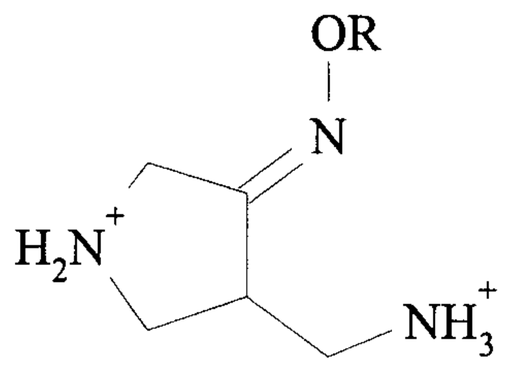
Example 5

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

(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):



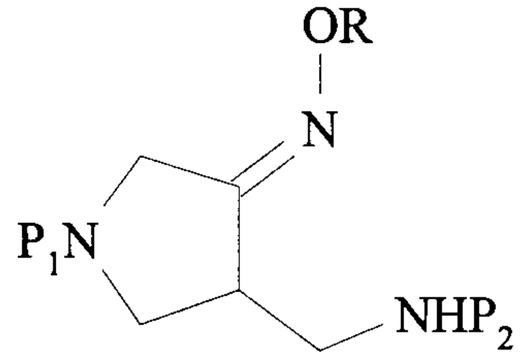
2.$CH_3SO_3^-$

(I)

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

2. 4-Aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate.

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



(II)

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

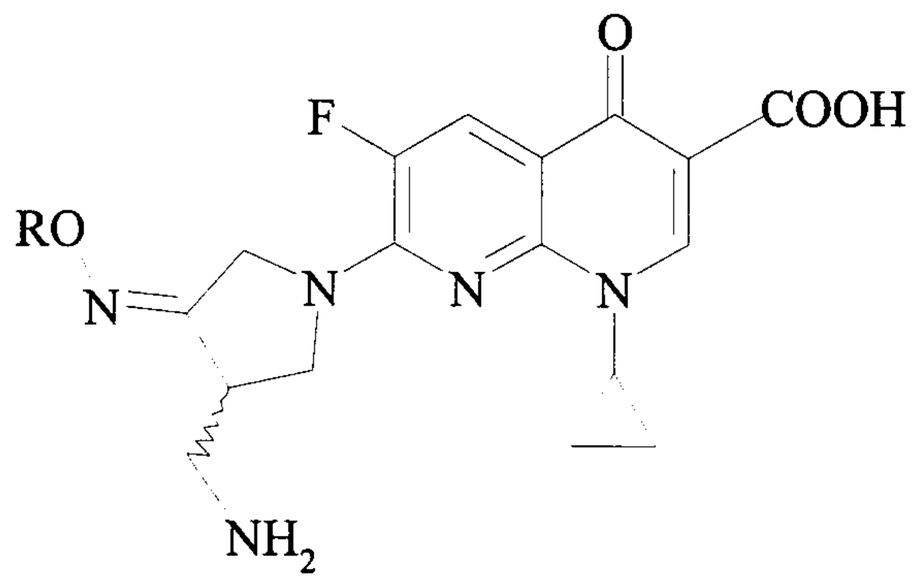
4. The process according to claim 3 wherein P_1 and P_2 are both t-butyloxycarbonyl.

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 about 10°C and about 50°C.

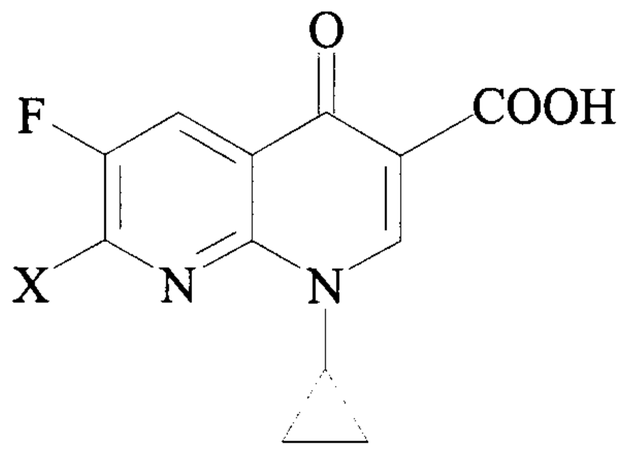
7. The process according to any one of claims 3 to 6 which is carried out in a solvent selected from methanol, ethanol, isopropanol, n-propanol, dichloromethane, acetonitrile, acetone, methyl iso-butyl ketone, DME, THF, tert-butylmethyl ether, dioxane and ethyl acetate.

