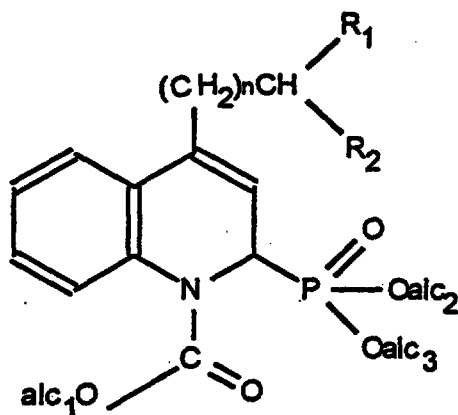


New derivatives of 1(2H) quinoline carboxylic acid, their preparation process and their use for the synthesis of products endowed with antibiotic properties.

5 The present invention relates to new derivatives of 1(2H) quinoline carboxylic acid, their preparation process and their use for the synthesis of products endowed with antibiotic properties.

A subject of the invention is the compounds of formula
10 (I):



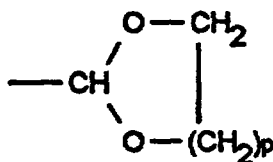
(I)

20

in which alk_1 , alk_2 and alk_3 identical to or different from each other represent an alkyl radical containing up to 8 carbon atoms, n represents an integer which can vary from 0 to 8, R_1 and R_2 represent an O-alkyl radical containing up to 8 carbon atoms, or form together with the carbon atom to
25 which they are linked a cyclic acetal.

The alkyl radical is preferably a methyl, ethyl, *n*-propyl, isopropyl, butyl, isobutyl or *tert*-butyl radical.

When R_1 and R_2 form with the carbon atom to which they
30 are linked a cyclic acetal, it is preferably a:



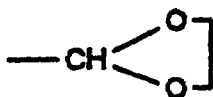
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group in which p represents the number 1, 2, 3 or 4.

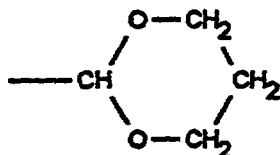
A quite particular subject of the invention is the compounds of formula (I) in which n represents the number 2,

as well as those in which alk_1 , alk_2 and alk_3 represent an ethyl radical.

Among the preferred compounds of the invention there can be mentioned the compounds of formula (I) in which R_1 and R_2 form together with the carbon atom to which they are linked a 1,3-dioxolane:



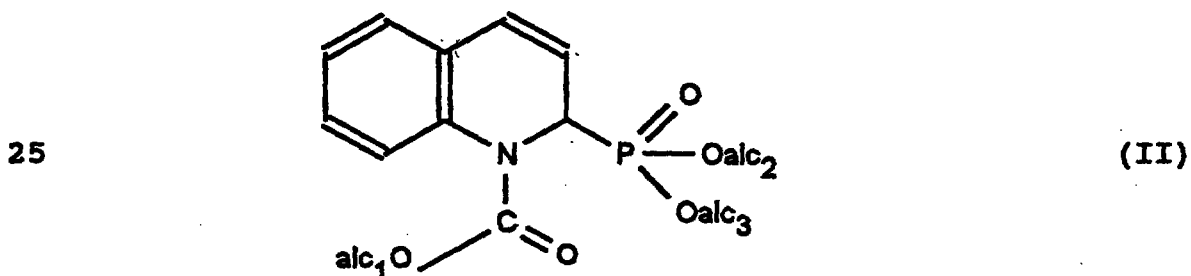
10 or 1,3-dioxane radical



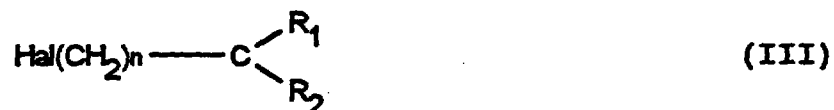
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A quite particular subject of the invention is the compound of formula (I) the preparation of which is given hereafter in the experimental part.

A subject of the invention is also a preparation process for compounds of formula (I), characterized in that a compound of formula (II):



in which alk_1 , alk_2 and alk_3 retain their previous meaning is subjected to the action of a compound of formula (III):



35 in which Hal represents a halogen atom and R_1 , R_2 and n retain their previous meaning, in order to obtain the corresponding compound of formula (I).

