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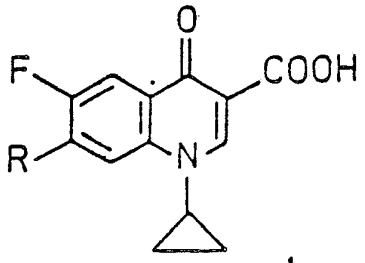
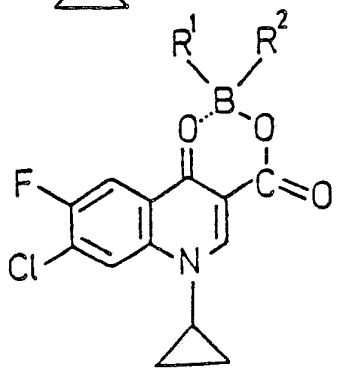
(54) Title: PROCESS FOR THE PREPARATION OF QUINOLINE CARBOXYLIC ACIDS



/I/

/III/



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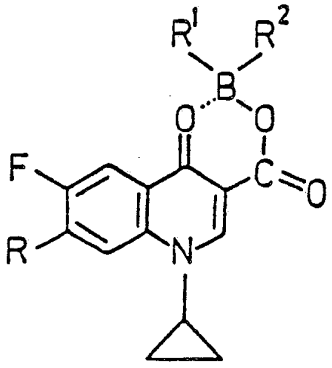

/IV/

(57) Abstract

The invention relates to a new process for the preparation of compounds of general formula (I), (wherein R stands for piperazinyl, 4-methyl-piperazinyl or 4-ethyl-piperazinyl group) and pharmaceutically acceptable salts thereof which comprises reacting a compound of general formula (II), (wherein R^1 and R^2 stand for halogen, for an aliphatic acyloxy group containing 2 to 6 carbon atoms and optionally substituted by halogen, or for an aromatic acyloxy group containing 7 to 11 carbon atoms) with a piperazine derivative of general formula (III), (wherein R^3 stands for hydrogen, methyl or ethyl) or a salt thereof and subjecting the compound of general formula (IV) thus obtained, (wherein R, R^1 and R^2 are as stated above) to hydrolysis after or without isolation and if desired converting the compound of general formula (I) thus obtained into a salt thereof or setting free the same from its salt. The compounds of general formula (I) are known antibacterial agents. The advantage of the present invention is that it makes the desired compounds of general formula (I) available in a simple manner, with high yields and in a short reaction time.

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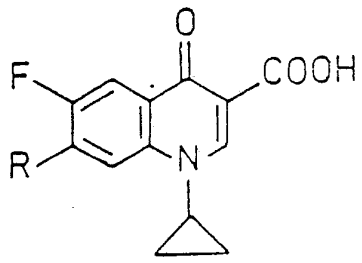
PROCESS FOR THE PREPARATION OF QUINOLINE CARBOXYLIC ACIDS

This invention relates to a new process for the preparation of 1-cyclopropyl-7-substituted-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid derivatives and pharmaceutically acceptable salts thereof.

It is known that the 1-cyclopropyl-7-substituted-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid derivatives of the general Formula I

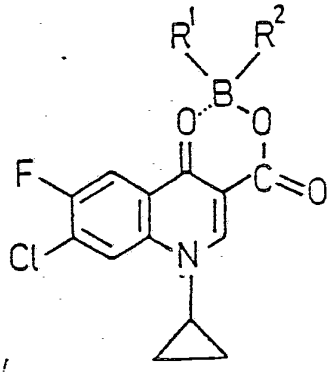


/I/

/wherein R stands for piperazinyl, 4-methyl-piperazinyl or 4-ethyl-piperazinyl group/ possess high antibacterial activity /Eur. J. Clin. Microbiol. 1983, 2, page 111; J. Clin. Pharmacol. 1985, 25, page 82; Drugs Exptl. Clin. Res. 1985, 5, page 317./

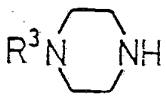
The quinoline carboxylic acids of the general Formula I can be prepared by reacting 1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid and a cyclic amine in the presence of a solvent at a temperature of 135-140 °C for 2 hours /German Off. 3.033.157; German Off. 3.142.854/.

