Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2137523 C 2007/05/22

(11)(21) 2 137 523

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(22) Date de dépôt/Filing Date: 1994/12/07

(41) Mise à la disp. pub./Open to Public Insp.: 1995/06/11

(45) Date de délivrance/Issue Date: 2007/05/22

(30) Priorité/Priority: 1993/12/10 (DEP 4342186.5)

(51) Cl.Int./Int.Cl. *C07D 498/04* (2006.01),
C07D 215/56 (2006.01), *C07D 401/04* (2006.01),
C07D 413/04 (2006.01), *C07D 417/04* (2006.01),
C07D 471/04 (2006.01)

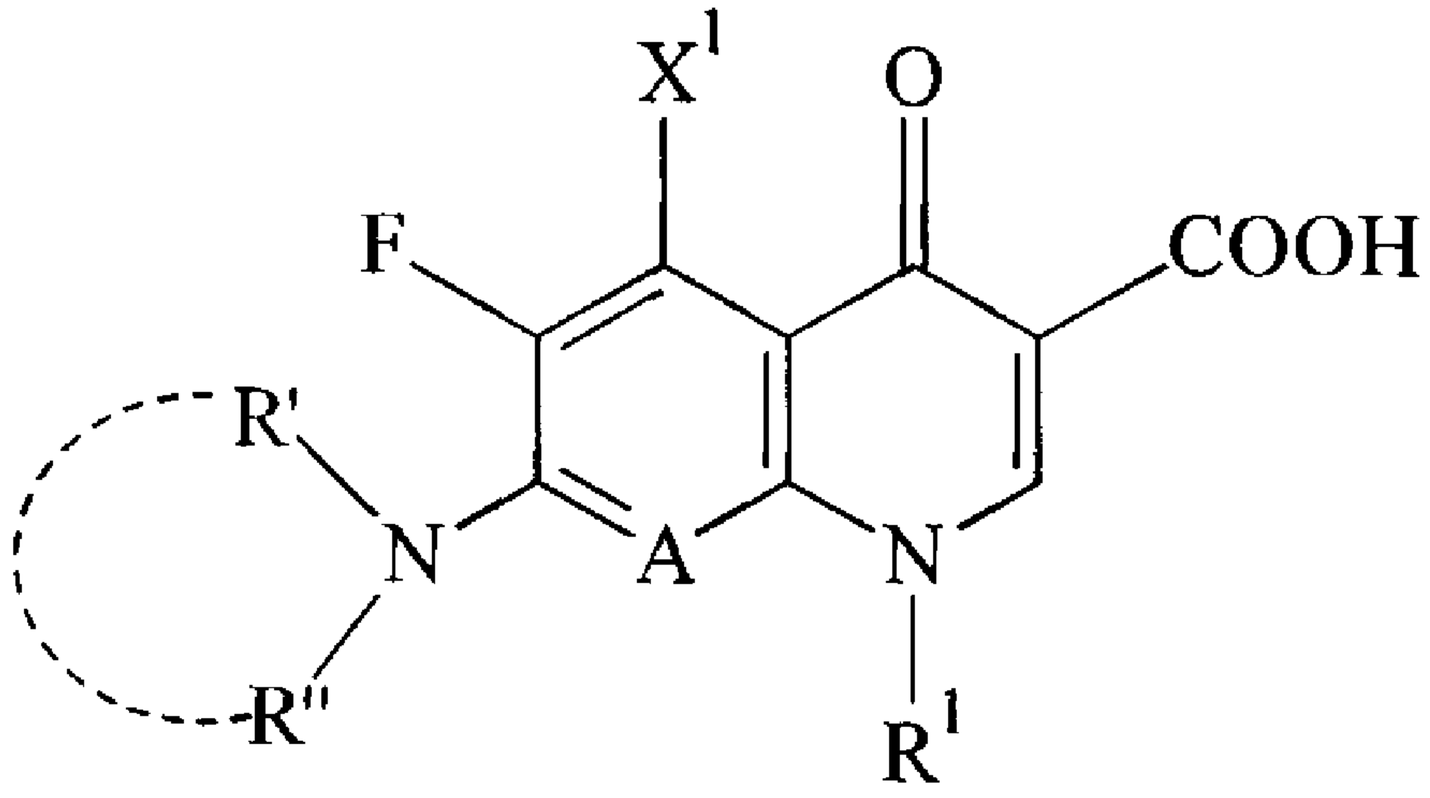
(72) Inventeurs/Inventors:
ZERBES, RUDOLF, DE;
NAAB, PAUL, DE;
FRANCKOWIAK, GERHARD, DE;
DIEHL, HERBERT, DE

(73) Propriétaire/Owner:
BAYER AKTIENGESELLSCHAFT, DE

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : METHODE EN CUVE UNIQUE POUR LA PREPARATION DE DERIVES DE L'ACIDE QUINOLONE-3-CARBOXYLIQUE

(54) Title: ONE-POT PROCESS FOR THE PREPARATION OF 3-QUINOLONECARBOXYLIC ACID DERIVATIVES



(Ia)

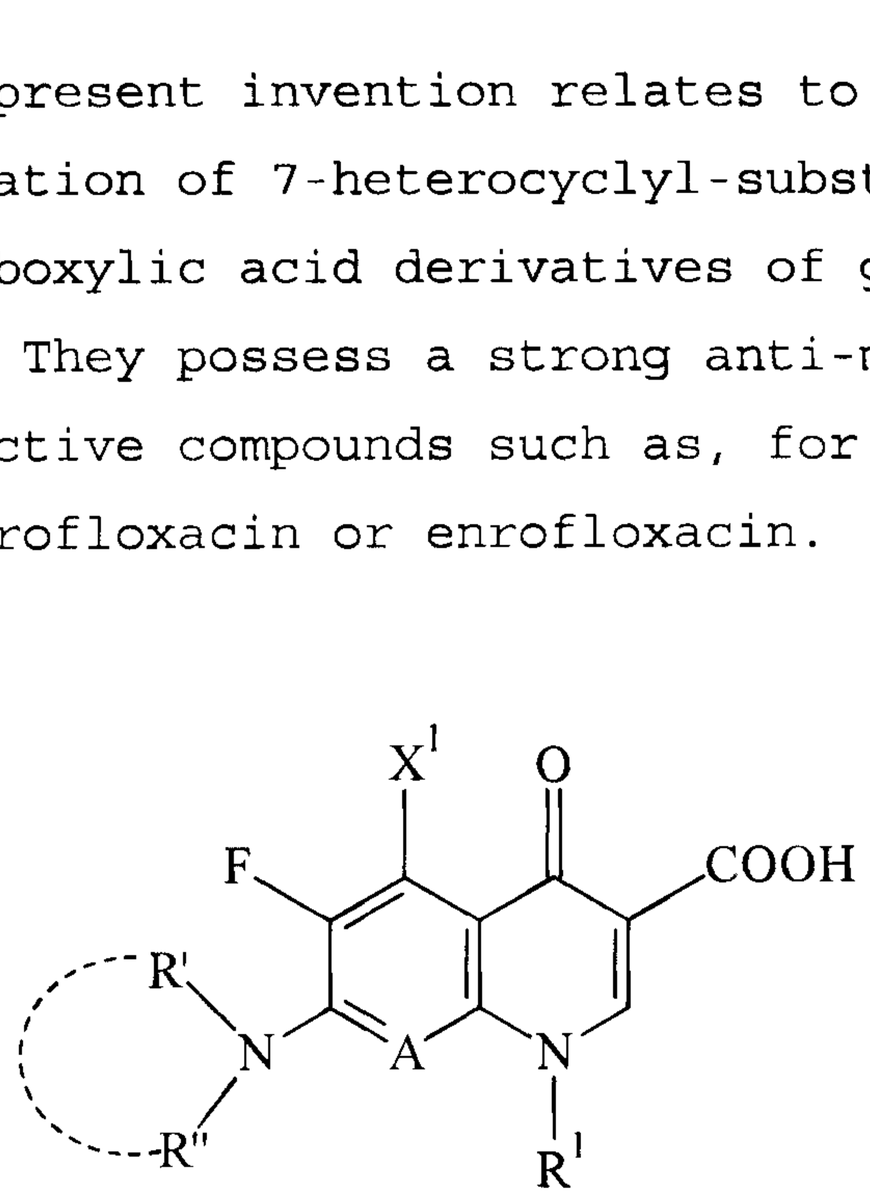
(57) Abrégé/Abstract:
The present invention relates to a one-pot process for the preparation of 7-heterocyclyl-substituted 3-quinolonecarboxylic acid derivatives of general formula (Ia). They possess a strong anti-microbial effect. They include active compounds such as, for example, ofloxacin, ciprofloxacin or enrofloxacin. (see Formula Ia) wherein: R' and R'', together with the nitrogen atom to which they are bonded, form a monocyclic or bicyclic heterocycle which optionally contain further nitrogen, oxygen or sulphur hetero atoms, and which are optionally substituted; A represents CH, CF, CCl, C-OCH_3 or C-CH_3; X^1 represents H, a halogen atom, NH_2 or CH_3; and R^1 represents: (i) C_1-C_3-alkyl or FCH_2CH_2-, or (ii) cyclopropyl or phenyl which are optionally substituted once to three times by a halogen atom.

30725-120

One-pot process for the preparation of 3-quinolone-carboxylic acid derivatives

Abstract

The present invention relates to a one-pot process for the preparation of 7-heterocyclyl-substituted 3-quinolonecarboxylic acid derivatives of general formula (Ia). They possess a strong anti-microbial effect. They include active compounds such as, for example, ofloxacin, ciprofloxacin or enrofloxacin.



(Ia)

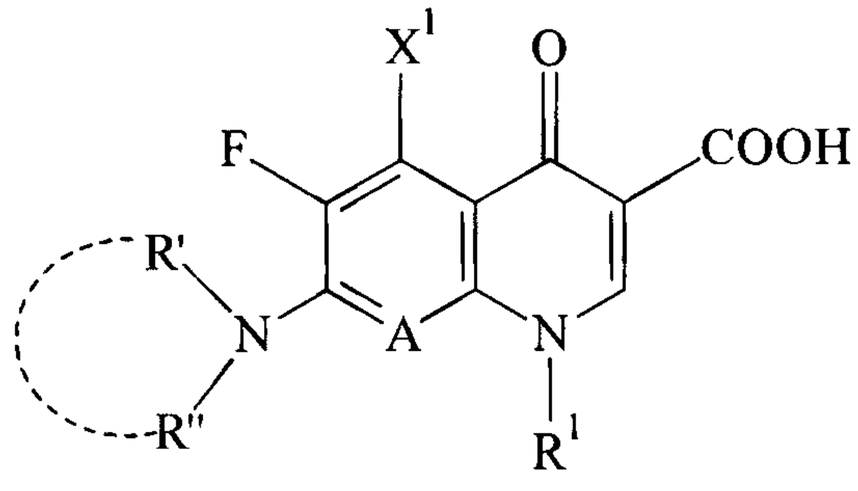
wherein: R' and R'', together with the nitrogen atom to which they are bonded, form a monocyclic or bicyclic heterocycle which optionally contain further nitrogen, oxygen or sulphur hetero atoms, and which are optionally substituted; A represents CH, CF, CCl, C-OCH_3 or C-CH_3; X^1 represents H, a halogen atom, NH_2 or CH_3; and R^1 represents: (i) C_1-C_3-alkyl or FCH_2CH_2-, or (ii) cyclopropyl or phenyl which are optionally substituted once to three times by a halogen atom.

30725-120

The present invention relates to a one-pot process for the preparation of 7-heterocyclyl-substituted 3-quinolonecarboxylic acid derivatives. Compounds of this type are known per se. They possess a strong anti-microbial effect. They include active compounds such as, for example, ofloxacin, ciprofloxacin or enrofloxacin.

Compounds of this class which are to be prepared in accordance with the invention are substituted in the 7 position by heterocycles which, as the hetero atom, contain at least one nitrogen atom, but can, additionally, also contain oxygen, sulphur or additional nitrogen atoms. These heterocycles may also be substituted. Examples of monocyclic substituents which may be mentioned are piperazinyl, N-ethylpiperazinyl, pyrrolidinyl, 3-aminopyrrolidinyl, morpholinyl or thiomorpholinyl.

In one aspect, the invention provides a one-pot process for the preparation of a 3-quinolonecarboxylic acid derivative of the general formula (Ia):

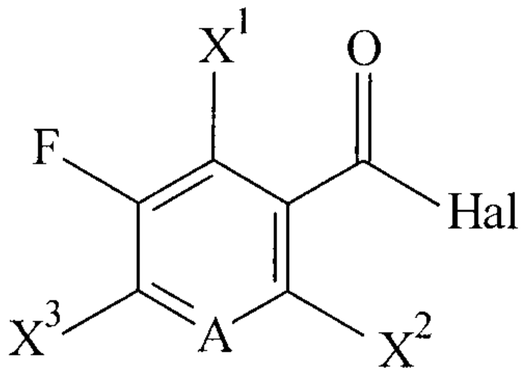


(Ia)

wherein: R' and R'', together with the nitrogen atom to which they are bonded, form a monocyclic or bicyclic heterocycle which optionally contain further nitrogen, oxygen or sulphur hetero atoms, and which are optionally substituted; A represents CH, CF, CCl, C-OCH_3 or C-CH_3; X^1 represents H, a halogen atom, NH_2 or CH_3; and R^1 represents: (i) C_1-C_3-alkyl or FCH_2CH_2-, or (ii) cyclopropyl or phenyl which are optionally substituted once to three times by a

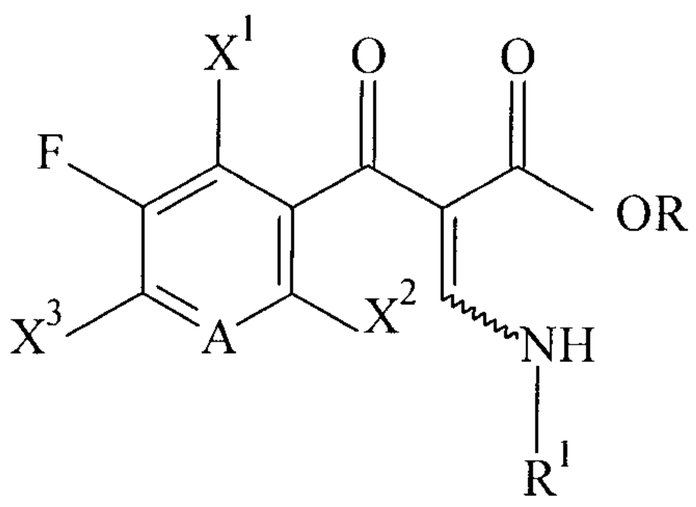
30725-120

halogen atom; wherein the process, without isolation of the intermediates after each step, comprises: (A) an acid halide of the general formula (XXVI):



(XXVI)

wherein Hal, X^2 and X^3 represent a halogen atom, and A and X^1 are as defined above, is either: (a) reacted in a solvent with a dimethylaminoacrylic acid ester of the general formula: $(CH_3)_2N-CH=CH-COOR$, after which the aminoacrylic ester of the general formula (XIII) is produced by adding an amine of the general formula: R^1-NH_2, with amine exchange in the acrylic ester moiety of the product of the reaction of the acid halide of the general formula (XXVI) with the dimethylaminoacrylic acid ester, or (b) the acid halide of the general formula (XXVI) is rapidly reacted with an aminoacrylic ester of the general formula: $R^1NH-CH=CH-COOR$, wherein the amine exchange of step (a) is not effected and the aminoacrylic ester of the general formula (XIII) is produced directly:

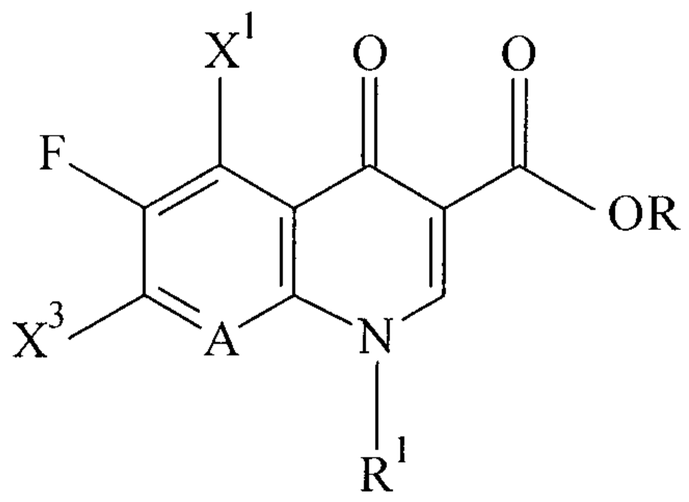


(XIII)

wherein A, X^1, X^2, X^3 and R^1 are as defined above, and R represents a radical which is suitable for ester formation; (B) the aminoacrylic ester of the general formula (XIII) is

30725-120

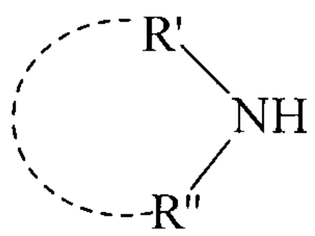
heated in a solvent with an auxiliary base, and thereby cyclized to form a compound of the general formula (XIV):



(XIV)

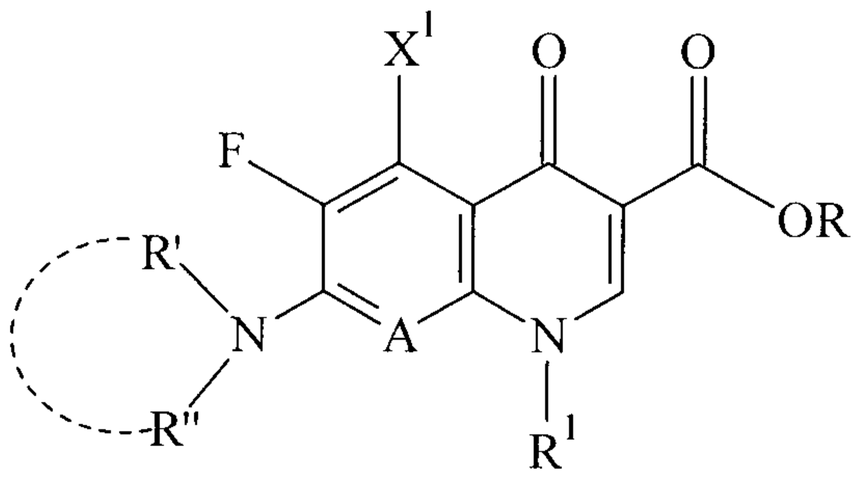
wherein A, R, R^1, X^1 and X^3 are as defined above; and

(C) the compound of the general formula (XIV) is converted by reaction with a heterocyclic compound of the general formula (V):



(V)

wherein R' and R'' are as defined above, into an ester of the general formula (XXVIII):



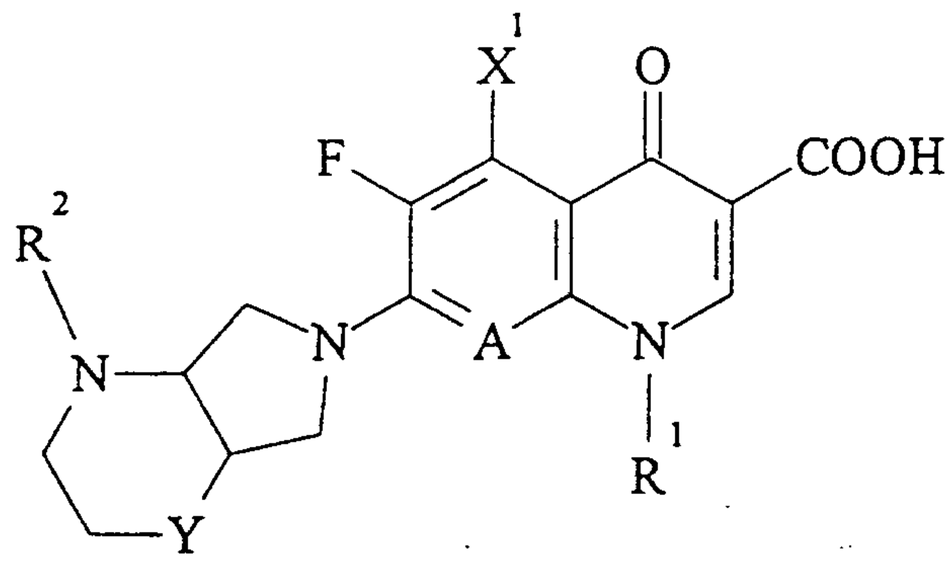
(XXVIII)

wherein A, R, R^1, R', R'' and X^1 are as defined above,

wherein the 3-quinolonecarboxylic acid derivative of the general formula (Ia) is obtained by means of alkaline hydrolysis of the ester function of the ester of the general formula (XXVIII), and wherein the 3-quinolonecarboxylic acid derivative of the general formula (Ia) is precipitated by neutralizing the reaction mixture.

30725-120

In one embodiment, the present invention relates to those 3-quinolonecarboxylic acid derivatives which are substituted in the 7 position by a bicyclic heterocycle, that is to say a one-pot process for the preparation of 3-quinolonecarboxylic acid derivatives of the general formula



(I),

in which

A represents CH, CF, CCl, C-OCH_3 or C-CH_3,

X^1 represents H, halogen, NH_2 or CH_3,

Y represents CH_2 or O,

R^1 represents C_1-C_3-alkyl, FCH_2CH_2- or cyclopropyl, or phenyl or cyclopropyl which are optionally substituted once to three times by halogen,

R^2 represents hydrogen, 5-methyl-2-oxo-1,3-dioxolen-4-yl-methyl, C_2-C_5-oxoalkyl, CH_2-CO-C_6H_5, $CH_2CH_2CO_2R^6$, R^6O_2C-CH=C-CO_2R^6, -CH=CH-CO_2R^6 or CH_2CH_2-CN,

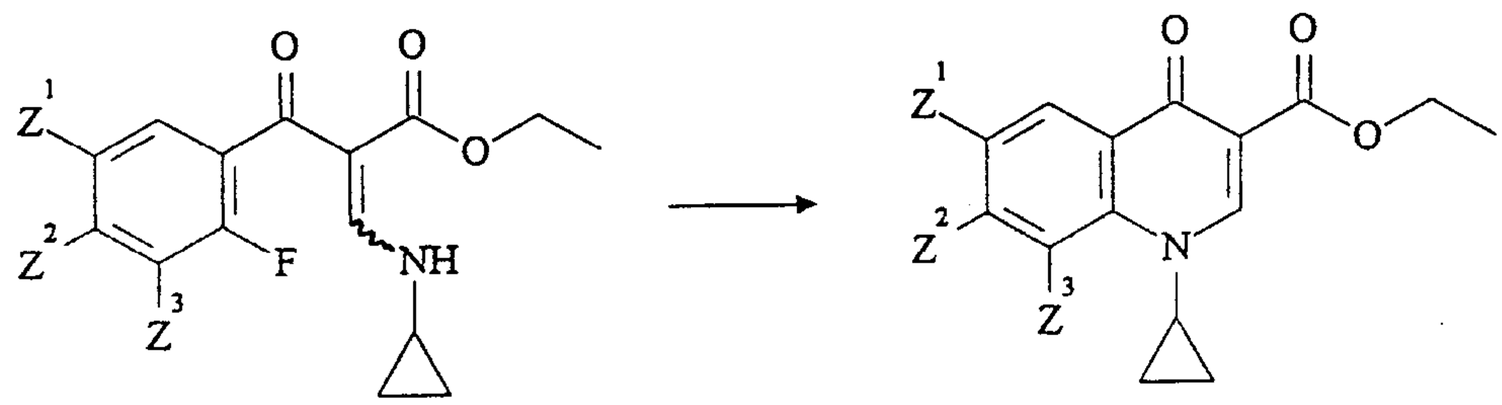
in which

R^6 denotes hydrogen or C_1-C_3-alkyl.

Quinolonecarboxylic acid derivatives of this type are valuable pharmaceutical active compounds. They are suitable for use in the preparation of anti-microbial agents.

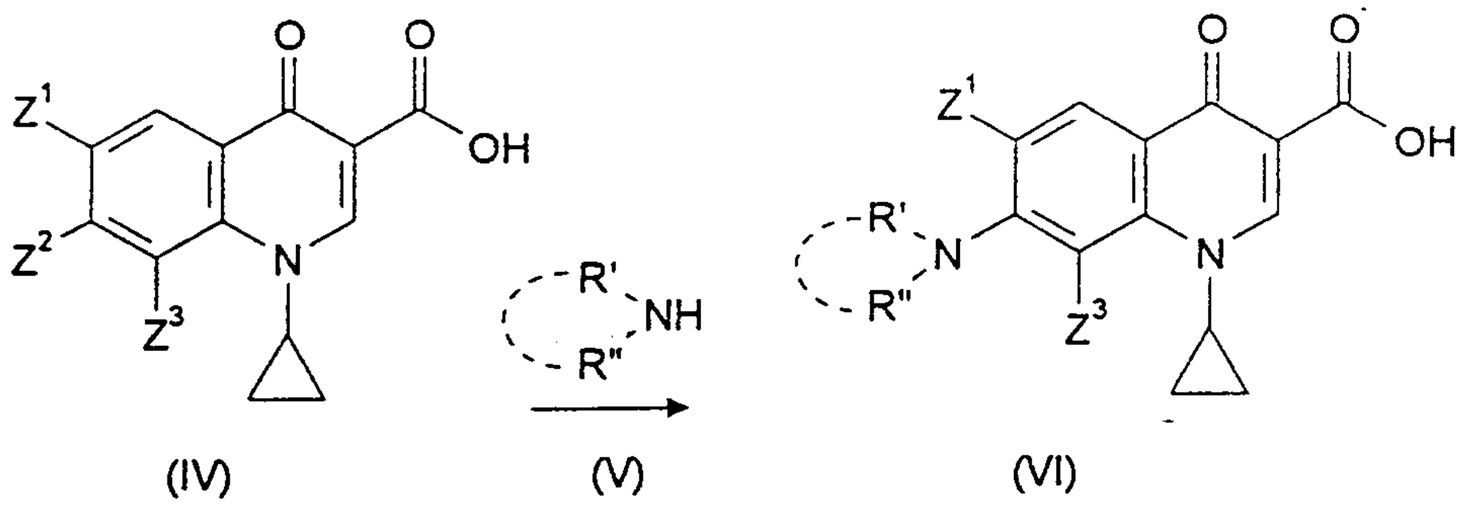
Various processes for the preparation of quinolone-carboxylic acid derivatives have been known hitherto.

According to EP-A-0 167 763, compounds of the formula (II) (Z^1, Z^2 and Z^3 are, independently of each other, fluorine or chlorine)



(II) (III)

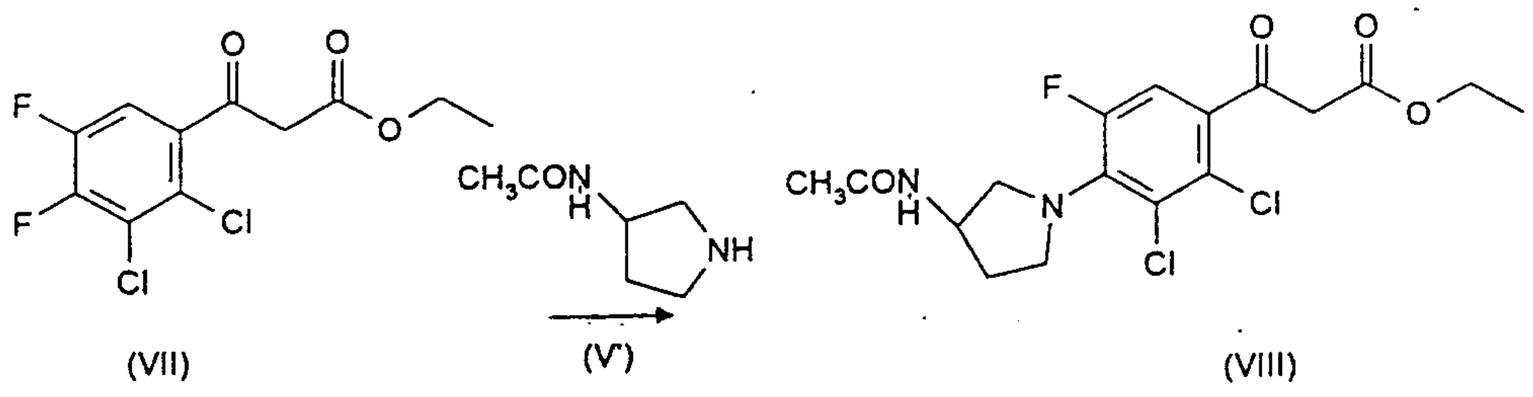
are cyclized at temperatures of from 60°C to 300°C in the presence of a base such as alkali metal fluoride or alkali metal carbonate in a solvent such as DMF, HMPT or NMP. The ester (III) is hydrolysed in a following step to the acid (IV). The latter is subsequently reacted with optionally cyclic amines (V), preferably in solvents, to form the substituted derivatives (VI).



(IV) (V) (VI)

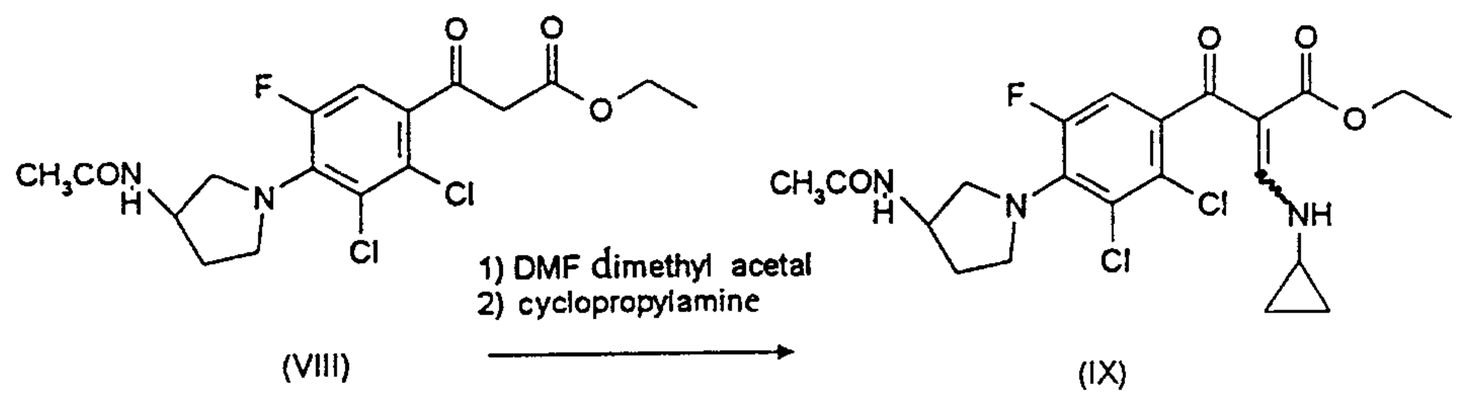
However, the total yield from (II) to (VI) is, at 56%, unsatisfactory. Moreover, in association with the alkaline hydrolysis of the ester (III), by-products can arise in which Z^2 was substituted by hydroxyl or alkoxy, as can oligomers and polymers, in particular when Z^2 represents fluorine. If the hydrolysis is carried out under acidic conditions, hydrogen fluoride is liberated, leading to corrosion of the production plant and to contamination of the product with complex metal fluorides. This is particularly the case when, after the cyclization of (II) to (III), in which HF arises and is bound to a base, this reaction mixture is employed, without prior isolation of the ester (III), for the acid hydrolysis, during which, inevitably, the hydrogen fluoride which was previously bound to base is liberated once more.