The compounds of formula (II) used as starting products

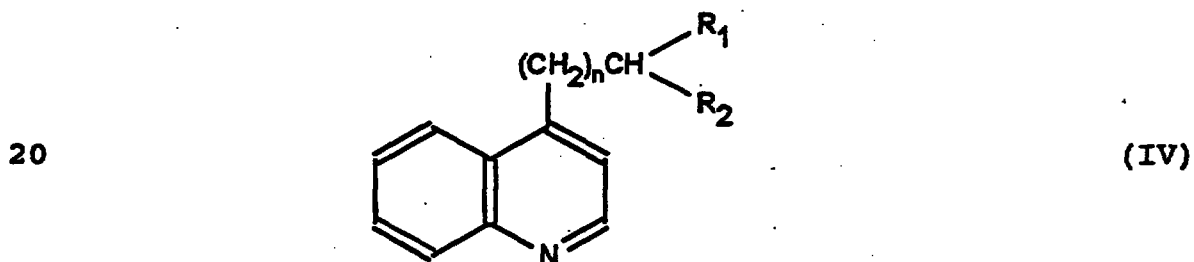
for the process of the invention can be prepared according to the processes described in Tetrah. Lett. 23(16), 1709-12 (1982) or in the Japanese Patent Application 1221-102.

In a preferred implementation of the process of the invention, Hal is a bromine or chlorine atom.

A particular subject of the invention is a process characterized in that the operation is carried out in the presence of a strong base.

The base used is butyllithium, or an alkaline or alkali earth alcoholate, for example lithium, sodium, or potassium *tert*-butylate or *tert*-amylate or also lithium hydroxide. Sodium or potassium *tert*-butylate or *tert*-amylate is preferably used.

Furthermore a subject of the invention is the use characterized in that a compound of formula (I) is subjected to the action of a strong base in order to obtain the corresponding compound of formula (IV):



in which n , R_1 and R_2 retain their previous meaning.

25 A more particular subject of the invention is the use characterized in that the strong base can be soda or preferably sodium ethylate.

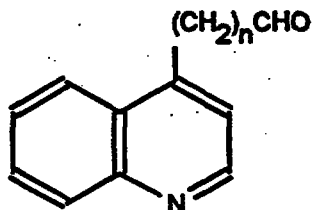
The operation can also be carried out in the presence of an alkaline iodide such as sodium iodide in an aprotic polar solvent at high temperature.

30 Advantageously, and in particular when R_1 and R_2 form together with the carbon atom to which they are linked a cyclic acetal, the product of formula (IV) is purified in the form of the hydrochloride but it can also be in the form of the aldehyde hydrate.

A more particular subject of the invention is the use of the compound of Example 1 or 2, for the preparation of the products of formula (IV) described in the experimental part.

The compounds of formula (IV) are products known in a general fashion; they can also be prepared according to the process described in European Patent Application 676409.

The products of formula (IV) can be converted into the 5 corresponding aldehydes:



10

and then be converted into products having antibiotic properties according to the process described in the aforementioned Patent Application.

15 In this way, starting from the product of the application described in the experimental part, 11,12-dideoxy-3-de((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribohexopyranosyl) oxy)-6-O-methyl-3-oxo-12,11-(oxycarbonyl(2-(3-(4-quinolinyl) propyl) hydrazono))-
20 erythromycin can be prepared, which is a product having useful antibiotic properties as indicated in the aforementioned European Patent Application.

The following examples illustrate the invention without however limiting it.

25 **EXAMPLE 1:** Ethyl 2-(diethoxyphosphinyl)-4-(2-(1,3-dioxolan-2-yl) ethyl)-1(2H)-quinoline carboxylate

75 ml of a 1.6 M solution of n-butyllithium in hexane is added at -78°C, to a solution containing 33.933 g of ethyl 2-(diethoxyphosphinyl-1(2H)-quinoline carboxylate in 500 ml of
30 tetrahydrofuran. Next 18 ml of 2-(2-bromoethyl)-1,3-dioxolane is added. The reaction medium is allowed to return to ambient temperature, then maintained under agitation for 5 hours. 300 ml of water is added, followed by agitation and decanting. The organic phase is washed with water and dried followed by
35 filtration and elimination of the solvent. 63.45 g of product is obtained which is purified by chromatography eluting with ethyl acetate. In this way the sought product is obtained.

R_f = 0.16. Yield 62.7 %.

NMR CDCl₃ ppm

0.97 (t), CH₃ of N-COOEt; 1.18 (t) - 1.33 (t), the CH₃'s of P-OEt; 1.91 (m) (2H), CH-CH₂-CH₂; 2.60 (m) (2H), =C-CH₂-CH₂; ~
 5 3.70 to 4.40 (~ 11H), the CH₂'s of P-OEt and COOEt, the Q-CH₂'s of the ketal; 4.96 (t) (1H), O-CH-CH₂; 5.52 (wd) (1H), P-CH-N; 5.90 (wt), H₃; 7.11 (m) (1H), 7.20 to 7.35 (m) (2H).