According to the present invention there is provided a new process for the preparation of 1-cyclopropyl-7-substituted-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid derivatives of the general Formula I /wherein R has the same meaning as stated above/ which comprises reacting a compound of the general Formula II



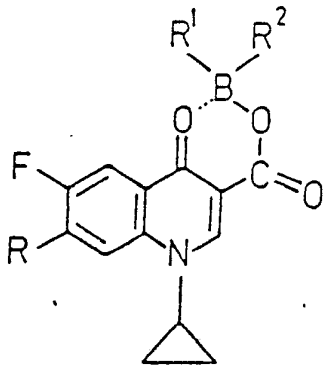
/II/

/wherein R^1 and R^2 are the same or different and stand for halogen, for an aliphatic acyloxy group containing 2 to 6 carbon atoms optionally substituted by halogen, or for an aromatic acyloxy group containing 7 to 11 carbon atoms/ with a cyclic amine of the general Formula



/III/

/wherein R^3 stands for hydrogen, methyl or ethyl/ or a salt thereof and subjecting the compound of the general Formula IV



/IV/

/wherein R, R^1 and R^2 are the same as stated above/ thus obtained to hydrolysis.

The advantage of the process of the present invention is that it makes the desired compound of the general Formula I available in a simple manner with high yields and in a short reaction time.

According to a preferred form of embodiment of the process of the present invention the borate derivative of the general Formula IV /wherein R, R^1 and R^2 are as stated above/ is converted into the desired quinoline-3-carboxylic acid of the general Formula I without isolation.

The borate derivatives of the general Formula IV are new compounds.

The borate derivatives of the general Formula II and the cyclic amine of the general Formula III can be reacted optionally in the presence of an inert organic solvent and an acid binding agent.

As inert organic solvents preferably acid amides /e.g. dimethyl formamide, dimethyl acetamide/, ketones /e.g. acetone, methyl ethyl ketone/, ethers /e.g. dioxane, tetrahydrofuran, diethyl ether/, esters /e.g. ethyl acetate,

methyl acetate, ethyl propionate/, sulfoxides /e.g. dimethyl sulfoxide/, alcohols /e.g. methanol, ethanol, 1-decanol, butanol/ may be used.

As acid binding agent an organic or inorganic base may be used. From the group of organic bases trialkyl amines /e.g. triethyl amine, tributyl amine/, cyclic amines /e.g. pyridine, 1,5-diazabicyclo/5.4.0/undec-5-ene, 1,5-diazabicyclo/4.3.0/non-5-ene, 1,4-diazabicyclo-/2.2.2/octane/ can be mentioned, while as inorganic base preferably hydroxides or carbonates of alkali or alkaline earth metals can be applied. Thus as acid binding agent preferably potassium carbonate, potassium hydrogen carbonate, sodium hydroxide, calcium hydroxide, etc. or an excess of the amine of the general Formula III can be used.

The borone derivative of the general Formula II and the cyclic amine of the general Formula III can be reacted at a temperature ranging from 0 to 200 °C, depending on the solvent used. The reaction time may vary between half an hour and 10 hours depending on the reaction temperature. If the reaction is carried out at an elevated temperature, the reaction time can be shortened. The above reaction conditions are but preferable values and other conditions may be used as well.

The borates of the general Formula IV /wherein R, R^1 and R^2 are as stated above/ can be hydrolysed to the desired quinoline-3-carboxylic acids of the general Formula I, after or without isolation, under acidic

or basic conditions. The compound of the general Formula IV /wherein R is as stated above/ precipitates from the reaction mixture e.g. on cooling and can be separated e.g. by filtration or centrifuging, if desired.

Basic hydrolysis may preferably be carried out by heating an aqueous solution of hydroxydes or carbonates of alkali metals or hydroxides of alkaline earth metals, One may preferably use an aqueous solution of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, calcium hydroxide, potassium hydrogen carbonate. Organic amines /e.g. triethyl amine/ may also be applied in the hydrolysis step.

Acidic hydrolysis may preferably be accomplished by using an aqueous mineral acid. One may preferably proceed by hydrolysing a borate of the general Formula IV by heating same with an aqueous solution of hydrochloric acid, hydrogen bromide, sulfuric acid or phosphoric acid. Hydrolysis may also be accomplished by using organic acids /e.g. acetic acid, propionic acid, etc/.

Hydrolysis of the compounds of the general Formula IV may also be carried out in aqueous medium in the presence of a water-miscible organic solvent. For this purpose e.g. alcohols /e.g. methanol, ethanol/, ketones /e.g. acetone/, ethers /e.g. dioxane/, acid amides /e.g. formamide, dimethyl formamide/, sulfoxides /e.g. dimethyl sulfoxide/, or pyridine may be used.

The quinoline-3-carboxylic acid of the general Formula I thus obtained may be isolated e.g. by adjusting the pH value of the aqueous solution to a suitable value and separating the precipitated crystals e.g. by filtration or centrifuging or by liophylization of the aqueous reaction mixture.