According to EP-A-0 275 971, compounds of the formula (XI) can be obtained by introducing the amine (V') prior to the ring closure:



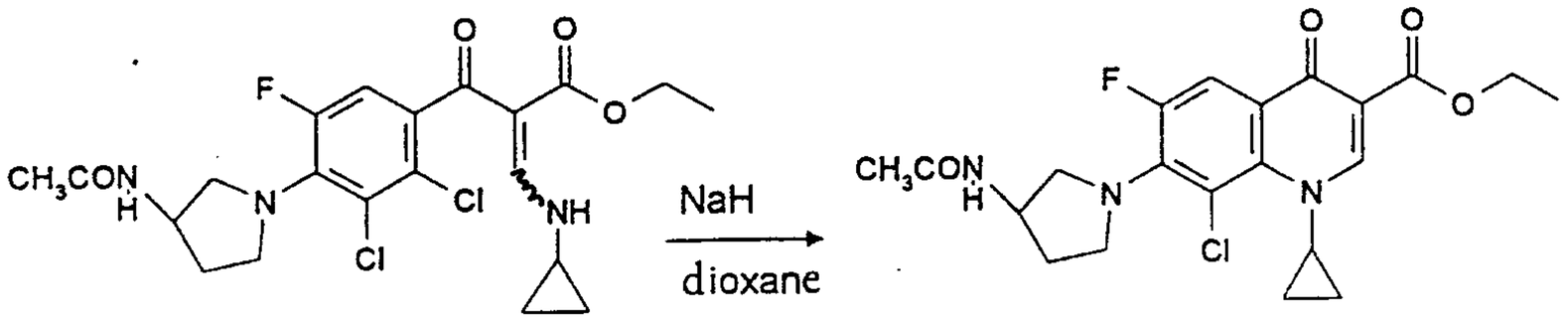
(VII) (V') (VIII)

The cyclopropylaminoacrylate precursor (IX) corresponding to the above compound (II) is then synthesized:



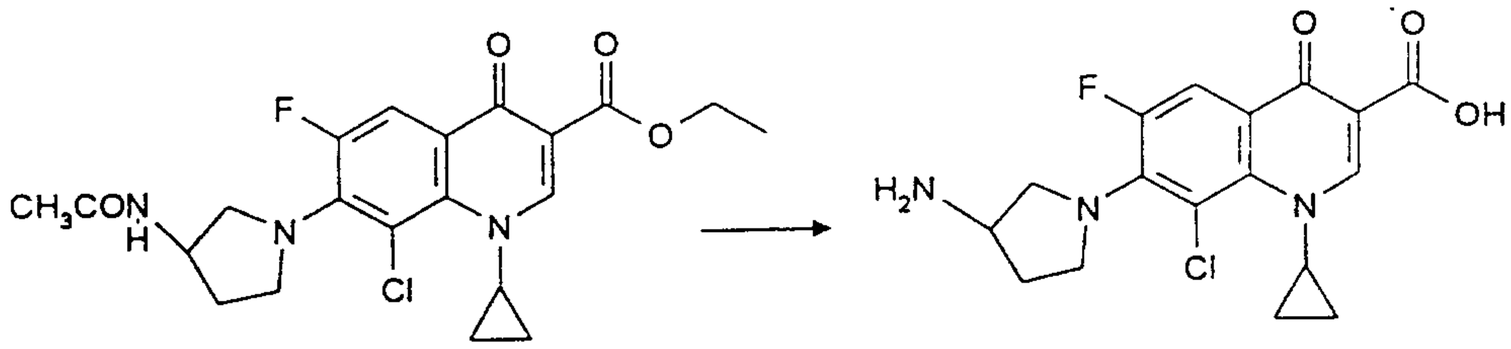
(VIII) (IX)

The cyclization of (IX) in the presence of strong bases, such as, for example NaH, gives rise to the ester (X):



(IX) (X)

Finally, the target compound (XI) is obtained by hydrolysing (X):

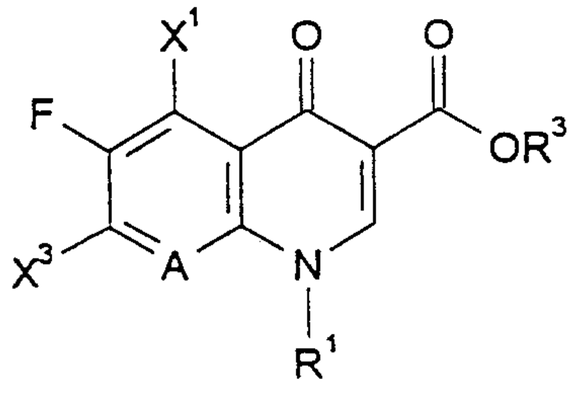


(X) (XI)

However, the total yield from (VII) to (XI) is only 15%, so that a process of this type is very uneconomical.

EP-A-0 350 733 also discloses a multi-step process according to which quinolonecarboxylic acids with an anti-bacterial action are obtained by reacting the carboxylic acids (XII, R^3 = H) with amines, some of which are bicyclic.

However, the yield, proceeding from the aminoacrylate precursor, is, at approximately 60%, not satisfactory. Moreover, in this case as well, there exists the problem of the undesirable substitution of the 7 halogen by hydroxyl or alkoxy, especially in association with the alkaline hydrolysis of the ester (XII, R^3 = alkyl).



(XII)

A, X^1, R^1 cf. (I)

X^3 = halogen, preferably fluorine

These disadvantages - multi-step synthesis, low yields, formation of corrosive cleavage products, and contamination of the end products - render the large-scale production of these active compounds more difficult.

In order to avoid multi-step synthesis processes, consideration can be given to the development of so-called one-pot processes. In these processes, the synthesis is carried out in one and the same reaction vessel, without isolating the intermediates, by consecutive addition of the reactants. EP-A-0 300 311 discloses such a process for synthesizing type (IV) precursors of (VI) quinolonecarboxylic acid derivatives.

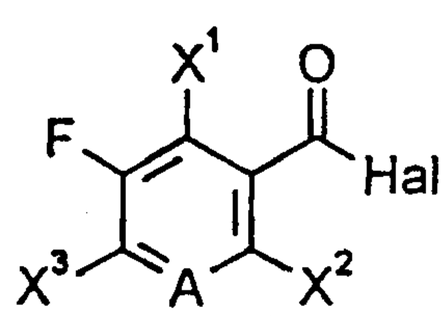
However, the process described in that publication ends at the step of a quinolonecarboxylic acid (analogous to IV), which would subsequently have to be reacted with the amine to be introduced in the 7 position. Accordingly, the above-described disadvantages cannot be avoided.

An advantageous one-pot process for the preparation of 7-heterocyclyl-substituted quinolonecarboxylic acid derivatives has now been found, in which process it is not only the above-described disadvantages with regard to the formation of undesirable 7-hydroxy by-products and the plant corrosion due to liberated hydrogen fluoride which are dispensed with in their entirety. In addition to this, the desired active compounds (I) are made available, at high purity, in yields which are usually

30725-120

greater than 90%, based on the step (XIII) or the step (XXVI).

According to the invention, an acid halide of the formula (XXVI)



(XXVI)

in which

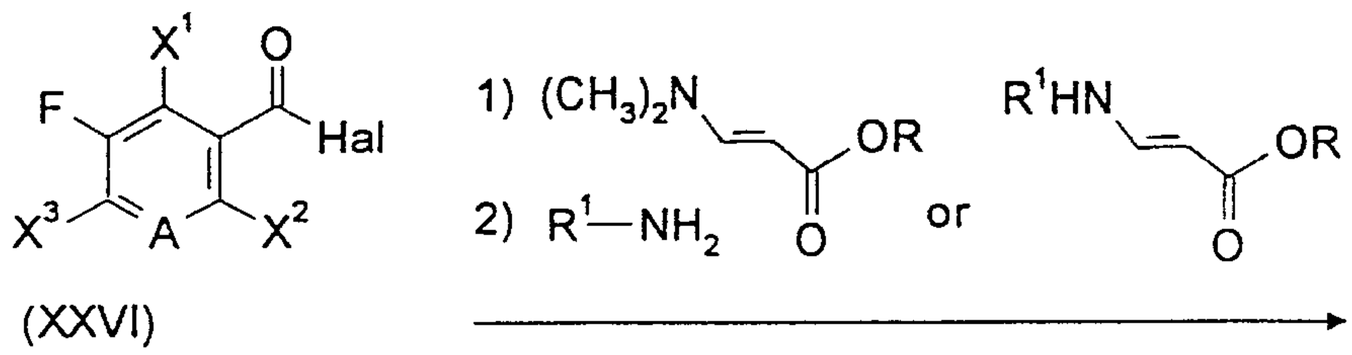
Hal, X^2 and X^3 represent fluorine or chlorine, and A and X^1 have the meanings given for formula (I),

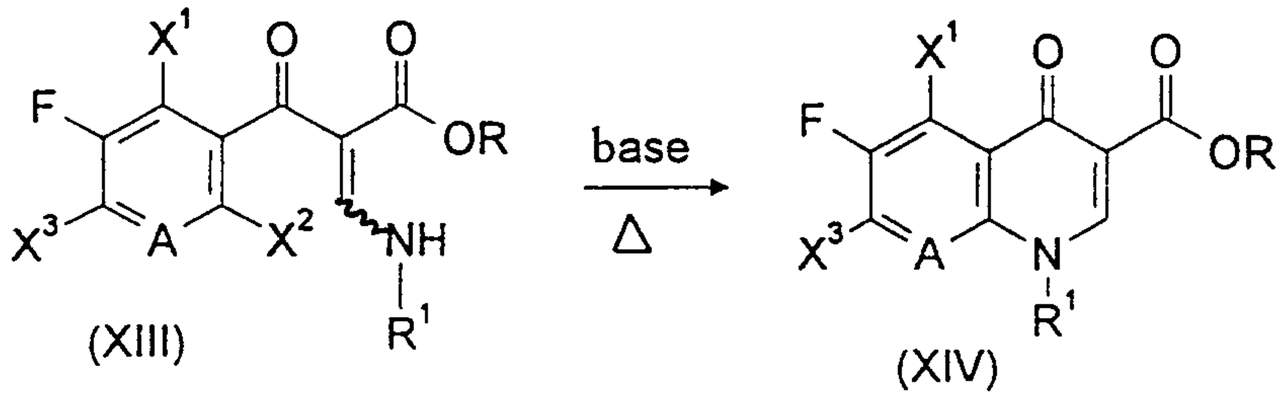
is either reacted in a solvent with a dimethylamino-acrylic acid ester of the formula $(CH_3)_2N$-CH=CH-COOR, after which the aminoacrylic ester (XIII) is produced by adding an amine R^1-NH_2, with amine exchange in the acrylic ester moiety of the primary product, or the acid halide (XXVI) is immediately reacted with an aminoacrylic ester of the formula R^1NH-CH=CH-COOR, in which case the above-described amine exchange is dispensed with and the compound (XIII) is produced directly.

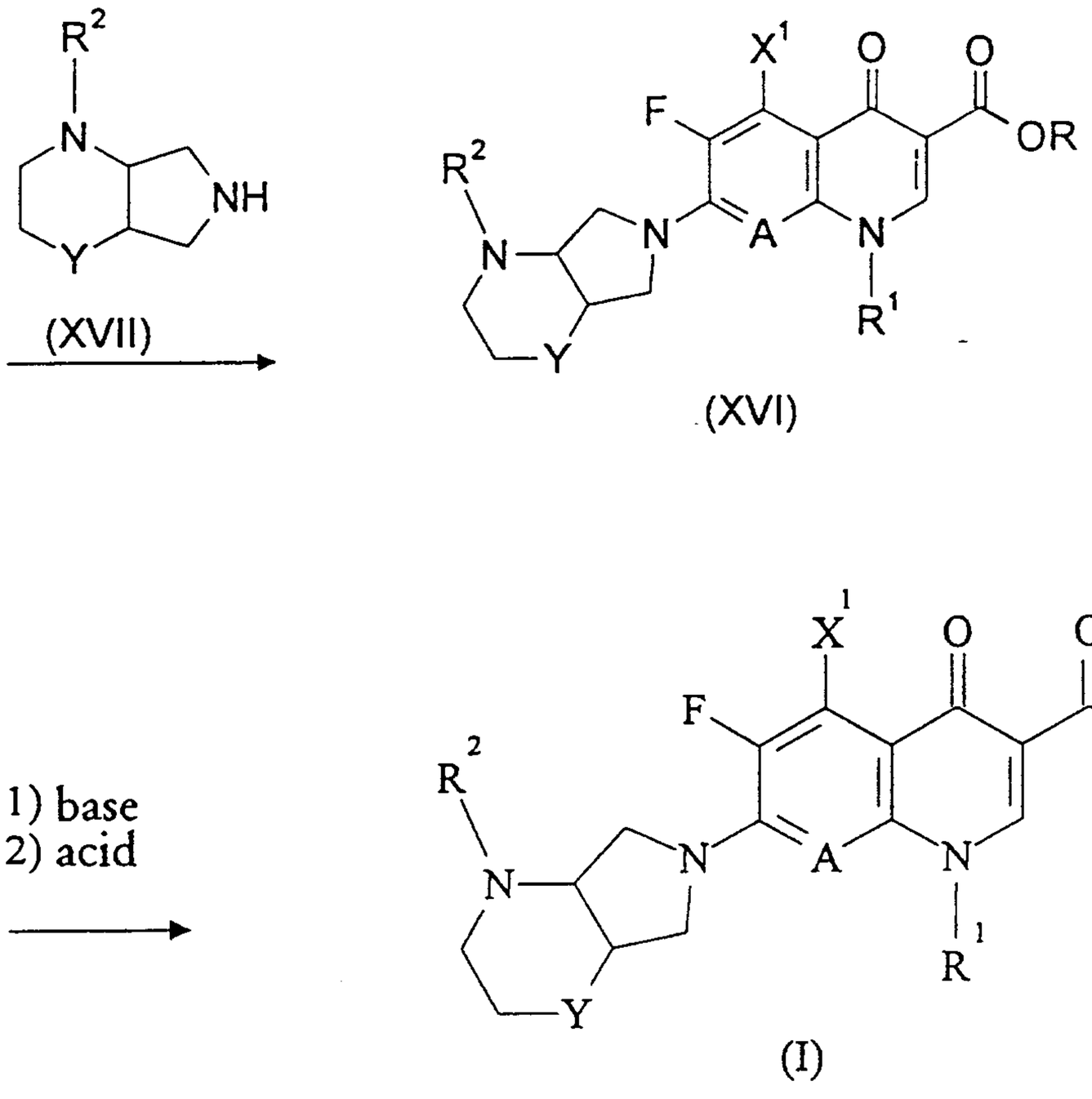
This aminoacrylic ester of the formula (XIII), in which A, X^1 and R^1 have the meanings given for formula (I), X^2 and X^3 represent halogen, and R represents a customary organic radical which is suitable for ester formation, preferably methyl, ethyl or propyl, is heated in a

solvent with an auxiliary base, and thereby cyclized to form the ester (XIV).

