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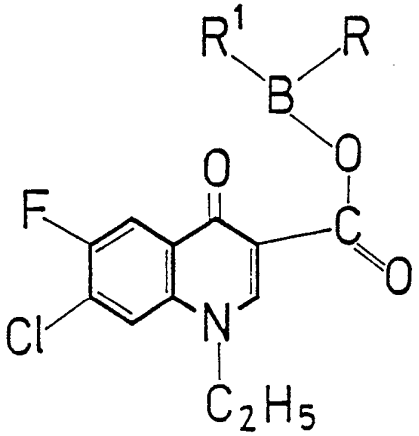
(54) Title: NORFLOXACIN INTERMEDIATE



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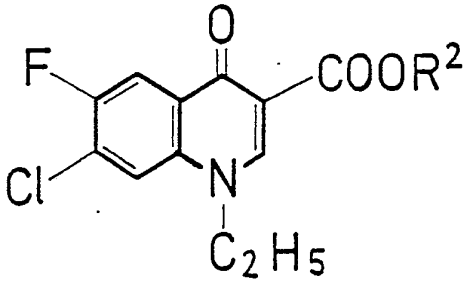

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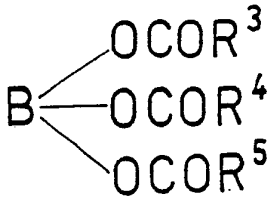

/III/

(57) Abstract

A process for the preparation of compounds of general formula (I), (wherein R and R^1 stand for an aliphatic acyloxy group comprising 2-5 carbon atoms and optionally substituted by halogen or for an aromatic acyloxy group comprising 7-11 carbon atoms), which comprises reacting a compound of general formula (II), (wherein R^2 stands for hydrogen or alkyl comprising 1-4 carbon atoms) with a borone derivative of general formula (III), (wherein R^3, R^4 and R^5 stand for an alkyl group comprising 1-4 carbon atoms and optionally substituted by halogen or for an aryl group comprising 6-10 carbon atoms). The new compounds of general formula (I) are useful pharmaceutical intermediates.

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NORFLOXACIN INTERMEDIATE

This invention relates to new intermediates useful in the preparation of Norfloxacin . More particularly it is concerned with new anhydrides of 1-ethyl-6-fluoro--7-chloro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid and boric acids and a process for the preparation thereof.

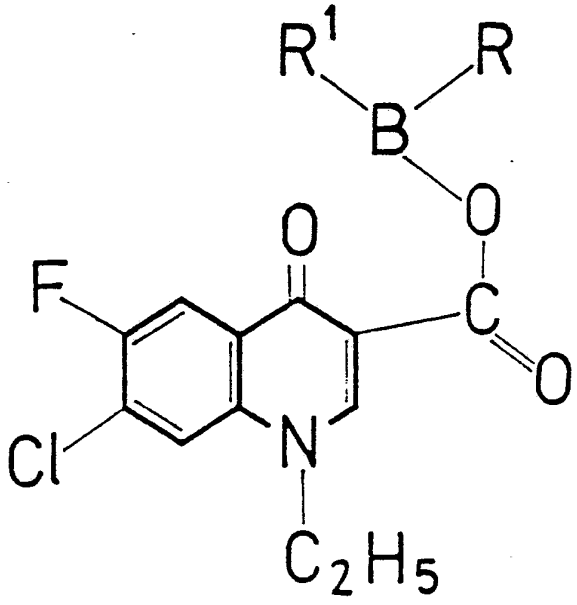
It is known that ethyl-1-ethyl-6-fluoro-7-chloro-4--oxo-1,4-dihydro-quinoline-3-carboxylate /Journal of Medicinal Chemistry 23, 1358 (1980); Japanese patent specification No. 80 33,453/ is an intermediate useful in the preparation of 1-ethyl-6-fluoro-7-substituted--4-oxo-1,4-dihydro-quinoline-3-carboxylic acids having antibacerial effect (Ann. Microbiol /Paris/ 1981, 132A, 267; Journal of Medicinal Chemistry 1980, 23, 1358; Pathol. Biol. 1982, 30, 394; Cyo Yakuri, 1983, 25, 475; Pathol. Biol. 1983, 31, 501; Antimicrob. Agents Chemother. 1980, 17, 103; 1981, 19, 188; 1981, 20, 265; C.R. Scances Acad. Sci., Ser. 3, 1981, 292, 37/.