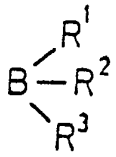
The compounds of the general Formula I can be converted into pharmaceutically acceptable salts thereof by methods known per se. Thus preferably acid addition salts formed with hydrogen halides, sulfonic acids, sulfuric acid or organic acids. One may preferably form chlorides, bromides, 4-methyl-phenyl-sulfonates, methane sulfonates, maleates, fumarates, benzoates, etc. The compounds of the general Formula I form salts with alkali or alkaline earth metals or other metal ions as well. Accordingly sodium, potassium, magnesium, silver, copper salts, etc. may be prepared.

The compounds of the general Formula I and pharmaceutically acceptable salts thereof can be converted into hydrates /e.g. hemihydrates, trihydrates, etc./ by methods known per se.

According to a further aspect of the present invention there are provided new compounds of the general Formula IV /wherein R, R^1 and R^2 are as stated above/.

The starting materials of the general Formula II can be prepared e.g. by reacting 1-cyclopropyl-6-fluoro-7-chloro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid /German Off. 3.141.854/ with a borone derivative /such

as a compound of the general Formula V



/V/

/wherein R^1, R^2 and R^5 stand for halogen, for an aliphatic acyloxy group containing 2 to 6 carbon atoms optionally substituted by halogen, or for an aromatic acyloxy group containing 7 to 11 carbon atoms/ or with fluoroborate in an aqueous or an organic medium.

Further details or the present invention are to be found in the following Examples without limiting the scope of protection to the said Examples.

Example 1

4.1 g of /1-cyclopropyl-6-fluoro-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylate-O^3,O^4/-bis/aceto-O/-borone and 2.8 g of piperazine anhydride are heated in 16 ml of dimethyl sulfoxide to 110 °C under stirring. 40 ml of a 3 w/v % aqueous sodium hydroxide solution are added to the brownish-red solution and the reaction mixture is boiled under reflux for an hour. The hot pale-yellow solution is filtered and the pH value is adjusted to 7 by adding 1.8 ml of 96 % acetic acid. The reaction mixture is cooled to room temperature, the precipitated white crystals are filtered, washed with water and methanol and dried. The crude product is purified by boiling in 10 ml water. Thus 2.99 g of 1-cyclopropyl-6-fluoro-7-/1-piperazinyl/-1,4-dihydro-4-oxo-quinoline-3-carboxylic

acid are obtained. The product decomposes at 255 °C.

Analysis for the Formula $C_{17}H_{18}FN_3O_3$:

Calculated: C=61.62 % H=5.48 % N=12.68 %

Found: C=61.58 % H=5.50 % N=12.61 %.

Example 2

By reacting /1-cyclopropyl-6-fluoro-4-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylate-O^3,O^4/-bis/acetato-O/-borone and N-methyl-piperazine according to Example 1. 1-cyclopropyl-6-fluoro-7-/4-methyl-piperazino/-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid is prepared. The product decomposes at 248-250 °C.

Example 3

4.1 g of /1-cyclopropyl-6-fluoro-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylate-O^3,O^4/-bis/acetato-O/-borone and 3.7 g of N-ethyl-piperazine are heated in 16 ml of dimethyl sulfoxide to 90 °C under stirring. After 10 minutes 40 ml of a 3 w/w % aqueous sodium hydroxide solution are added and the reaction mixture is boiled for an hour under reflux. The hot solution is filtered and the pH value is adjusted to 7 with 96 % acetic acid. The reaction mixture is cooled, the precipitated crystals are filtered and washed with water. Thus 3.3 g of 1-cyclopropyl-7-/4-ethyl-piperazinyl/-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid are obtained. M.p.: 183-185 °C.

Analysis for the Formula $C_{19}H_{22}FN_3O_3$:

Calculated: C=63.35 H=6.17 N=11.69

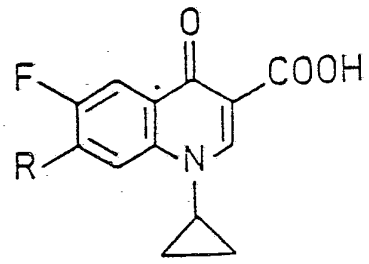
Found: C=63.31 H=6.21 N=11.70

Example 4

3.3 g of /1-cyclopropyl-6-fluoro-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylate-O^3,O^4/-difluoro-borone are reacted with 3.7 g of N-ethyl-piperazine according to Example 3. Thus 3.4 g of 1-cyclopropyl-7-/4-ethyl-1-piperazinyl/-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid are obtained which in admixture at any ratio with the product of Example 3 no depression of the melting point occurs.