The heterocycle, for example the amine (XVII), is then added to this mixture and, after formation of the 7-substitution product (XVI) is complete, the 3-ester function is hydrolysed by adding a strong base. The reaction mixture is finally rendered neutral by adding an acid and the product (I), which precipitates, is isolated. The following formula scheme illustrates, by way of example, the sequence of reactions in this one-pot process:







In the formulae (I) as well as (XIII), (XIV), (XVI) and (XVII), the symbols generally have the following meanings:

A represents CH, CF, CCl, C-OCH_3 or C-CH_3,

R represents a customary organic radical which is suitable for ester formation, preferably ethyl, methyl or propyl,

R^1 represents C_1-C_3-alkyl, FCH_2CH_2- or cyclopropyl, or phenyl or cyclopropyl which are optionally substituted once to three times by halogen,

R^2 represents hydrogen, 5-methyl-2-oxo-1,3-dioxolen-4-yl-methyl, C_2-C_5-oxoalkyl, CH_2-CO-C_6H_5, $CH_2CH_2CO_2R^6$, R^6O_2C-CH=C-CO_2R^6, -CH=CH-CO_2R^6 or CH_2CH_2-CN,

in which

R^6 denotes hydrogen or C_1-C_3-alkyl,

Y represents CH_2 or O,

X^1 represents H, halogen, NH_2 or CH_3, and

X^2 and X^3 represent halogen.

According to the invention, the synthesis of compounds (I) is preferably carried out using precursors (XIII) and (XVII) in which

A represents CH, CF, CCl, C-OCH_3 or C-CH_3,

R represents C_1-C_4-alkyl, C_6H_5 or $Si(CH_3)_3$,

R^1 represents C_2H_5, cyclopropyl which is optionally substituted once to three times by fluorine, or 2,4-difluorophenyl,

R^2 represents H, CH_2-O-CH_3, CH_2-O-C_6H_5, CH_2CH_2-CO-CH_3, $CH_2CH_2CO_2R^6$, R^6O_2C-CH=C-CO_2R^6, -CH=CO_2R^6 or CH_2CH_2CN, in which R^6 denotes C_1-C_3-alkyl,

Y represents CH_2 or O,

X^1 represents hydrogen or halogen, and

X^2 and X^3 represent chlorine or fluorine.

Compounds of the abovementioned formulae are preferred in which

A represents CH,

X^1 represents hydrogen,

X^2 represents fluorine or chlorine, and

X^3 represents fluorine.

Compounds of the abovementioned formulae are particularly preferred in which

A represents CCl or CF,

R represents CH_3 or C_2H_5,

R^1 represents cyclopropyl,

R^2 represents hydrogen,

Y represents CH_2

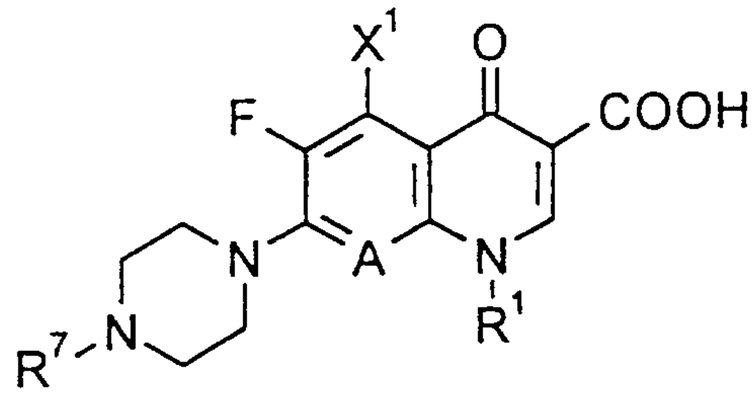
X^1 represents hydrogen,

X^2 represents fluorine or chlorine, and

X^3 represents fluorine.

3-Quinolonecarboxylic acid derivatives of the general

formula (Ib),



(Ib)

in which

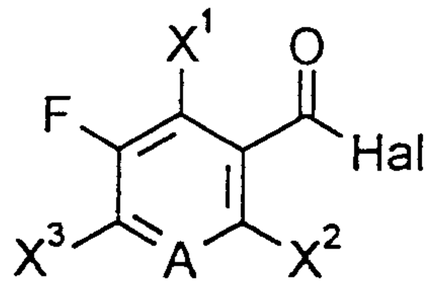
A represents CH, CF, CCl, C-OCH_3 or C-CH_3,

X^1 represents H, halogen, NH_2 or CH_3,

R^1 represents C_1-C_3-alkyl, FCH_2CH_2- or cyclopropyl, or phenyl or cyclopropyl which are optionally substituted once to three times by halogen, and

R^7 represents hydrogen, optionally substituted alkyl or phenyl, or a customary group which is suitable for protecting a nitrogen atom, preferably, however, ethyl,

are also prepared in accordance with the invention by reacting, without isolation of the intermediates, an acid halide of the formula (XXVI)



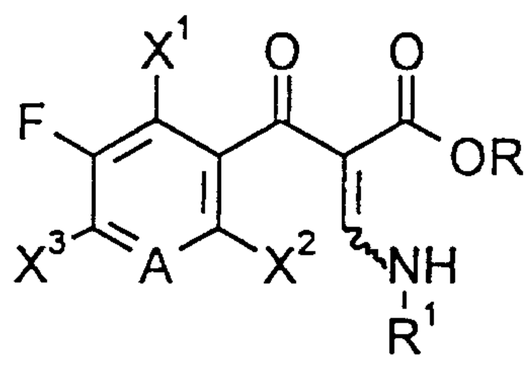
(XXVI)

in which

Hal, X^2 and X^3 represent fluorine or chlorine and A and X^1 have the abovementioned meanings, in a solvent with a dimethylaminoacrylic acid ester of the formula

$$(CH_3)_2N\text{-}CH{=}CH\text{-}COOR$$

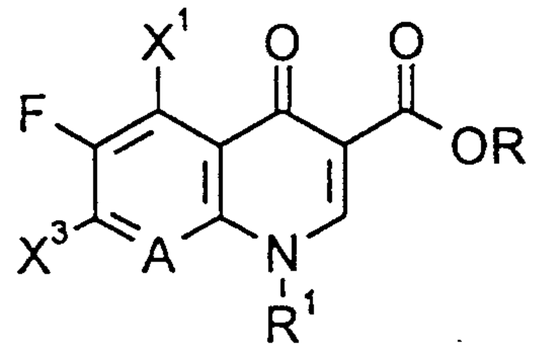
after which the aminoacrylic ester (XIII),



(XIII)

in which A, X^1 and R^1 have the meanings given for the formula (Ib), X^2 and X^3 represent halogen, and R represents a customary organic radical which is suitable for ester formation, preferably methyl, ethyl or propyl, is produced by adding an amine $R^1\text{-}NH_2$, with amine exchange in the acrylic ester moiety of the primary product, and is then heated in a solvent with an auxiliary base, and thereby

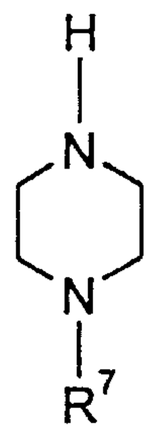
cyclized to form compounds of the general formula (XIV),



(XIV)

in which A, R, R^1, X^1 and X^3 have the abovementioned meanings,

which are converted, by reaction with compounds of the general formula (XV)

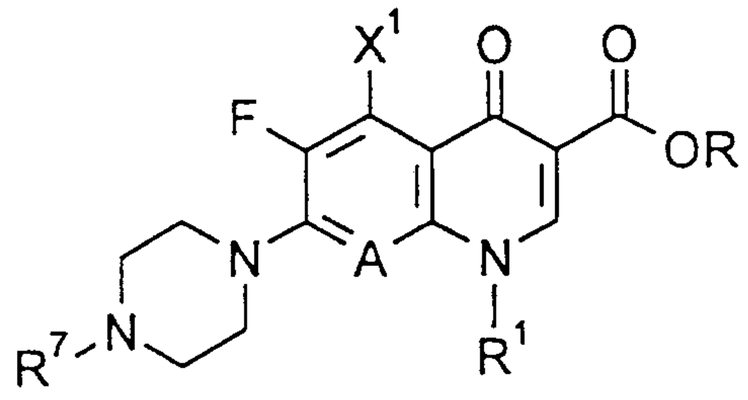


(XV)

in which

R^7 has the abovementioned meaning,

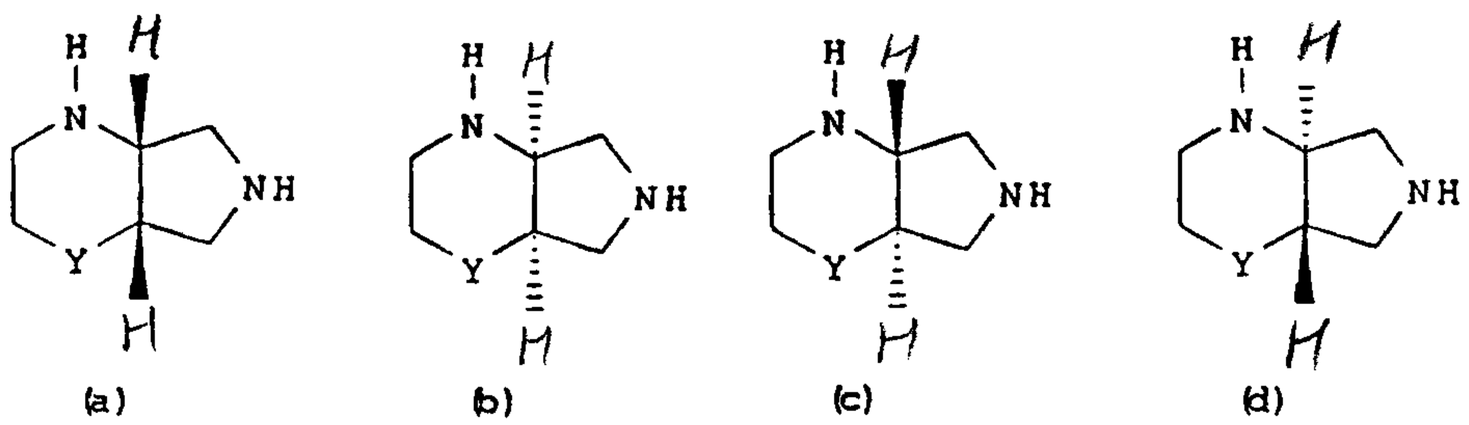
into esters of the general formula (XXVII)



(XXVII)

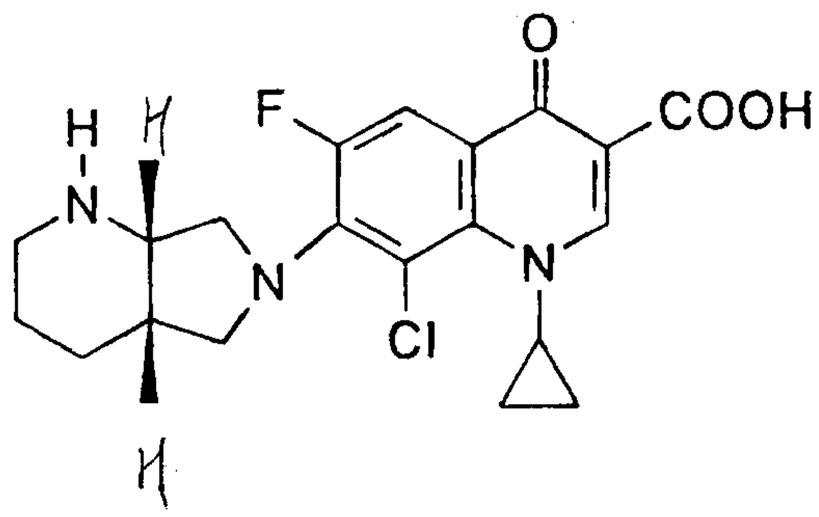
in which A, R, R^1, R^7 and X^1 have the abovementioned meanings, from which the 3-quinolonecarboxylic acid derivatives of the formula (Ib) result, by means of alkaline hydrolysis of the ester function, and are precipitated by neutralizing the reaction mixture.

The compounds (I) which are particularly preferably to be prepared by the process according to the invention also include optically active derivatives, obtainable by reacting (XIII) with enantiomerically pure amines (XVII a-d), which are described in DE-A-4 208 789 and DE-A-4 208 792.



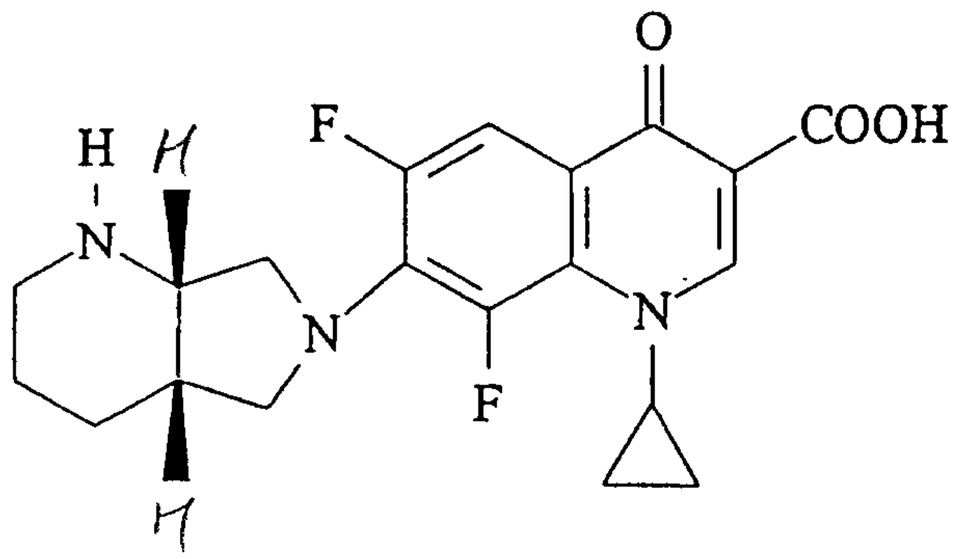
(XVII a-d)

Examples of individual compounds which may particularly preferably be prepared in accordance with the invention are



(XXX)

8-chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0.]-non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline-carboxylic acid (XXX) and



(XVIII)

1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0.]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (XVIII).

In principle, all common inert organic solvents may be used for carrying out the one-pot process according to the invention. Examples which may be mentioned are dimethylethyleneurea (DMEU), dimethylpropyleneurea (DMPU), N-methylcaprolactam, tert.-butanol, tetramethyl-urea, sulpholane and dimethoxyethane. Water-miscible solvents, such as N-methylpyrrolidone (NMP), diglyme, N,N-dimethylformamide (DMF) or dioxane, are preferably used, particularly preferably NMP.

The cyclization is carried out at the lowest temperature possible. Temperatures of from 60°C to 100°C are generally sufficient, something which can be ascertained, with the aid of exploratory preliminary experiments using the selected precursor (XIII) in the selected medium,

solvent/auxiliary base, just as easily as can the optimal quantity of solvent.

Acid binders which are customary in organic synthesis may be used as auxiliary bases in the cyclization. Potassium tert.-butoxide, butyl-lithium, phenyl-lithium, sodium methoxide, sodium hydride, sodium carbonate, potassium carbonate, potassium fluoride and sodium fluoride may be mentioned, by way of example, for this reaction step. It can be advantageous to employ an excess of up to 10 mol % of base, where appropriate an even greater excess.

Sodium carbonate or potassium carbonate are preferably employed.

After cyclization is complete, the amine (XV) or (XVII), for example, is metered in at the same temperature, or, where appropriate, at a temperature which has been further increased. The optimum reaction temperature depends on the reactants but can, in turn, be ascertained without difficulty in a preliminary experiment. In general, temperatures of from 60°C to 100°C are adequate.