The latter compounds can be prepared in two steps by reacting ethyl-1-ethyl-6-fluoro-7-chloro-4-oxo-1,4--dihydro-quinoline-3-carboxylate with a cyclic amine at a temperature above 100 ^{o}C in the presence of a solvent for several hours and subjecting the ethyl-1--ethyl-6-fluoro-7-substituted-4-oxo-1,4-dihydro-quinoline-3-carboxylate thus obtained to hydrolysis; the order of succession of the said two steps can be changed, if desired (Japanese patent specifications Nos. 79,138,582 and 80,33,453; Belgian patent specifications Nos. 863,429; 870,917; 879,106 and 890,223; DOS No. 2,840,910 and French patent publication No. 2,424,919).

The above processes are accompanied by several drawbacks. The reaction time used is long. Moreover the halogen/amine group replacement reaction is not selective and in addition to the desired chloro/amine reaction in position 7 also a fluoro/amine exchange in position 6 takes place to a considerable extent.

It has been found that the selectivity of the desired halogen/amine replacement reaction in position 7 can be increased significantly by reacting a cyclic amine with an anhydride of the general Formula I (wherein R and R^1 stand for an aliphatic acyloxy group comprising 2-5 carbon atoms and optionally substituted by halogen or for an aromatic acyloxy group comprising 7-11 carbon atoms). A further advantage of this process is that the reaction time is significantly shorter.

According to the present invention there is provided a process for the preparation of compounds of the general Formula I



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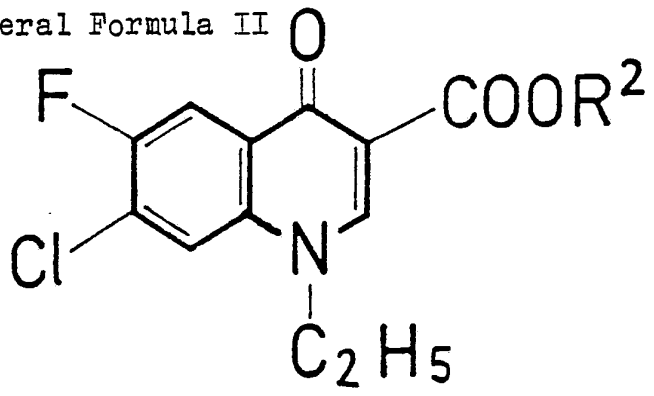
(wherein R and R^1 stand for an aliphatic acyloxy group comprising 2-5 carbon atoms and optionally substituted by halogen or for an aromatic acyloxy group comprising 7-11 carbon atoms), which comprises reacting a compound of the general Formula II



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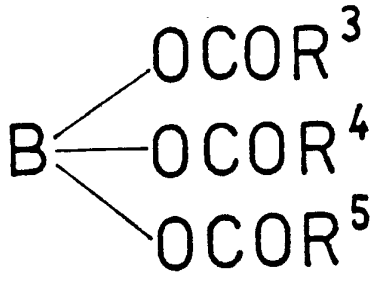
(wherein R^2 stands for hydrogen or alkyl comprising 1-4 carbon atoms) with a borone derivative of the general Formula III



/III/

(wherein R^3, R^4 and R^5 stand for an alkyl group comprising 1-4 carbon atoms and optionally substituted by halogen or for an aryl group comprising 6-10 carbon atoms).

The reaction of the quinoline-3-carboxylic acid of the general Formula II and the borone derivative of the general Formula III can preferably be carried out in an optionally halogenated organic carboxylic acid - which may also contain the corresponding acid anhydride - at a temperature between 0 and 200 °C. The compound of the general Formula I thus formed precipitates from the reaction mixture either spontaneously or under cooling and can be separated e.g. by filtration.

The reaction may however also be carried out in an other solvent (e.g. sulfoxide, amides, pyridine, aromatic hydrocarbons), if desired.

The borone derivatives of the general Formula III can be used in a molar ratio of 1-50 moles related to 1 mole of the quinoline-3-carboxylic acid derivative of the general Formula II.

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

Example 1

A mixture of 9.3 g of boric acid and 70 g of

propionic anhydride is stirred at 100 °C for 15 minutes whereupon the reaction mixture is heated to the boiling point. After half an hour the temperature is lowered to 110 °C and 29.8 g of ethyl-1-ethyl-6-fluoro-7-chloro--4-oxo-1,4-dihydro-quinoline-3-carboxylate are added. The reaction mixture, which turns to a thick suspension within some minutes, is stirred at 110 °C for 2 hours, then cooled to room temperature and diluted with 300 ml of water. The reaction mixture is cooled and the precipitated crystals are filtered. Thus 41.5 g of 1-ethyl--6-fluoro-7-chloro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid-borone-di(propionyloxy)-anhydride are obtained, yield: 97.7 %; Mp.: 252 °C (decomposition).