APPLICATION 1: 4-(2-(1,3-dioxolan-2-yl) ethyl-quinoline

10 A mixture containing 63.45 g of the product prepared in Example 1, 430 ml of a solution of 2N soda and 430 ml of absolute ethanol is heated under reflux for one hour under nitrogen.

The ethanol is eliminated and extraction is carried out
 15 with isopropyl ether. The organic phases are washed with water, dried and filtered. (Yield = 43 %). The solvent is distilled off and 11.263 g of product is obtained which is purified by chromatography on silica eluting with a 70-30 ethyl acetate-cyclohexane mixture. The sought product is
 20 obtained. R_f = 0.4.

NMR CDCl₃ ppm

2.13 (m), central -CH₂-; 3.22 (m), =C-CH₂-CH₂-; 3.86 to 4.11 (m), -O-CH₂-CH₂-O-; 5.00 (t), O-CH (ketal); 7.27 (d, j = 4.5) H₃; 8.81 (d, j = 4.5) H₂; 7.57 (dt) and 7.71 (dt), H₆ and H₇;
 25 8.10 (m, 2H), H₅ and H₈.

EXAMPLE 2: Ethyl 2-(diethoxyphosphinyl) 4-(2-(1,3-dioxan-2-yl) ethyl) 1(2H)-quinoline carboxylate

3.6 g of potassium terbutylate is added at 20 ± 2°C, to a solution containing 9 g of ethyl 2-(diethoxyphosphinyl)
 30 1(2H)-quinoline carboxylate and 45 ml of dimethylformamide. The reaction medium is maintained under agitation for 30 minutes. 9.7 g of 2-(2-iodoethyl) 1,3-dioxane is then introduced at -20° ± 2°C. 54 ml of water is added, the solution obtained is poured into 180 ml of water, extraction
 35 is carried out with isopropyl ether followed by washing with

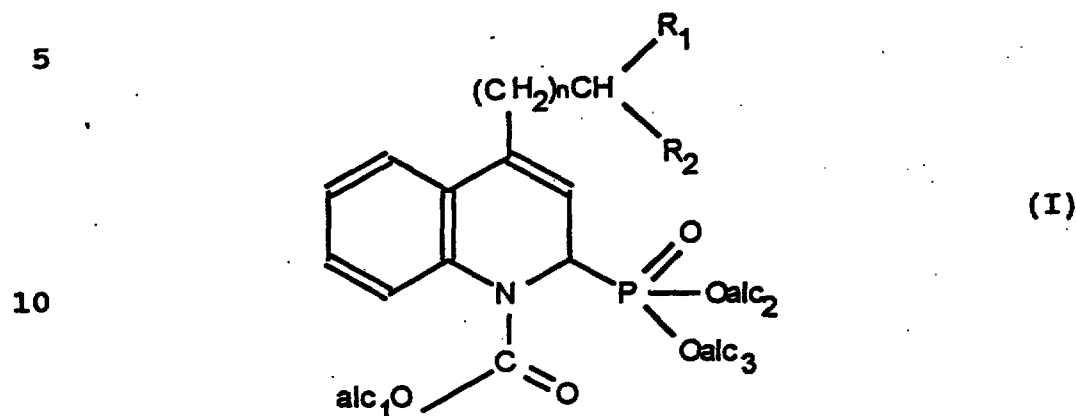
water, drying and washing again with isopropyl ether. The extracts are concentrated under reduced pressure in order to obtain 12 g of sought product.

APPLICATION 2: 4-(2-(1,3-dioxan-2-yl) ethyl quinoline
5 hydrochloride.

7.5 g of sodium ethylate is introduced at $+20^{\circ} \pm 2^{\circ}\text{C}$, into a solution containing 10 g of the product prepared in Example 1 or 2 and 50 ml of ethanol 100. The mixture obtained is taken to reflux for 1 hour followed by cooling down to $20^{\circ} \pm 2^{\circ}\text{C}$ then agitation is maintained for 1 hour and 30 minutes. Distillation under reduced pressure is carried out and then 50 ml of water is added at $20^{\circ} \pm 2^{\circ}\text{C}$. Extraction is carried out with isopropyl ether followed by washing with water, drying over sodium sulphate, separation and washing with
15 isopropyl ether. Concentration is carried out and 3.89 g of sought product is obtained in the form of a base. 3.76 g of the product obtained is put into solution at 20°C in 19 ml of ethyl acetate, 7.6 ml of a solution of ethyl acetate with 10% hydrochloric acid is added over 20 minutes, the reaction
20 medium is maintained under agitation for 1 hour, filtered, the precipitate is washed with ethyl acetate, dried at 40°C for 2 hours and 2.56 g of the expected hydrochloride is obtained.