8. 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, which comprises reaction of a compound of formula (I) as defined in claim 1, with a compound of formula (IV):

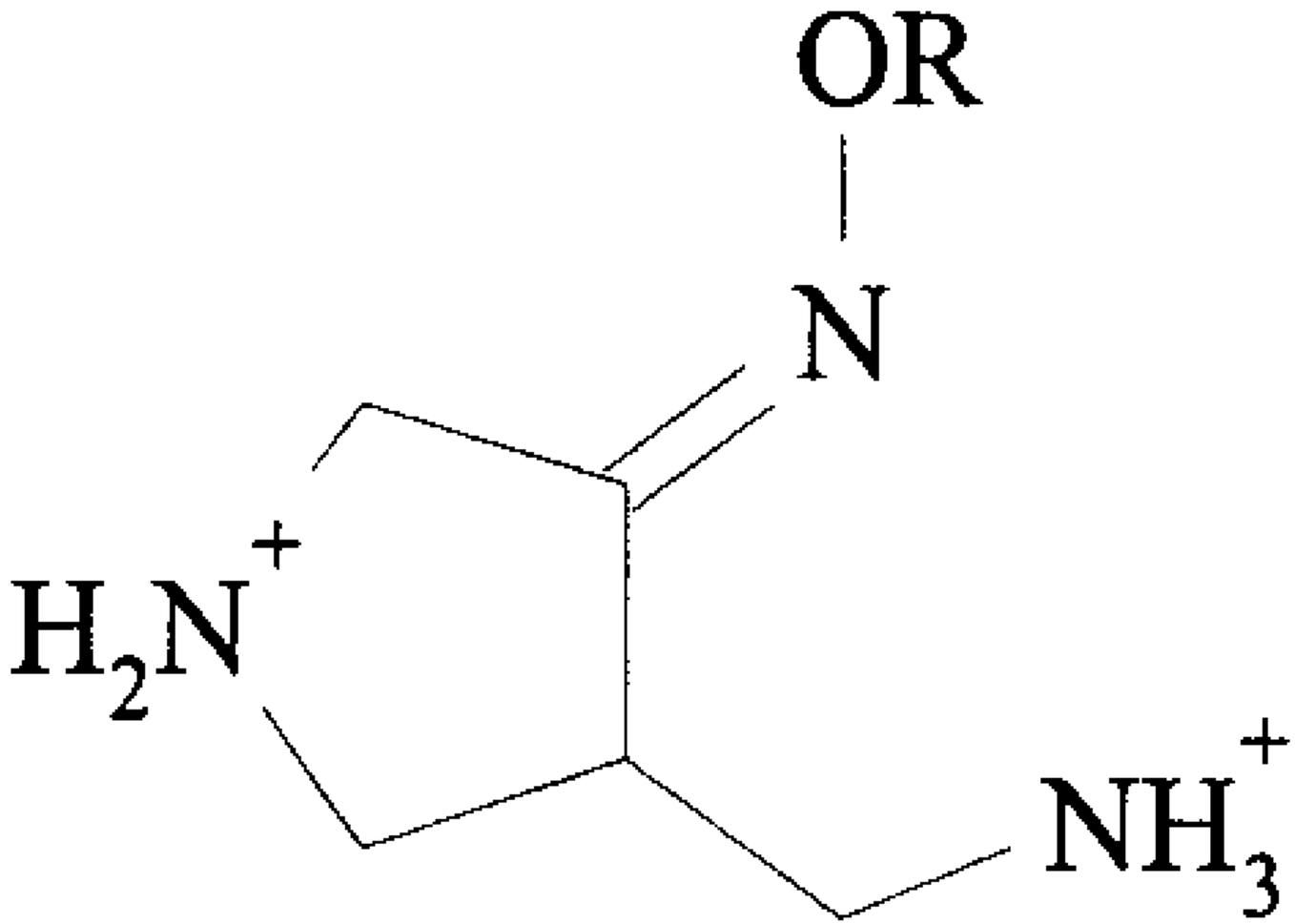


(IV)

wherein X is a leaving group; and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

9. The process according to claim 8 wherein the reaction of the compound of formula (I) and the compound of formula (IV) is conducted in a solvent in the presence of a base.

10. The process according to claim 8 or 9 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.



(I)

$2.CH_3SO_3^-$