(12) UK Patent Application (19) GB (11) 2 060 630 A

(21) Application No **8031120**
(22) Date of filing **27 Jul 1978**
Date lodged **26 Sept 1980**
(30) Priority data
(31) **52/096726**
(32) **12 Aug 1977**
(31) **52/160559**
(32) **28 Dec 1977**
(33) **Japan (JP)**
(43) Application published
7 May 1981
(51) **INT CL³**
C07D 471/04 241/36
(C07D 471/04 221/00
241/00)
(52) Domestic classification
C2C 1341 1344 155X
1628 200 213 215 247
250 251 252 25Y 28X
305 30Y 313 316 31Y 322
324 32Y 339 351 352 354
366 367 368 387 401 40Y
440 456 45Y 490 491 620
625 628 638 645 658
65X 670 675 678 67X
680 702 760 761 763 AA
LT MA TP TY
(56) Documents cited
None
(58) Field of search
C2C
(60) Derived from Application
No **31428/78** under
Section 15(4) of the
Patents Act 1977
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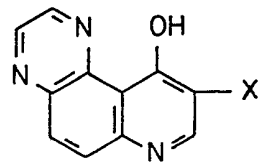
(54) Pyrazinoquinoline Derivatives

(57) Novel pyrazinoquinoline derivatives of the general formula



wherein X is carboxy, haloformyl, azidoformyl or activated ester, are prepared from a starting material 6-aminoquinoxaline. They are intermediate compounds in a synthesis of penicillin derivatives.

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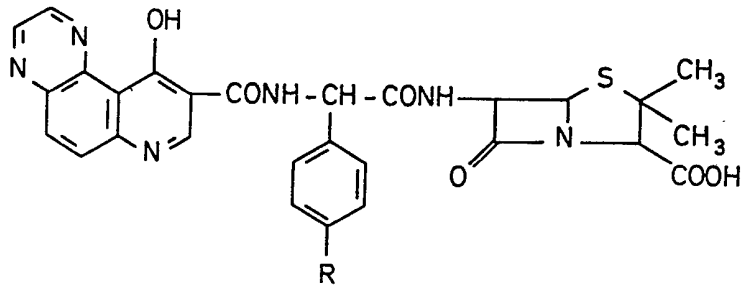
SPECIFICATION

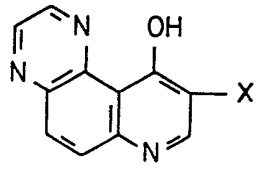
Pyrazinoquinoline Derivatives

The present invention relates to novel pyrazinoquinoline derivatives which are the intermediate compounds in a synthesis of the penicillin derivatives of the general formula



and pharmaceutically acceptable salts thereof, wherein R is hydrogen or hydroxy, that are described in detail in the specification of our copending application No. 31428/78 (Serial No. 2,004,877).

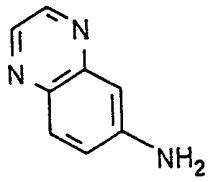
According to the present invention, there is provided pyrazinoquinoline derivatives of the general formula



(I)

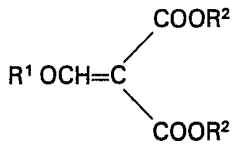
in which X is carboxy, haloformyl azidoformyl or activated ester.

In one aspect of the invention, there is provided a method of making an acid having the general formula (I) in which X is carboxy which method comprises condensing 6-aminoquinoxaline having the formula:



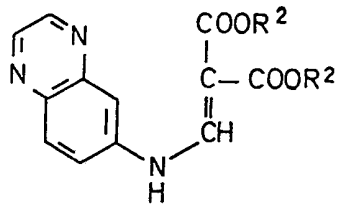
(II)

with a methylenemalonate having the formula:



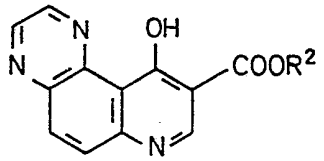
(III)

in which R^1 and R^2 are the same or different alkyl containing 1 to 3 carbon atoms to form a compound having the general formula:



(IV)

subjecting the compound of formula (IV) to a ring closure reaction to form a 4-hydroxy-pyrazino [2,3-f] quinoline-3-carboxylic acid ester having the general formula:



(V)

and thereafter hydrolysing the ester (V) to form the product acid.

Condensation of 6-aminoquinoxaline (II) with a methylenemalonate (III) may be carried out with heating at 100 to 150°C for 0.5 to 2 hours. Examples of methylenemalonate (III) are diethyl ethoxymethylenemalonate dimethyl ethoxymethylenemalonate, diisopropyl methoxymethylenemalonate, and diethyl methoxymethylenemalonate.

Ring closure of N-(6-quinoxalyl) aminomethylenemalonate (IV) may be carried out in the presence of an organic solvent such as diphenyl, diphenyl ether or dibutyl phthalate, at a temperature of 250°C to 300°C.

The compound of the general formula (I) wherein X is carboxy, i.e., 4-hydroxy-pyrazino [2,3-f] quinoline-3-carboxylic acid may be obtained by hydrolysing a 4-hydroxy-pyrazino 2,3-f quinoline 3-carboxylic acid ester (V) in the presence of a caustic alkali such as potassium hydroxide or sodium hydroxide at 25°C to the boiling temperature, in a known manner *per se.*

The compound of the general formula (I) wherein X is haloformyl (e.g., COCl and COBr), azidoformyl, and activated ester (e.g., N-hydroxysuccinimide and N-hydroxyphthalimide) may be prepared by reacting 4-hydroxy-pyrazino [2,3-f] quinoline-3-carboxylic acid with a corresponding halogenating agent, azide forming agent or ester forming agent in a known manner per se.