CLAIMS

1) The compounds of formula (I):

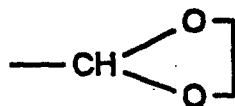


in which alk_1 , alk_2 and alk_3 identical to or different from each other represent an alkyl radical containing up to 8 carbon atoms, n represents an integer which can vary from 0 to 8, R_1 and R_2 represent an O-alkyl radical containing up to 8 carbon atoms, or form together with the carbon atom to which they are linked a cyclic acetal.

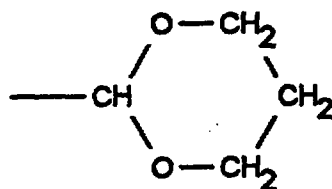
2) The compounds of formula (I) as defined in claim 1, in which n represents the number 2.

3) The compounds of formula (I) as defined in claim 1 or 2, in which alk_1 , alk_2 and alk_3 represent an ethyl radical.

4) The compounds of formula (I) as defined in any one of claims 1 to 3, in which R_1 and R_2 form together with the carbon atom to which they are linked a 1,3-dioxolane radical:



or a 1,3-dioxane radical



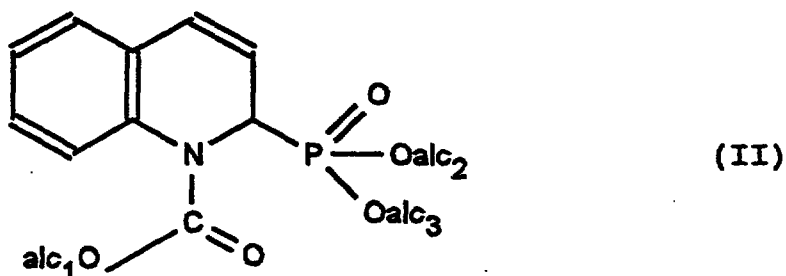
5) The compounds of formula (I) defined in claim 1, the names of which follow:

- ethyl 2-(diethoxyphosphinyl)-4-(2-(1,3-dioxolan-2-yl) ethyl)-1(2H)-quinolinecarboxylate,

5 - ethyl 2-(diethoxyphosphinyl) 4-(2-(1,3-dioxan-2-yl) ethyl) 1(2H)-quinoline carboxylate.

6) Preparation process for the compounds of formula (I) as defined in any one of claims 1 to 5, characterized in that a compound of formula (II):

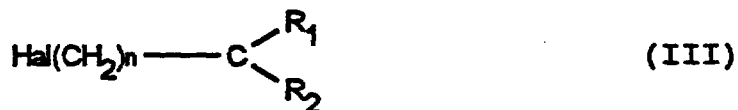
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in which alk_1 , alk_2 and alk_3 retain their previous meaning is subjected to the action of a compound of formula (III):

20



in which Hal represents a halogen atom and R_1 , R_2 and n retain their previous meaning, in order to obtain the
25 corresponding compound of formula (I).

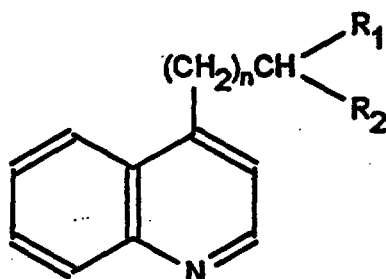
7) Process according to claim 6, characterized in that the operation is carried out in the presence of a strong base.

8) Process according to claim 7, characterized in that the base used is sodium or potassium *tert*-butylate or *tert*-amylate.

30 9) Use of the compounds of formula (I) as defined in any one of claims 1 to 5, characterized in that a compound of formula (I) is subjected to the action of a strong base in order to obtain the corresponding compound of formula (IV):



5



(IV)

in which n , R_1 and R_2 retain their previous meaning.

10 10) Use according to claim 9, characterized in that the strong base is sodium ethylate.

11) Use according to claim 9 or 10, characterized in that the product of formula (I) used is ethyl 2-(diethoxy phosphinyl) 4-(2-(1,3-dioxan-2-yl) ethyl) 1(2H)-quinoline carboxylate
 15 according to claim 5 and the product of formula (IV) prepared is 4-(2-(1,3-dioxolan-2-yl) ethyl)-quinoline.

12) Use according to claim 9 or 10, characterized in that the product of formula (I) used is ethyl 2-(diethoxy phosphinyl) 4-(2-(1,3-dioxan-2-yl) ethyl) 1(2H)-quinoline carboxylate
 20 according to claim 5 and the product of formula (IV) prepared is 4-(2-(1,3-dioxan-2-yl) ethyl) quinoline.