Once substitution of the 7 position in (XIV) is concluded, the reaction mixture is diluted and cooled by adding water. A volume of water corresponding approximately to that of the reaction mixture will generally be used. Alkali metal hydroxide solution, preferably sodium hydroxide solution, in equimolar quantity or up to an excess of about 10 mol %, is then added to hydrolyse the

ester function. The hydrolysis is preferably carried out at approximately 60°C.

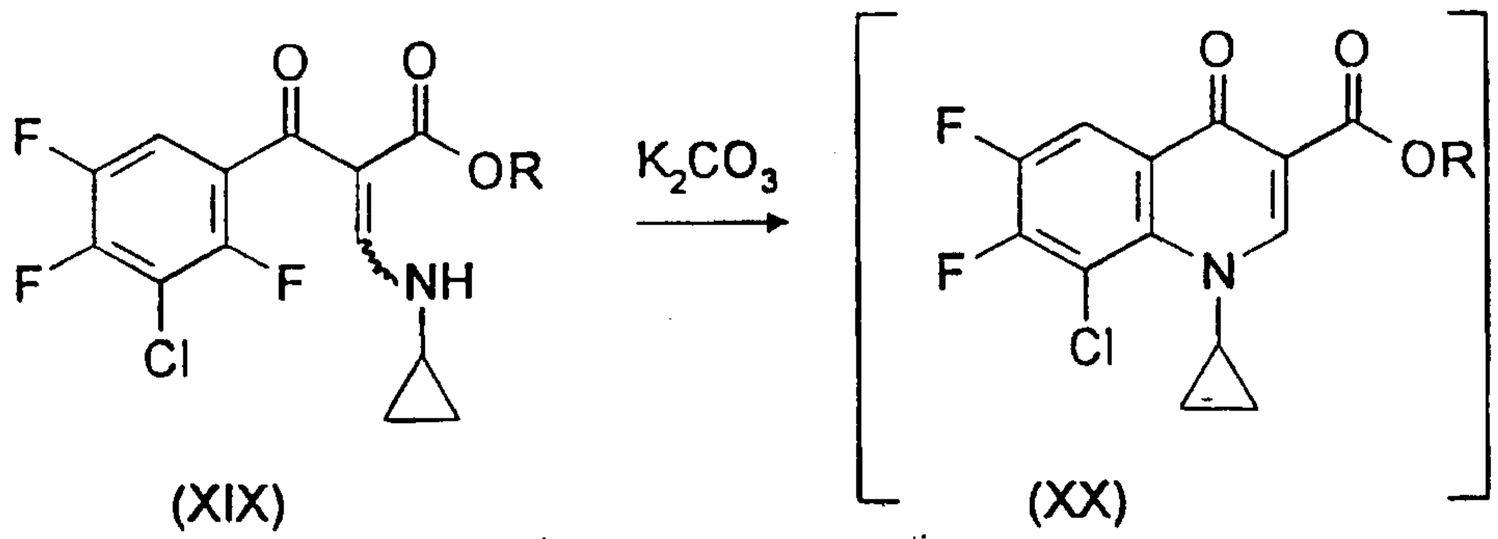
The reaction mixture is then further diluted with water, a volume of water as a rule being added which is approximately double that of the mixture. The mixture is adjusted to a pH of about 7.8 with mineral acid, preferably hydrochloric acid, or acetic acid, and is then, where appropriate, further cooled down to from 0 to 5°C.

The target product, for example (I) or (Ib), which precipitates at this stage is subsequently isolated, for example by filtration with suction.

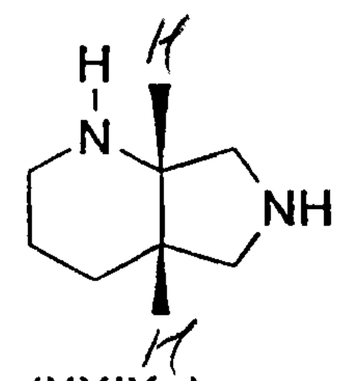
As a rule, the product, for example (I) or (Ib), is obtained at a purity of >95% and in a yield of >85%, usually, however, of >90%, based on the starting compound (XIII).

The following implementation examples illustrate the invention:

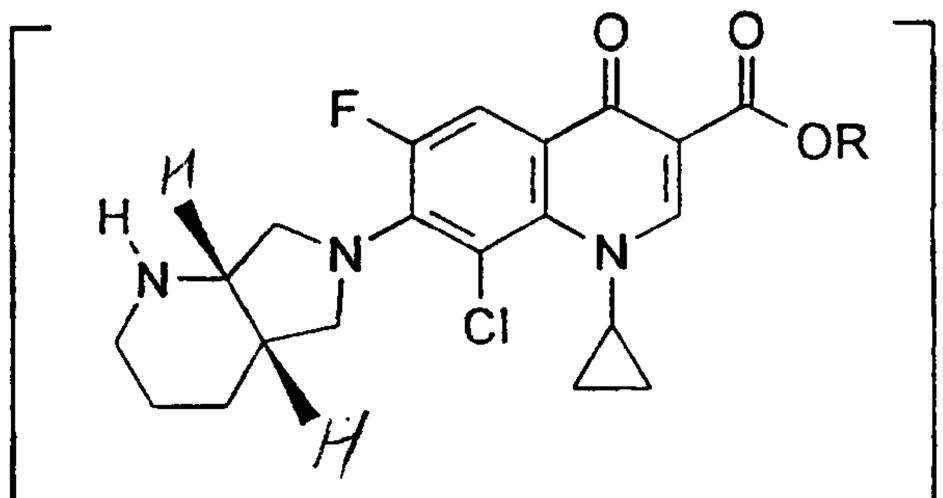
1) Synthesis of 8-chloro-1-cyclopropyl-7-([S,S]-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (XXX):



(XIX) (XX)

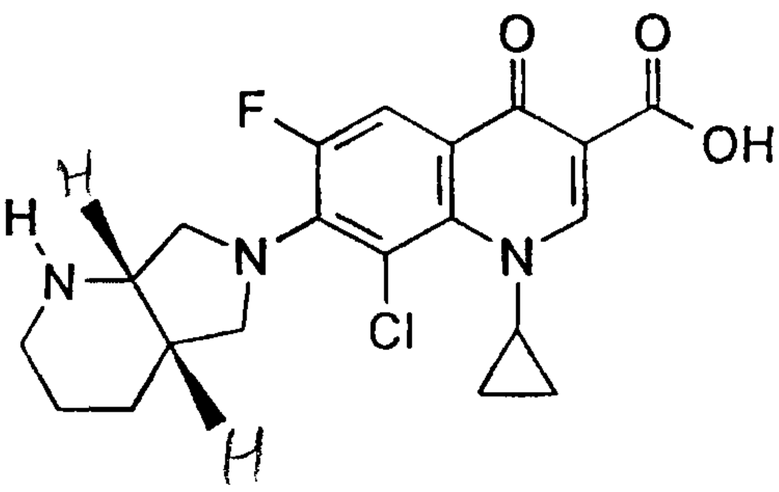


(XXIXa)



(XXII)

1) OH^- /aq.
2) H^+/aq.



(XXX)

a) Via methyl ester (R = CH_3)

10.2 g of K_2CO_3 and 17.7 g (0.053 mol) of XIX (methyl ester) are heated at 60°C for 50 min in 30 ml of NMP.

7.5 g (0.059 mol) of S,S-pyrrolopiperidine (XXIXa) are added and the mixture is stirred at 90°C for 90 min.

The resulting ester (XXII) is hydrolysed at 60°C in 50 min using 33 g of 8.5% sodium hydroxide solution. The mixture is diluted with 120 ml of water and then adjusted to a pH of 7.8 using 6N hydrochloric acid.

Once the mixture has been cooled down to 5°C, the precipitated product (XXX) is separated off on a Buchner funnel, then washed 3 x with 100 ml of water on each occasion, and dried at 80°C overnight in vacuo.

Yield: 19 g $\hat{=}$ 86.1% of theory (at 97.5% by weight)

b) Via ethyl ester (R = C_2H_5)

20.4 g of K_2CO_3 and 36.8 g (0.106 mol) of (XIX) are heated at 80°C for 2.5 hours in 60 ml of diglyme.

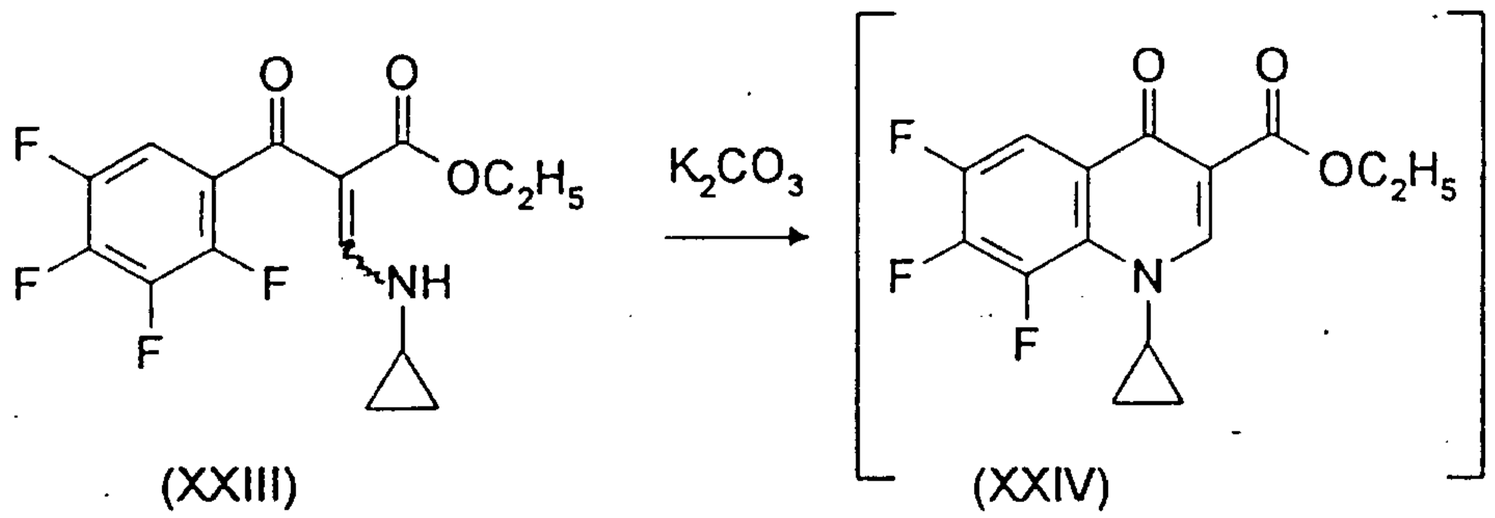
After adding 15 g (0.118 mol) of S,S-pyrrolopiperidine (XXIXa), the mixture is stirred at from 90 to 100°C for 4 hours.

The resulting ester (XXII) is hydrolysed at 80°C within 2.5 hours after adding 60 ml of water and 22 g of 45% sodium hydroxide solution. The mixture is diluted with 240 ml of water and adjusted to a pH of 7.8 with 6N hydrochloric acid.

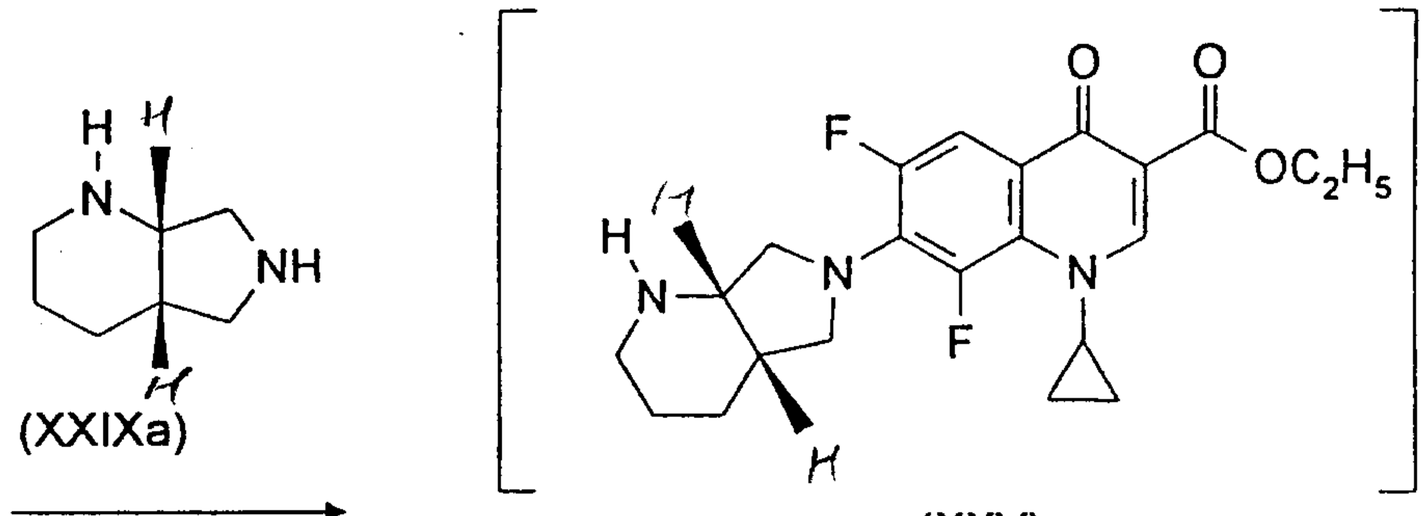
Once the mixture has been cooled down to 5°C, the product (XXX) is filtered off with suction, washed with water, and dried at 70°C in vacuo.

Yield: 43 g ≙ 96.5% of theory (at 96.5% by weight)

2) Synthesis of 1-cyclopropyl-7-([S,S]-2,8-diaza-bicyclo[4.3.0]non-8-yl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (XVIII).



(XXIII) (XXIV)



(XXIXa) (XXV) (XVIII)

1) OH^- /aq.

2) H^+ /aq.

20.4 g of K_2CO_3 and 35.2 g (0.106 mol) of (XXIII) are heated at 60°C for 1 hour in 60 ml of NMP. (By HPLC, 97.6% of (XXIV) has resulted after 40 min).

15.5 g (0.12 mol) of S,S-pyrrolopiperidine (XXIXa) are added. 0.2% of (XXIV) is still present (HPLC) after 2 hours at 80°C.

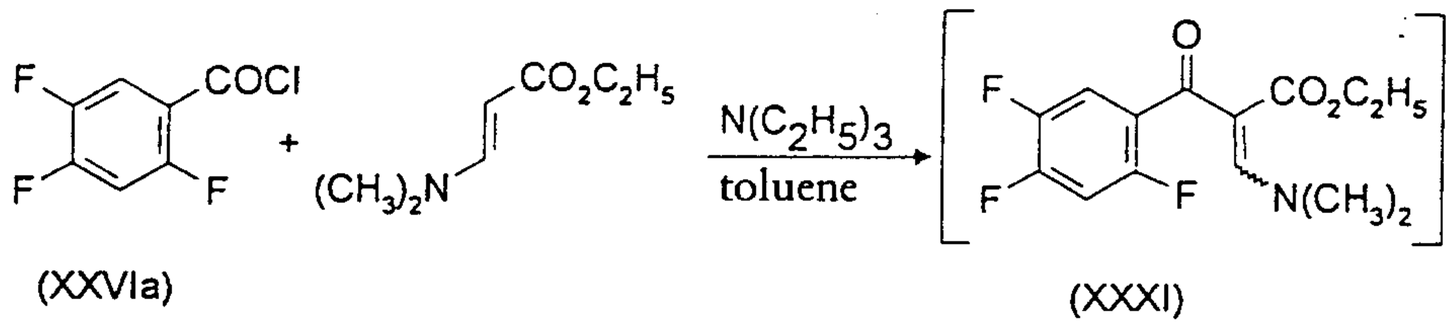
Following the addition of 60 ml of water and 12 g of NaOH, the resulting ester (XXV) is hydrolysed to (XVIII) in 4 hours at 60°C.