Following is a description by way of example only of methods of carrying the invention into effect.

Example 1

A mixture of 6-aminoquinoxaline (19.2g) and diethyl ethoxymethylenemalonate (34.8g) was heated for an hour at 110°C. After filtration, the crystals thus obtained were crystallized from ethanol to give diethyl N-(6-quinoxalyl) aminomethylenemalonate (37.5g) as pale yellow needles, m.p. 112—114°C.

Diethyl N-(6-quinoxalyl)aminomethylenemalonate (37.5g) was gradually added to diphenyl ether (300 ml) at 260—280°C. The resulting mixture was heated for a further hour at the same temperature. After cooling, the mixture was mixed with n-hexane (500 ml), and filtered off. The resulting solid was washed with n-hexane and acetone to give ethyl 4-hydroxy-pyrazino [2,3-f] quinoline-3-carboxylate (28.8g) as colourless powders, m.p. 223—225°C.

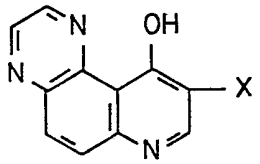
A mixture of ethyl 4-hydroxy-pyrazino [2,3-f] quinoline-3-carboxylate (28.8g) and 10% potassium hydroxide solution (350 ml) was heated under reflux for an hour. The resulting reaction solution was acidified with a concentrated hydrochloric acid. After filtration, the resulting solid was washed with water and acetone, and then dried over phosphorus pentoxide to give 4-hydroxy-pyrazino [2,3-f] quinoline-3-carboxylic acid (23.5g) as pale yellow crystalline powders, m.p. >300°C. Anal. Calcd. for $C_{11}H_7N_3O_3$: C, 59.75; H, 2.93; N, 17.42. Found C, 59.40; H, 3.17; N, 17.23.

Example 2

4-hydroxy-pyrazino [2,3-f] quinoline-3-carboxylic acid (2.41g) was refluxed with thionyl chloride (15 ml) for an hour and then concentrated in vacuo. To the residue were added N-hydroxysuccinimide (1.27g), N,N-dimethylformamide (50 ml) and pyridine (2 ml). The resultant mixture was stirred for 2 hours at room temperature. The solid product was collected, washed with N, N-dimethylformamide and acetone, and then dried over phosphorus pentoxide to give N-hydroxysuccinimede ester of 4-hydroxy-pyrazino [2,3-f] quinoline-3-carboxylic acid (2.34g), m.p. 261—263°C (decomp.).

Claims

1. A compound having the general formula:



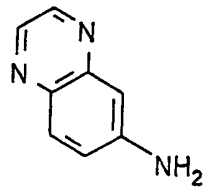
(I)

in which X is carboxy, haloformyl, azidoformyl or activated ester.

2. A compound as claimed in claim 1 wherein the active ester radical is based on N-hydroxysuccinimide or N-hydroxyphthalimide.

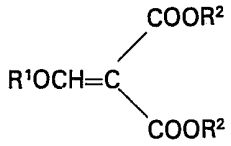
3. 4-hydroxy-pyrazino [2,3-f] quinoline-3-carboxylic acid.

4. A method of making an acid having the general formula claimed in claim 1 in which X is carboxy which method comprises condensing 6-aminoquinoxaline having the formula:



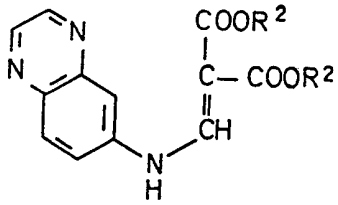
(II)

with a methylenemalonate having the formula:



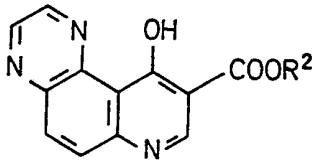
(III)

in which R^1 and R^2 are the same or different alkyl containing 1 to 3 carbon atoms to form a compound having the general formula:



(IV)

subjecting the compound of formula (IV) to a ring closure reaction to form a 4-hydroxypyrazino [2,3-f] quinoline-3-carboxylic acid ester having the general formula



(V)

and thereafter hydrolysing the ester (V) to form the product acid.

5. A method as claimed in claim 4 wherein the methylene malonate is selected from diethyl ethoxymethylenemalonate, dimethyl ethoxymethylenemalonate, diisopropylmethoxymethylenemalonate and diethylmethoxymethylenemalonate.

6. A method as claimed in claim 4 or claim 5 wherein the condensation reaction is carried out at a temperature of 100°C. to 150°C. for 0.5 to 2.0 hours.

7. A method as claimed in any one of claims 4 to 6 wherein the ring closure reaction is carried out in the presence of an organic solvent at a temperature of 250°C. to 300°C.

8. A method as claimed in claim 7 wherein the organic solvent is selected from diphenyl, diphenyl ether, or dibutyl phthalate.

9. A method as claimed in any one of claims 4 to 8 wherein the hydrolysis is carried out in the presence of a caustic alkali at a temperature of 25°C to boiling temperature.

10. A method as claimed in claim 4 and substantially as described in any one of the specific examples hereinbefore set forth.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1981. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.