Analysis for the Formula $C_{18}H_{18}BFClNO_7$

calculated	C = 50.79 %,	H = 4.26 %,	N = 3.29 %;
found	C = 50.94 %,	H = 4.15 %,	N = 3.41 %.

Example 2

A mixture of 46.3 g of boric acid and 345 g of propionic anhydride is stirred at 100 °C for 15 minutes whereupon the reaction mixture is heated to boiling. After half an hour the reaction temperature is lowered to 110 °C and 134.5 g of 1-ethyl-6-fluoro-7-chloro-4-oxo--1,4-dihydro-quinoline-3-carboxylic acid are added. The reaction mixture is stirred at 110 °C for 2 hours and cooled under 10 °C. The reaction mixture is diluted with 150 ml of water and allowed to crystallize in a refrigerator overnight. Next morning the precipitated crystals are filtered, washed with water and dried in vacuo. Thus 208.6 g of 1-ethyl-6-fluoro-7-chloro-4-oxo--1,4-dihydro-quinoline-3-carboxylic acid——borone-di(propionyloxy)-anhydride are obtained, yield: 98 %. The product melts at 269 °C (decomposition). A mixture of the product-formed with any amount of the compound prepared according to Example 1 shows no melting point depression.

Example 3

A mixture of 9.3 g of boric acid and 54.1 g of acetic anhydride is heated at 110 °C for 30 minutes. The reaction mixture is cooled to 80 °C and 29.8 g of ethyl-1-ethyl-6-fluoro-7-chloro-4-oxo-1,4-dihydro--quinoline-3-carboxylate are added. The reaction mixture is stirred at 110 °C for 2 hours, cooled below 10 °C and diluted with 100 ml of water. The cooled reaction mixture is allowed to crystallize in a refrigerator overnight. Next morning the precipitated crystals are filtered, washed with water and dried. Thus 33.5 g of 1-ethyl-6-fluoro-7-chloro-4-oxo-1,4-dihydro-quinoline--3-carboxylic acid-borone-di(acetoxy)-anhydride are obtained. Yield: 84.4 %. The product decomposes at 274 °C.

Analysis for the Formula $C_{16}H_{14}FClBNO_7$

calculated	C = 48.34 %,	H = 3.54 %,	N = 3.52 %;
found	C = 48.48 %,	H = 3.43 %,	N = 3.57 %.

Example 4

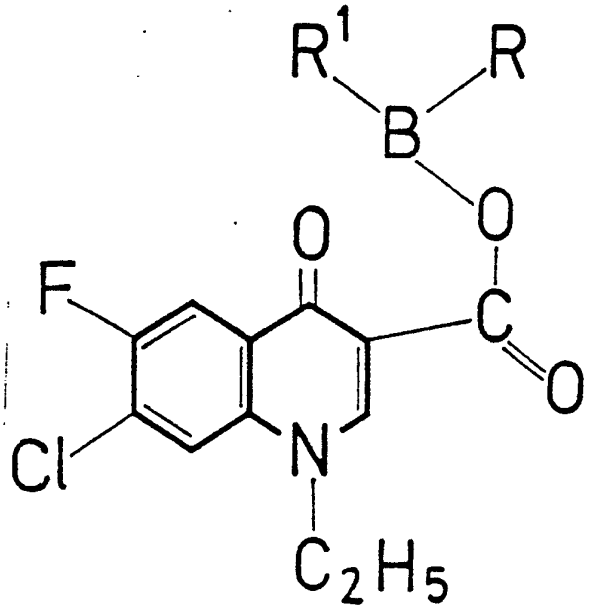
2.74 g of boric acid and 22.6 g. of acetic acid anyhdride are reacted in the presence of 2 mg of zinc chloride. The boric acid is gradually added to the acetic acid anhydride while the reaction temperature raises to 88 °C. The temperature of the reaction mixture is then slowly raised to 110 °C and 8.79 g. of ethyl--1-ethyl-6-fluoro-1,4-dihydro-7-chloro-4-oxo-3-quinoline--carboxylate are added, which had been previously dissolved in 18 ml. of hot 96 % by W/V acetic acid. The orange-red clear solution is stirred for 2 hours at 110 °C and then allowed to cool. The precipitated crystals are filtered and washed several times with water and once with methanol and dried. 10.8 g (92.1 %) off--white (1-ethyl-6-fluoro-7-chloro-1,4-dihydro-4-oxo--3-quinoline-carboxylate-$\underline{O}^3$,$\underline{O}^4$)-bis(acetate-O)-boron are obtained, decomposing at 273 °C.