The mixture is diluted with 240 ml of water and adjusted to a pH of 7.8 with 6N hydrochloric acid.

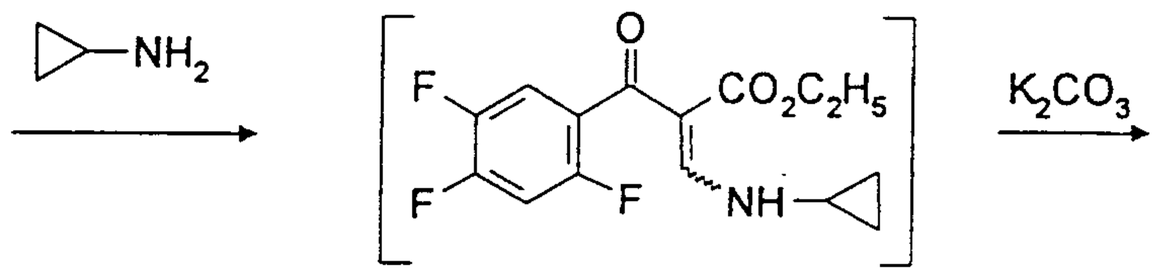
The product is filtered off with suction, washed with water and dried at 70°C in vacuo.

Yield: 38.1 g ≙ 91.4% of theory (at 98.9% by weight)

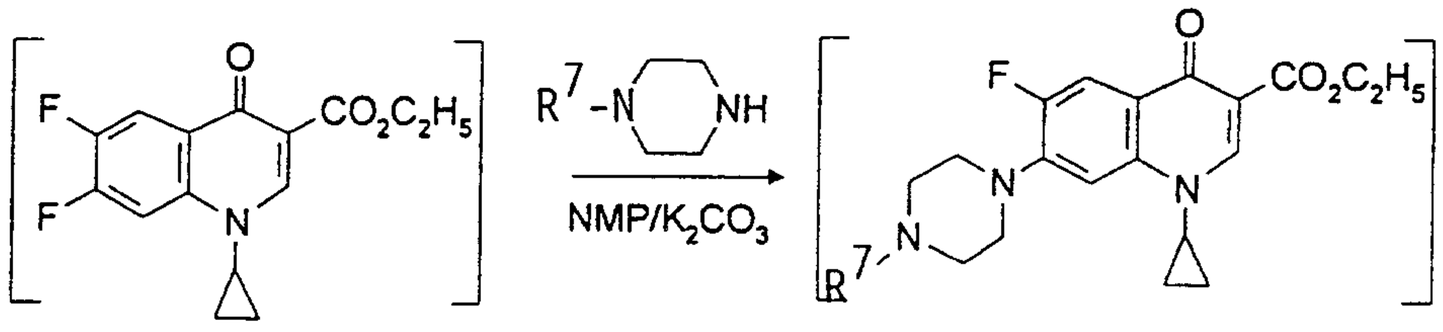
3) Synthesis of 1-cyclopropyl-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (XXXIVa) and 1-cyclopropyl-6-fluoro-7-(4-ethyl-1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (XXXIVa, b)



(XXVIa) (XXXI)



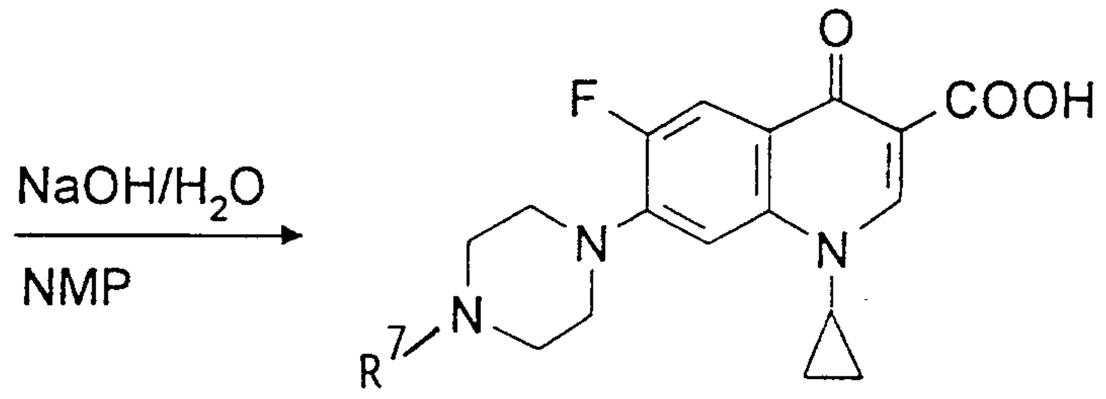
(XXXII)



(XXXIII)

(XVa R^7= H)
(XVb R^7= C_2H_5)

(XXVIIa R^7= H)
(XXVIIb R^7= C_2H_5)



(XXXIVa R^7 = H)
(XXXIVb R^7 = C_2H_5)

35.8 g (0.25 mol) of ethyl dimethylaminoacrylate and 27.3 g (0.27 mol) of triethylamine are initially introduced in 50 ml of toluene, and 48.6 g (0.25 mol) of 2,4,5-trifluorobenzoyl chloride (XXVIa) are added dropwise at 50°C within 30 minutes. The mixture is subsequently stirred at from 50 to 55°C for 1 hour and 17.3 g (0.28 mol) of glacial acetic acid and 15.5 g (0.27 mol) of cyclopropylamine are then added dropwise at from 30 to 36°C. After 1 hour, the salts are extracted with 100 ml of water. The organic phase is concentrated by evaporation in water pump vacuum at 40°C. 80.3 g of (XXXII) are obtained as an oily residue.

The oil (XXXII) is dissolved by adding 250 ml of N-methylpyrrolidone and heated to from 80 to 90°C together with 48.4 g (0.35 mol) of potassium carbonate. After 1 hour, 86 g (1 mol) of piperazine (XVa) or 114 g (1 mol) of N-ethylpiperazine (XVb), respectively, are added. The mixture is stirred at from 80 to 90°C for one hour and then diluted with 150 ml of water.

After adding 20 g (0.5 mol) of NaOH, the temperature is maintained at 70°C for 1 hour and the mixture is then further diluted with 500 ml of water. Small quantities of impurities in the solution are filtered off and the pH is adjusted to 7.5 with half-concentrated hydrochloric acid.

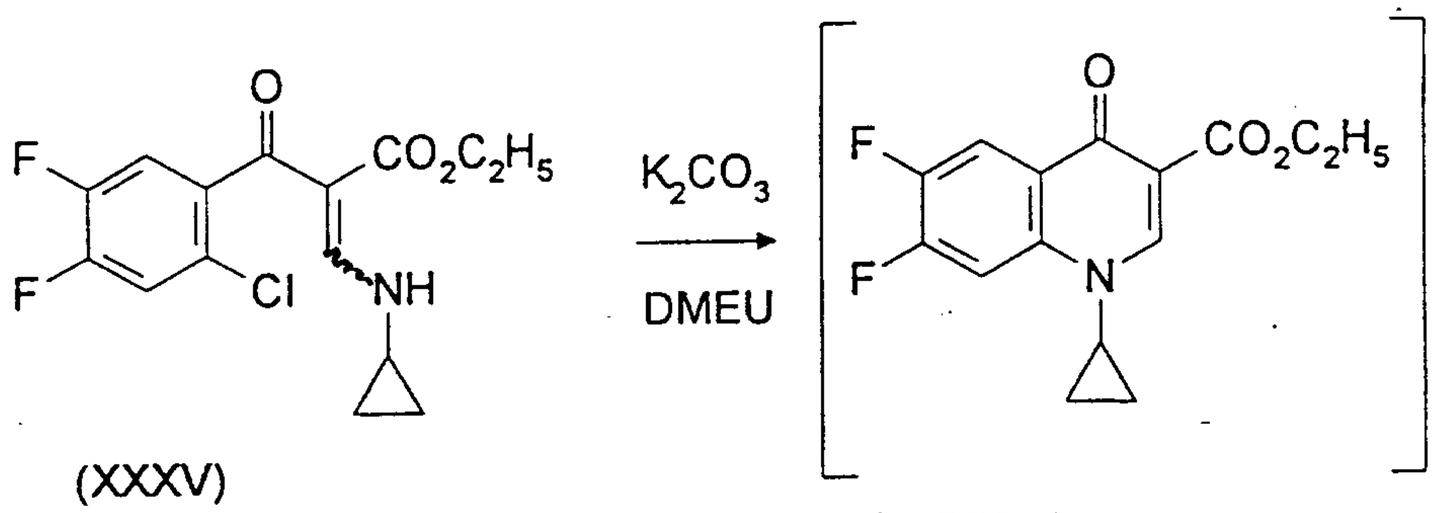
Once the mixture has been cooled down to from 0 to 5°C, the betain (XXXIV) is filtered off with suction after 2 hours and washed 2 x with 200 ml of water on each

occasion; the product is dried overnight in vacuo.

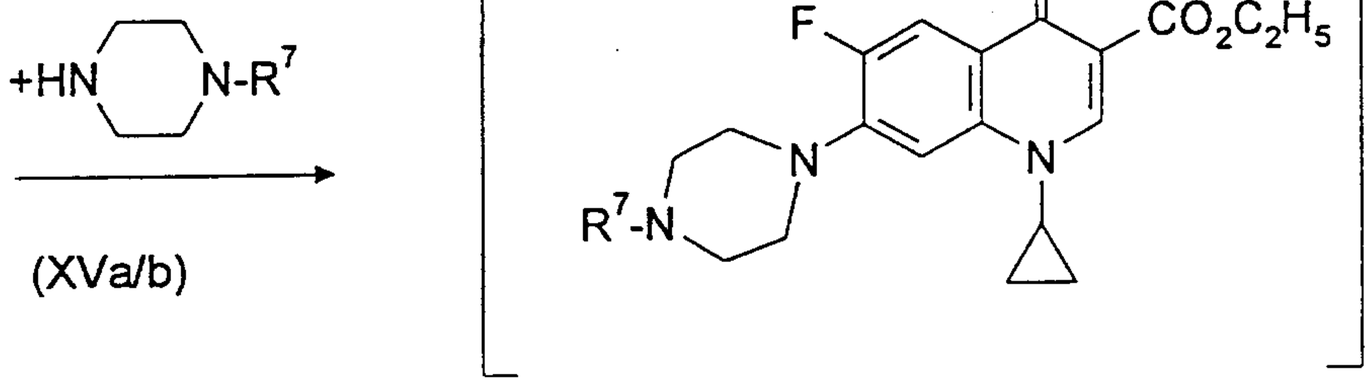
Yields: XXXIVa 71.4 g (98.0% by weight, HPLC) ≙ 84.5% of theory

XXXIVb 78.2 g (98.5% by weight, HPLC) ≙ 87.0% of theory

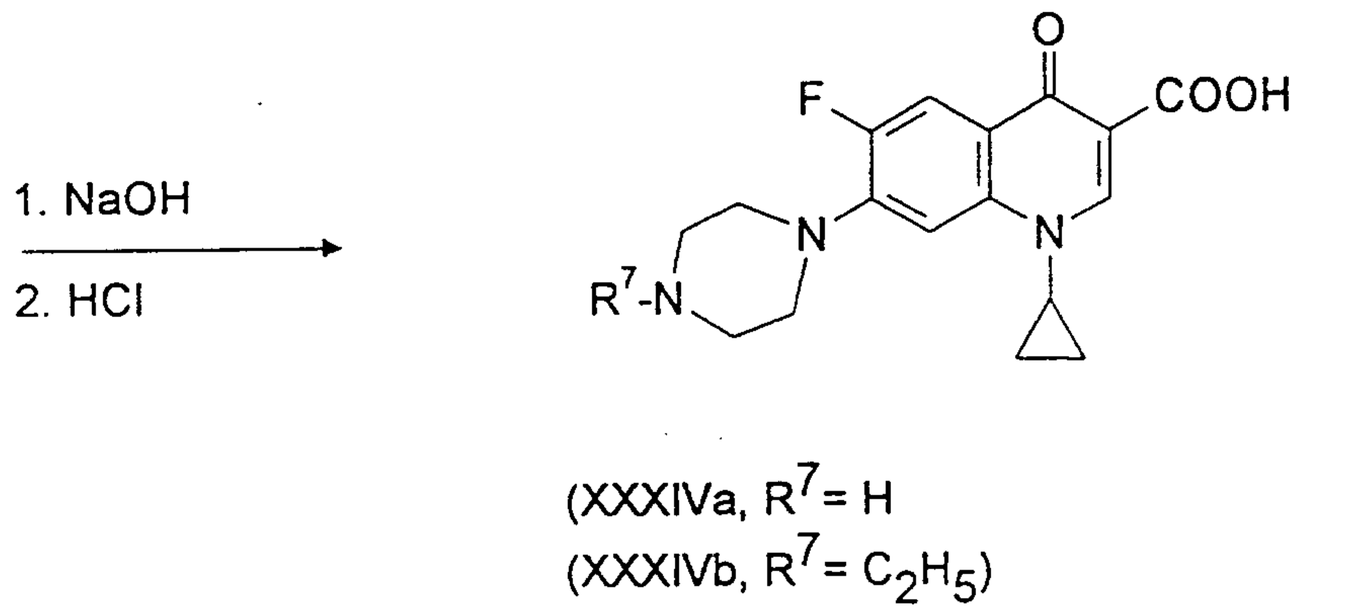
4) Synthesis of 1-cyclopropyl-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (XXXIVa) and 1-cyclopropyl-6-fluoro-7-(4-ethyl-1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (XXXIVb)



(XXXV)



(XXXIII)



(XXVIIa, R^7 = H
(XXVIIb, R^7 = C_2H_5)

(XXXIVa, R^7 = H
(XXXIVb, R^7 = C_2H_5)

82.4 g of (XXXV) are dissolved in 250 ml of DMEU and heated to from 100 to 120°C together with 48.4 g (0.35 mol) of potassium carbonate.

After 2 hours, 86 g (1 mol) of piperazine (XVa) or 114 g (1 mol) of N-ethylpiperazine (XVb), respectively, are added. The mixture is stirred at from 80 to 90°C for one hour and then diluted with 150 ml of water.