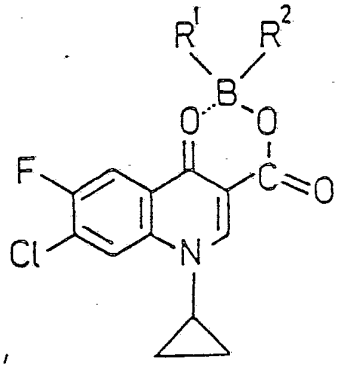
WHAT WE CLAIM IS:

1. Process for the preparation of compounds of the general Formula I



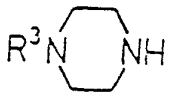
/I/

/wherein R stands for piperazinyl, 4-methyl-piperazinyl or 4-ethyl-piperazinyl group/ and pharmaceutically acceptable salts thereof which comprises reacting a compound of the general Formula II



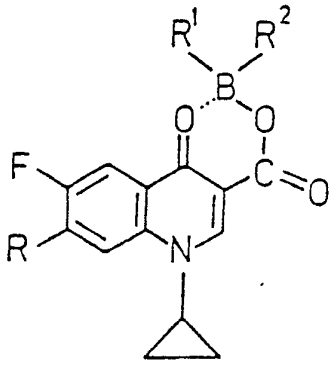
/II/

/wherein R^1 and R^2 stand for halogen, for an aliphatic acyloxy group containing 2 to 6 carbon atoms optionally substituted by halogen, or for an aromatic acyloxy group containing 7 to 11 carbon atoms/ with a piperazine derivative of the general Formula III



/III/

/wherein R^3 stands for hydrogen, methyl or ethyl/ or a salt thereof and subjecting the compound of the general Formula IV



/IV/

thus obtained /wherein R, R^1 and R^2 are as stated above/ to hydrolysis after or without isolation and if desired converting the compound of the general Formula I thus obtained into a salt thereof or setting free the acid from its salt.

2. Process according to Claim 1 which comprises reacting a compound of the general Formula II with a piperazine derivative of the general Formula III in the presence of an organic solvent, preferably an acid amide, sulfoxide, ketone, alcohol, ether or ester.

3. Process according to Claim 2 which comprises using dimethyl sulfoxide as organic solvent.

4. Process according to Claim 1 which comprises carrying out the reaction of the compounds of the general Formulae II and III in the presence of an acid binding agent.

5. Process according to Claim 4 which comprises using an amine or an excess of the compound of the general Formula III as acid binding agent.

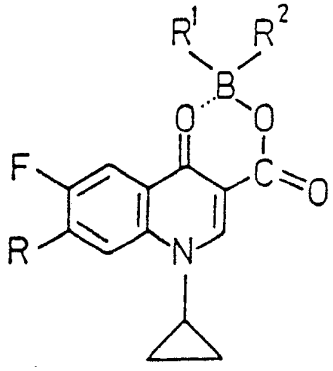
6. Process according to Claim 1 which comprises carrying out the hydrolysis in acidic medium.

7. Process according to Claim 6 which comprises carrying out the reaction by using as acid an organic or inorganic acid, preferably hydrochloric acid, sulfuric acid or acetic acid.

8. Process according to Claim 1 which comprises carrying out the hydrolysis in a basic medium.

9. Process according to Claim 8 which comprises using as a base an alkali metal hydroxide, an alkaline earth metal hydroxide or an organic base, preferably an aqueous triethyl amine solution.

10. Compounds of the general Formula IV



/IV/

/wherein R stands for piperazinyl, 4-methyl-piperazinyl or 4-ethyl-piperazinyl group, R^1 and R^2 stand for halogen, for an aliphatic acyloxy group containing 2 to 6 carbon atoms optionally substituted by halogen, or for an aromatic acyloxy group containing 7 to 11 carbon atoms/.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 88/00019

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 215/56; C 07 F 5/02 // A 61 K 31/47

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl.[4]	C 07 D 215/56; C 07 F 5/02,5/04.

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	Chemical Abstracts, vol. 103, no. 15, issued 1985, October 14 (Columbus, Ohio, USA), Daiichi Seiyaku "Oxazines" see page 730, column 1, abstract-no. 123 491p & JP, A, 60-78 986 (DAIICHI SEIYAKU) 04 May 1985.	(1,3,8)
Y	Chemical Abstracts, vol. 102, no. 7, issued 1985, February 18 (Columbus, Ohio, USA), Daiichi Seiyaku "1-Ethyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydro-quinoline-3-carboxylic acids" see page 605, column 1, abstract-no. 62 272y & JP, A, 59-122 470 (DAIICHI SEIYAKU) 14 July 1984.	(1,3,8)

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27 June 1988 (27.06.88)	01 July 1988 (01.07.88)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	Prippram

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 88/00019

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

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Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
JP-A2-60-078 986	04/05/1985	None	
JP-A2-59-122 470	14/07/1984	None	