Analysis for the formula $C_{16}H_{14}BClFNO_7$

calculated:	C= 48.35 %	H = 3.55 %	N = 3.52 %
found:	C =48.2 %	H = 3.5 %	N = 3.2 %.

WHAT WE CLAIMS IS:

1. Compounds of the general Formula I



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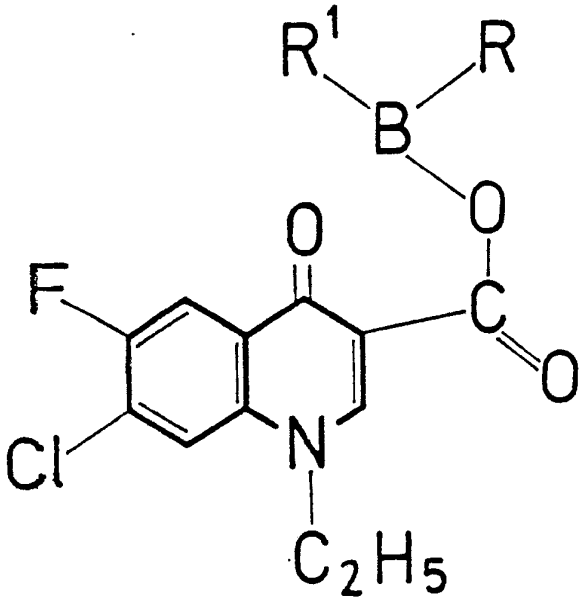
(wherein R and R^1 stand for an aliphatic acyloxy group comprising 2-5 carbon atoms and optionally substituted by halogen or for an aromatic acyloxy group comprising 7-11 carbon atoms).

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



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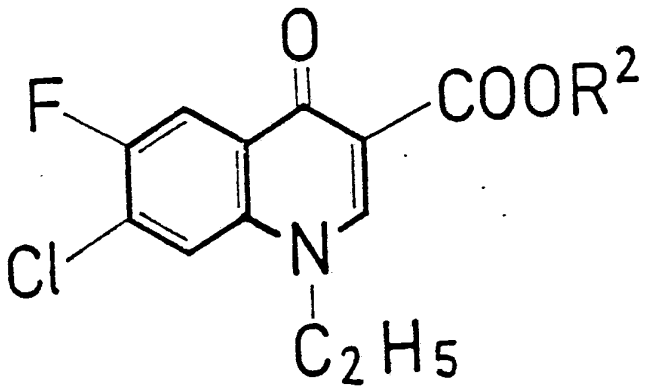
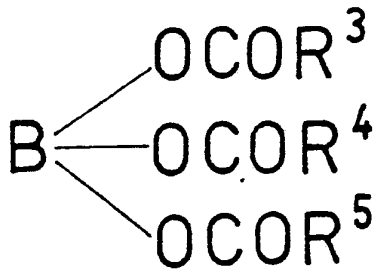
(wherein R and R^1 stand for an aliphatic acyloxy group comprising 2-5 carbon atoms and optionally substituted by halogen or for an aromatic acyloxy group comprising 7-11 carbon atoms), which comprises reacting a compound of the general Formula II



/II/

(wherein R^2 stands for hydrogen or alkyl comprising 1-4 carbon atoms) with a borone derivative of the general Formula III



/III/

(wherein R^3, R^4 and R^5 stand for an alkyl group comprising 1-4 carbon atoms and optionally substituted by halogen or for an aryl group comprising 6-10 carbon atoms).

3. Process according to Claim 2 which comprises carrying out the reaction of the compounds of the general Formulae II and III in the presence of a solvent.

4. Process according to Claim 2 which comprises carrying out the reaction of the Compounds of the general Formulae II and III at a temperature between 0 and 150 °C.

5. Compounds of the general Formula I whenever prepared by the process according to any of Claims 2-4.

6. A process as substantially described herein with particular references to the Examples.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 86/00068

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 F 5/02 // C 07 D 215/56

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]
A	Patent Abstracts of Japan, unexamined applications, C field, vol. 8, no. 241, issued 1984, November 6 (The Patent Office Japanese Government), DAIICHI SEIYAKU K.K. "Preparation of Quinoline-3-carboxylic Acid Derivative" see page 73 C 250, Kokai-no. 59-122 470 (A).	(1,2)

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
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