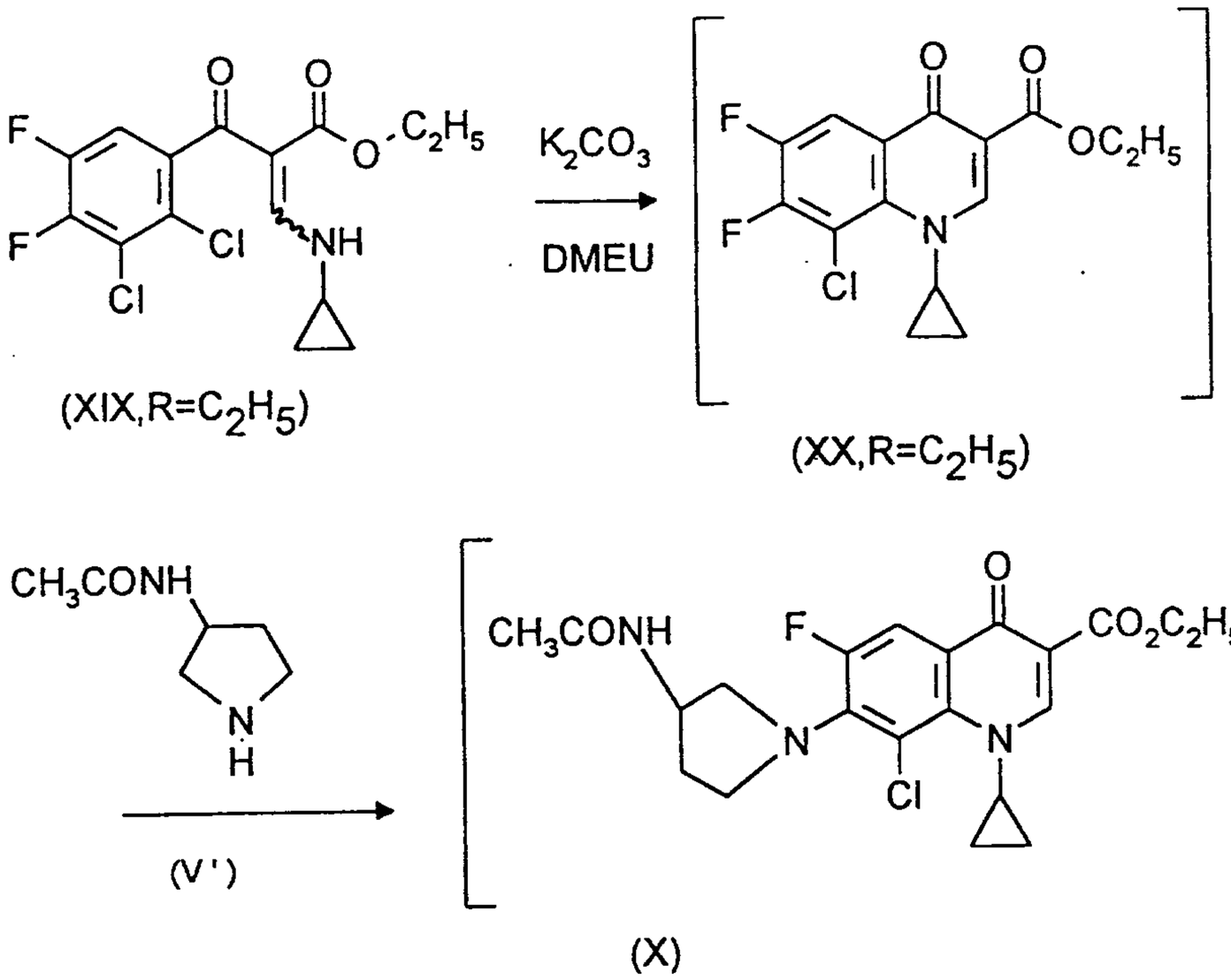
After adding 20 g (0.5 mol) of NaOH, the temperature is maintained at 70°C for 1 hour and the mixture is then diluted further with 500 ml of water. Small quantities of impurities in the solution are filtered off and the pH is adjusted to 7.5 with half-concentrated hydrochloric acid.

Once the mixture has been cooled down to from 0 to 5°C, the betain (XXXIV) is filtered off with suction after 2 hours and washed 2 × with 200 ml of water on each occasion; the product is dried overnight in vacuo.

Yield: (XXXIVa): 73.0 g (98.5% by weight) $\hat{=}$ 86.8% of theory

(XXXIVb): 77.2 g (99.0% by weight) $\hat{=}$ 85.1% of theory

5) 7-(3-Amino-1-pyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (XI)



(XIX, $R=C_2H_5$)

(XX, $R=C_2H_5$)

(X)

(XI)

20.6 g of (XIX, $R = C_2H_5$) are dissolved in 65 ml of DMEU and heated at from 100 to 120°C for 2 hours together with 12.2 g of K_2CO_3.

8.5 g of 3-acetamidopyrrolidine (V') are added, and the reaction mixture is subsequently stirred at from 80°C to 90°C for 1 hour. It is then diluted with 40 ml of water, and 10 g of NaOH are added. After 4 hours at from 90 to

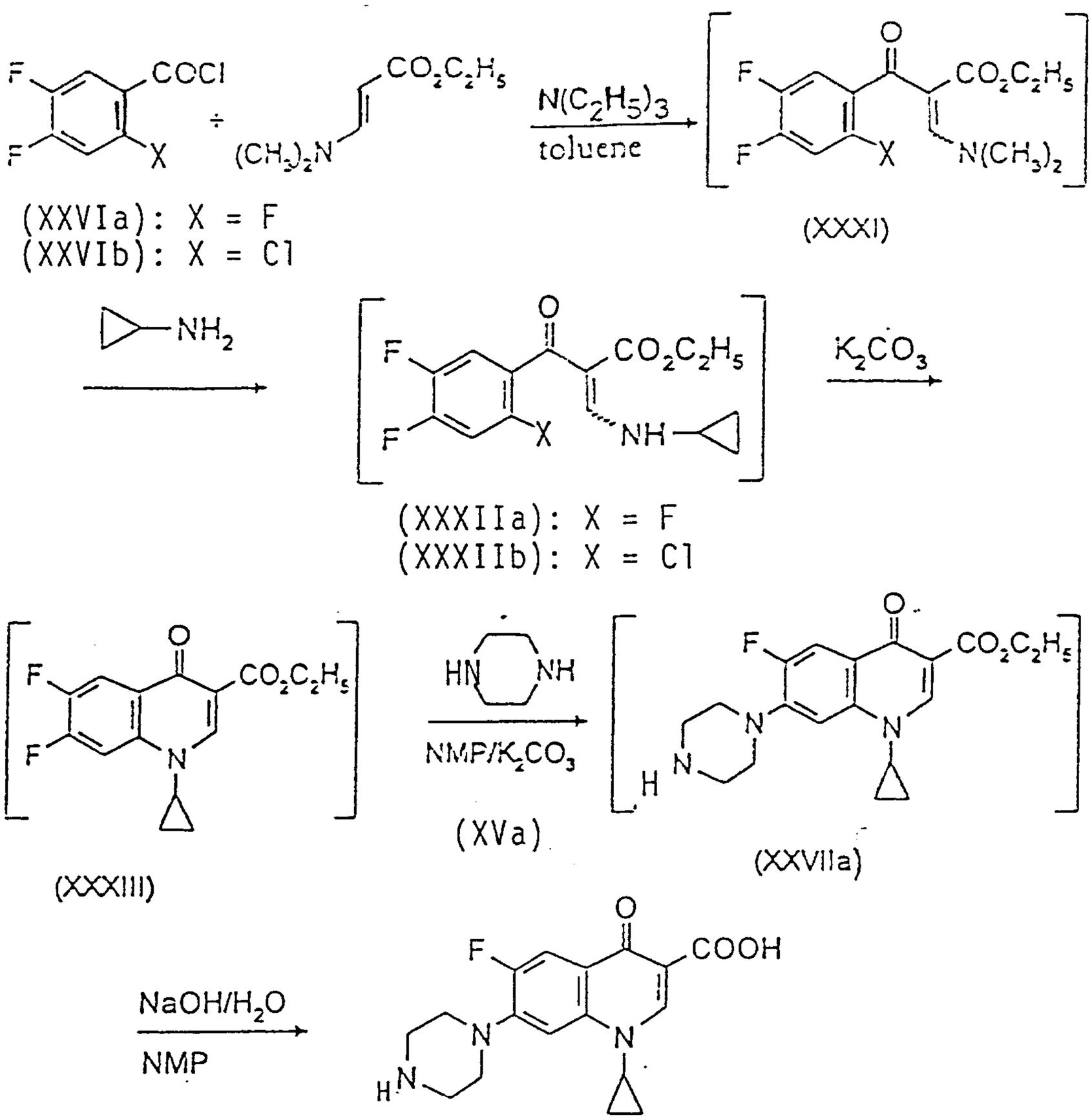
100°C, the mixture is diluted with a further 125 ml of water, filtered and neutralized with half-concentrated hydrochloric acid.

The solid is filtered off, washed with water and isopropanol, and dried overnight in vacuo.

Yield: 17.3 g of (XI) (98.7% by weight, HPLC) ≙ 83% of theory.

Example

Synthesis of 1-cyclopropyl-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (XXXIVa)



(XXVIa): X = F
(XXVIb): X = Cl

(XXXI)

(XXXIIa): X = F
(XXXIIb): X = Cl

(XXXIII)

(XVa)

(XXVIIa)

(XXXIVa)

35.8 g (0.25 mol) of ethyl dimethylaminoacrylate and 27.3 g (0.27 mol) of triethylamine are initially introduced in 50 ml of toluene, and a mixture of 24.3 g (0.125 mol) of 2,4,5-trifluorobenzoyl chloride (XXVIa) and 26.3 g (0.125 mol) of 2-chloro-4,5-difluorobenzoyl chloride (XXVIb) are added dropwise at 50°C within 30 minutes. The mixture is subsequently stirred at from 50 to 55°C for 1 hour and 17.3 g (0.28 mol) of glacial acetic acid and 15.5 g (0.27 mol) of cyclopropylamine are then added dropwise at from 30 to 36°C. After 1 hour, the salts are extracted with 100 ml of water. The organic phase is concentrated by evaporation in water pump vacuum at 40°C. 81.5 g of (XXXIIa/b) are obtained as an oily residue.

The oil (XXXIIa/b) is dissolved by adding 250 ml of N-methylpyrrolidone and heated to from 90°C to 120°C together with 48.4 g (0.35 mol) of potassium carbonate. After 2 hours, 86 g (1 mol) of piperazine (XVa) are added. The mixture is stirred at from 80 to 90°C for one hour and then diluted with 150 ml of water.

After adding 20 g (0.5 mol) of NaOH, the temperature is maintained at 70°C for 1 hour and the mixture is then further diluted with 500 ml of water. Small quantities of impurities in the solution are filtered off and the pH is adjusted to 7.5 with half-concentrated hydrochloric acid.

Once the mixture has been cooled down to from 0 to 5°C, the betain (XXXIV) is filtered off with suction after 2 hours and washed 2 × with 200 ml of water on each

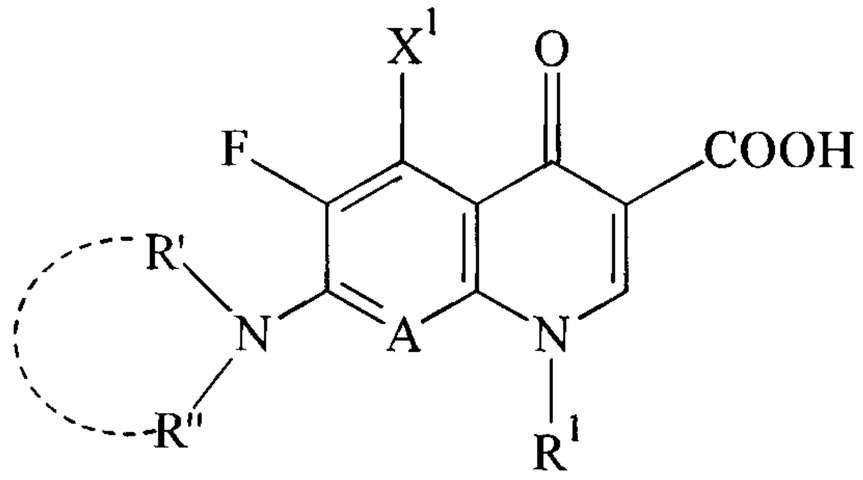
occasion; the product is dried overnight in vacuo.

Yields: XXXIVa 73,4 g (98.0% by weight, HPLC) $\hat{=}$ 86.5% of theory.

30725-120

CLAIMS:

1. A one-pot process for the preparation of a 3-quinolonecarboxylic acid derivative of the general formula (Ia):



(Ia)

wherein:

R' and R'', together with the nitrogen atom to which they are bonded, form a monocyclic or bicyclic heterocycle which optionally contain further nitrogen, oxygen or sulphur hetero atoms, and which are optionally substituted;

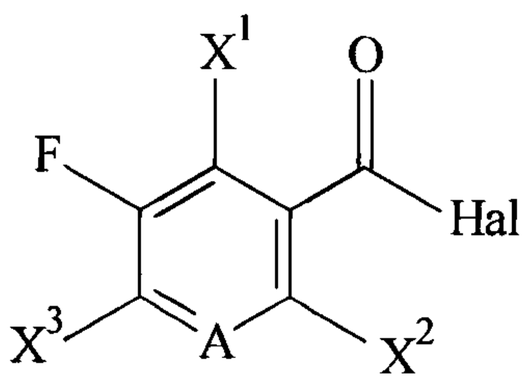
A represents CH, CF, CCl, C-OCH_3 or C-CH_3;

X^1 represents H, a halogen atom, NH_2 or CH_3; and

R^1 represents: (i) C_1-C_3-alkyl or FCH_2CH_2-, or (ii) cyclopropyl or phenyl which are optionally substituted once to three times by a halogen atom;

wherein the process, without isolation of the intermediates after each step, comprises:

(A) an acid halide of the general formula (XXVI):

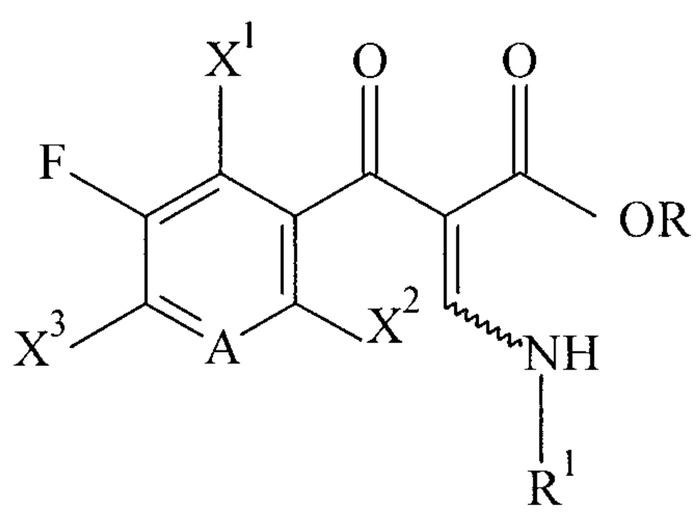


(XXVI)

30725-120

wherein Hal, X^2 and X^3 represent a halogen atom, and A and X^1 are as defined above, is either:

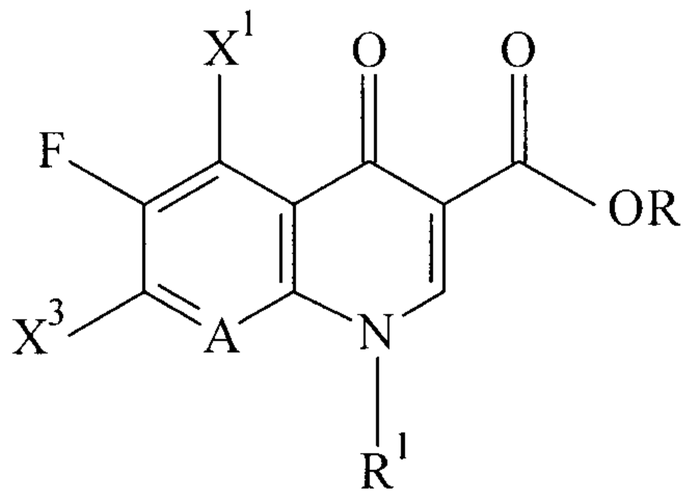
(a) reacted in a solvent with a dimethylaminoacrylic acid ester of the general formula: $(CH_3)_2N-CH=CH-COOR$, after which the aminoacrylic ester of the general formula (XIII) is produced by adding an amine of the general formula: R^1-NH_2, with amine exchange in the acrylic ester moiety of the product of the reaction of the acid halide of the general formula (XXVI) with the dimethylaminoacrylic acid ester, or (b) the acid halide of the general formula (XXVI) is rapidly reacted with an aminoacrylic ester of the general formula: $R^1NH-CH=CH-COOR$, wherein the amine exchange of step (a) is not effected and the aminoacrylic ester of the general formula (XIII) is produced directly:



(XIII)

wherein A, X^1, X^2, X^3 and R^1 are as defined above, and R represents a radical which is suitable for ester formation;

(B) the aminoacrylic ester of the general formula (XIII) is heated in a solvent with an auxiliary base, and thereby cyclized to form a compound of the general formula (XIV):

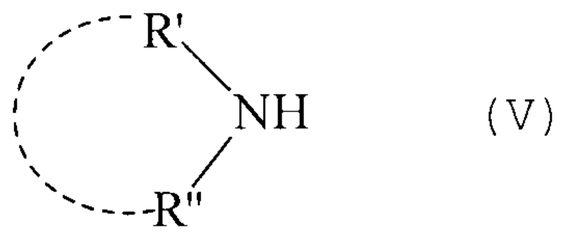


(XIV)

30725-120

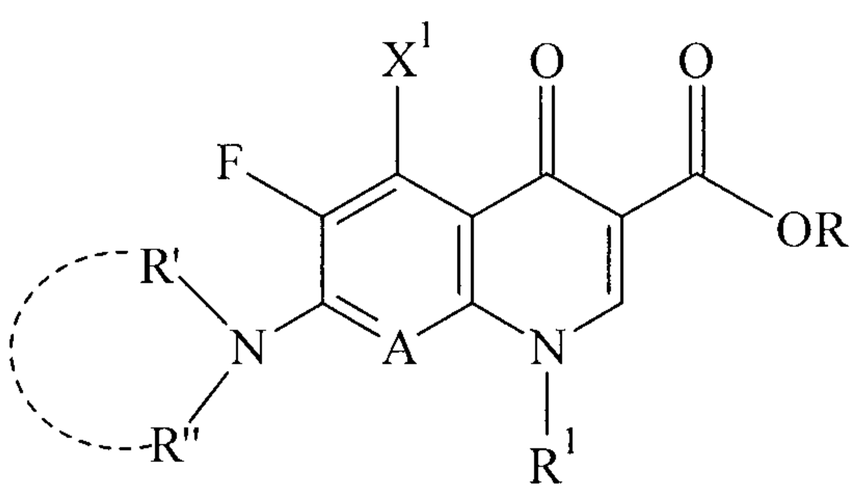
wherein A, R, R^1, X^1 and X^3 are as defined above; and

(C) the compound of the general formula (XIV) is converted by reaction with a heterocyclic compound of the general formula (V):



(V)

wherein R' and R'' are as defined above, into an ester of the general formula (XXVIII):

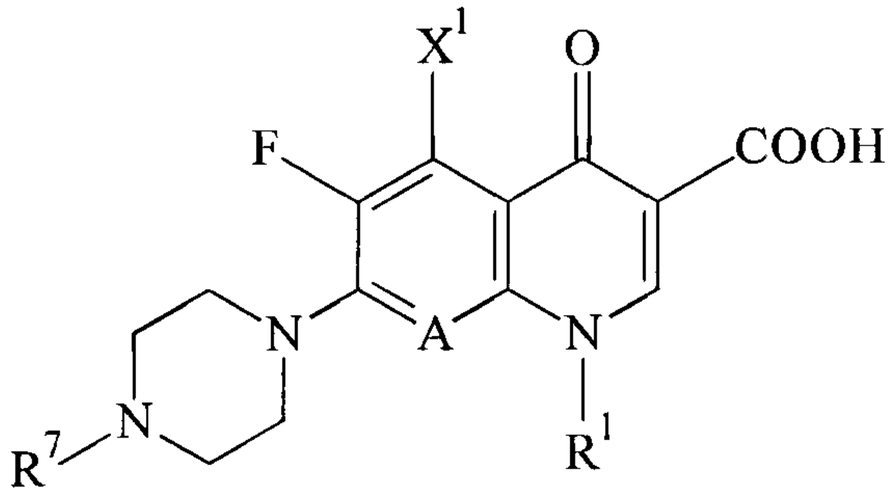


(XXVIII)

wherein A, R, R^1, R', R'' and X^1 are as defined above, wherein the 3-quinolonecarboxylic acid derivative of the general formula (Ia) is obtained by means of alkaline hydrolysis of the ester function of the ester of the general formula (XXVIII), and wherein the 3-quinolonecarboxylic acid derivative of the general formula (Ia) is precipitated by neutralizing the reaction mixture.

2. A process according to claim 1, for the preparation of a 3-quinolonecarboxylic acid derivative of the general formula (Ib):

30725-120



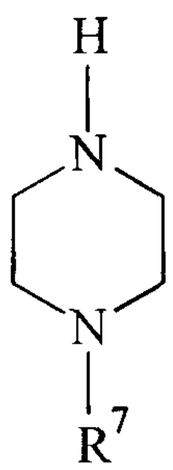
(Ib)

wherein:

A, X^1 and R^1 are as defined in claim 1; and

R^7 represents H, optionally substituted alkyl or phenyl, or a group which is suitable for protecting a nitrogen atom;

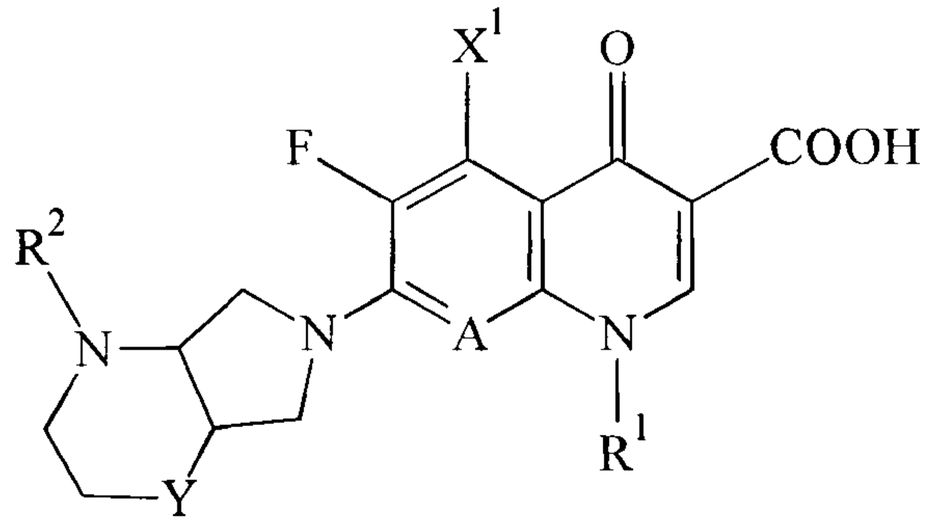
wherein in step (A), step (a) is effected, and wherein in step (C) the heterocyclic compound of the general formula (V) is a heterocyclic compound of the general formula (XV):



(XV)

wherein R^7 is as defined above.

3. A process according to claim 1, for the preparation of a 3-quinolonecarboxylic acid derivative of the general formula (I):



(I)

30725-120

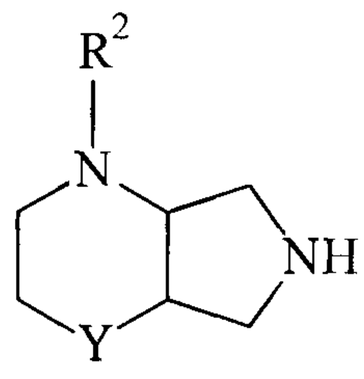
wherein:

A, X^1 and R^1 are as defined in claim 1;

Y represents CH_2 or O; and

R^2 represents H, 5-methyl-2-oxo-1,3-dioxolen-4-yl-methyl, CH_2CH_2-CO-CH_3, C_2-C_5-oxoalkyl, CH_2-CO-C_6H_5, $CH_2CH_2CO_2R^6$, R^6O_2C-CH=C-CO_2R^6, -CH=CH-CO_2R^6 or CH_2CH_2-CN, wherein R^6 represents H or C_1-C_3-alkyl;

wherein in step (A), step (a) is effected, and wherein in step (C) the heterocyclic compound of the general formula (V) is a heterocyclic compound of the general formula (XVII):



(XVII)

wherein Y and R^2 are as defined above.

4. A process according to claim 3, wherein for the heterocyclic compound of the general formula (XVII), R^2 represents H, CH_2-O-CH_3, CH_2-O-C_6H_5, CH_2CH_2-CO-CH_3, $CH_2CH_2CO_2R^6$, R^6O_2C-CH=C-CO_2R^6, -CH=CH-CO_2R^6 or CH_2CH_2CN, wherein R^6 represents C_1-C_3-alkyl, and Y represents CH_2 or O.

5. A process according to claim 2, wherein:

for the acid halide of the general formula (XXVI):

A represents CH,

X^1 represents H,

X^2 represents F or Cl, and

30725-120

X^3 represents F; and

for the heterocyclic compound of the general formula (XV), R^7 represents H or ethyl.

6. A process according to claim 4, wherein:

for the aminoacrylic ester of the general formula (XIII):

A represents CCl or CF,

R represents CH_3 or C_2H_5,

R^1 represents cyclopropyl,

X^1 represents H,

X^2 represents F or Cl, and

X^3 represents F; and

for the heterocyclic compound of the general formula (XVII):

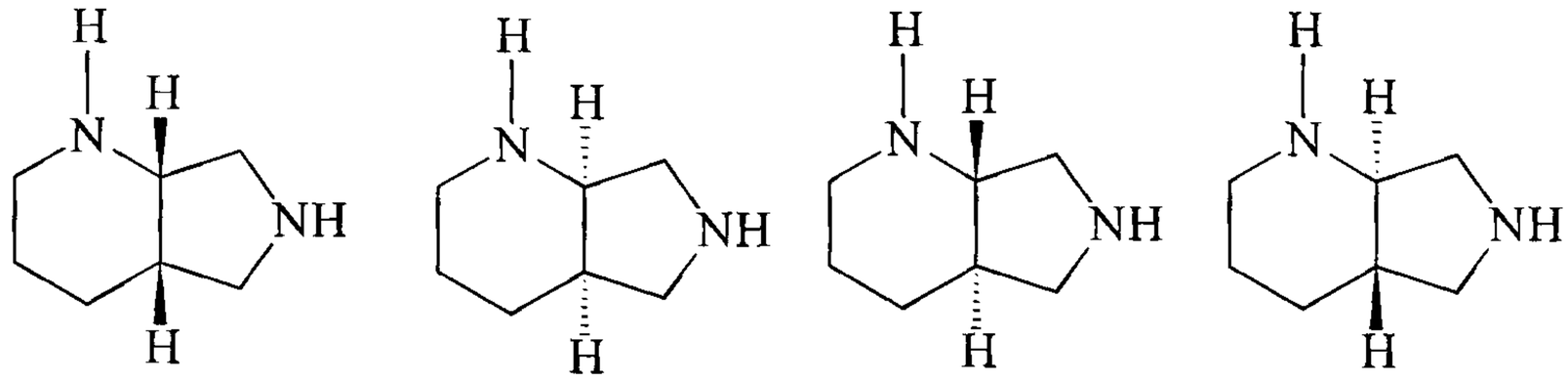
R^2 represents H, and

Y represents CH_2.

7. A process according to claim 3, 4 or 6, wherein the heterocyclic compound of the general formula (XVII) is enantiomerically pure.

8. A process according to claim 6, wherein the heterocyclic compound of the general formula (XVII) is an enantiomerically pure compound selected from the group of the compounds of the formulae (XXIXa) to (XXIXd):

30725-120



(a) (b) (c) (d)

(XXIX a-d) .

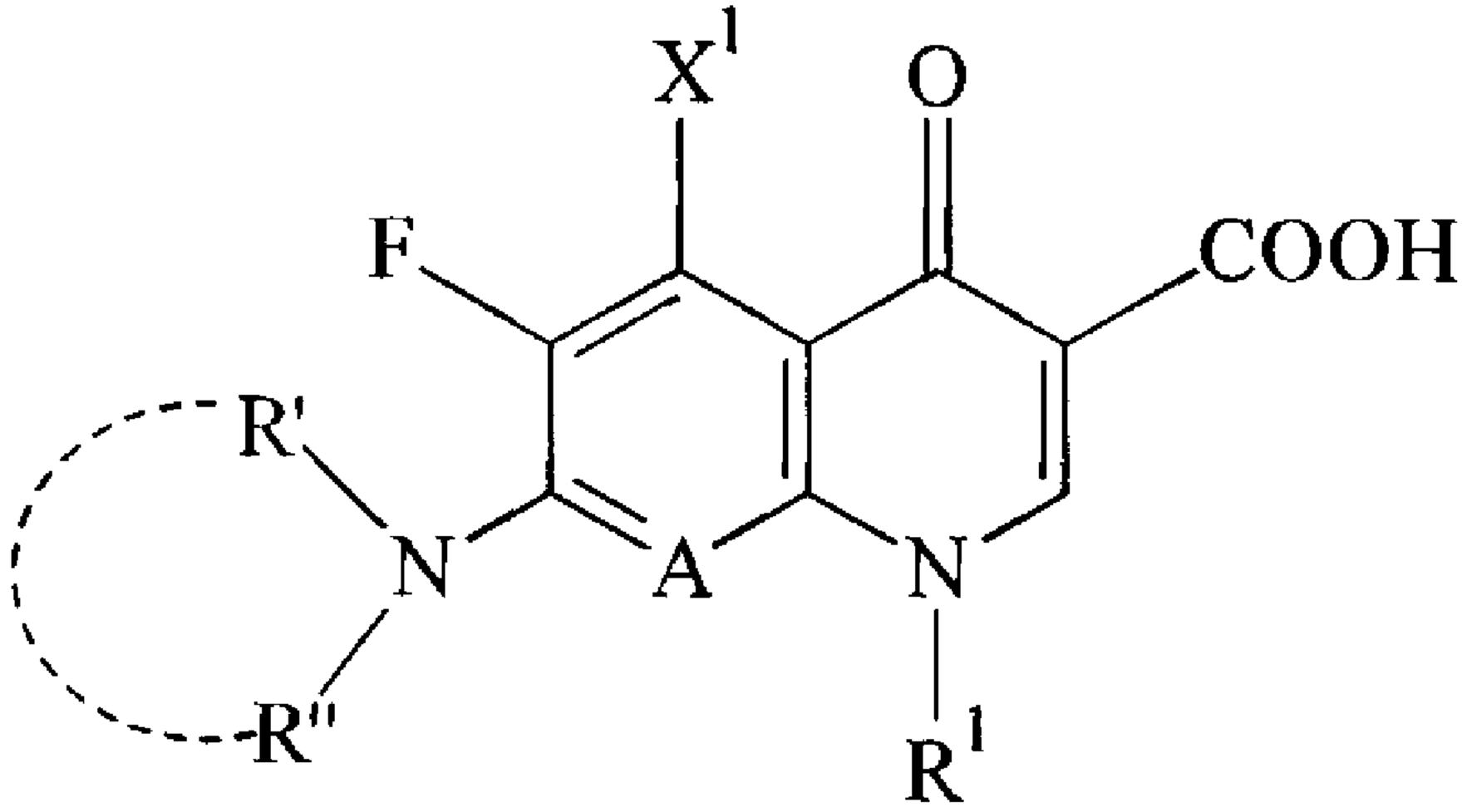
9. A process according to any one of claims 1 to 8, wherein in step (B), the auxiliary base is potassium carbonate.

10. A process according to claim 1, 2 or 3, wherein for the aminoacrylic ester of the general formula (XIII), R is methyl, ethyl or propyl.

11. A process according to claim 3, wherein for the aminoacrylic ester of the general formula (XIII), R is methyl, ethyl or phenyl.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS



(Ia)