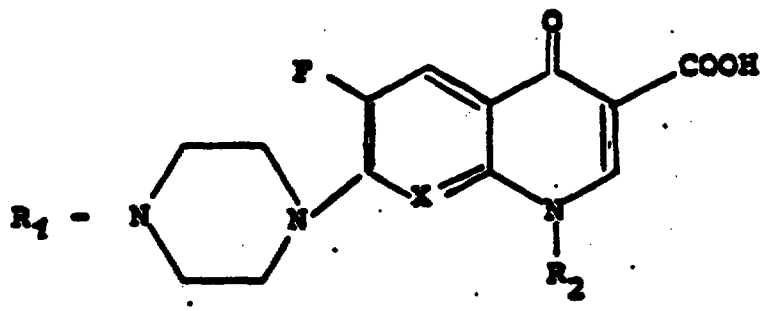
Description

The invention relates to solutions of piperazinyl-quinolone- and piperazinyl-azaquinolone-carboxylic acids, and in particular both ready-to-use injection and/or infusion solutions and solutions which can be seduced [sic] into such injection and/or infusion solutions before use.

The solutions according to the invention are characterised in that, besides the lactic acid salt of the active substance and, if appropriate, customary auxiliaries, they additionally contain at least one acid which does not lead to precipitates, in particular lactic acid.

Possible active substances are at least one of the compounds of the general formulae I or II



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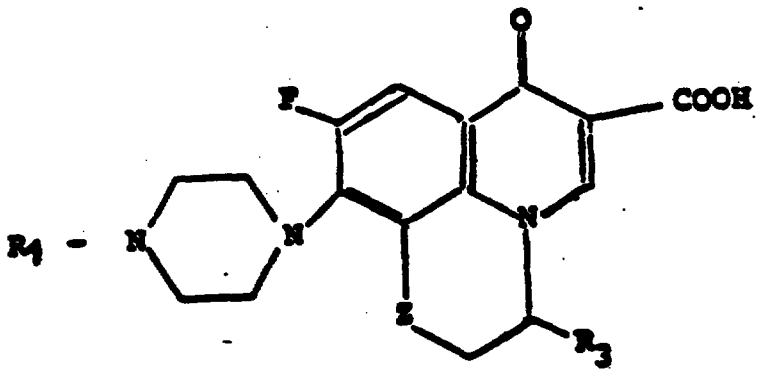


(II)

in which

X denotes N, C-H or C-F,

Z denotes O or CH_2,

R_1 denotes hydrogen, methyl, ethyl or β-hydroxy-ethyl,

R_2 denotes cyclopropyl or ethyl and

R_3 denotes hydrogen, methyl or ethyl.

Compounds which may be mentioned in particular are: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinoline-3-carboxylic acid (compound A); ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinoline-3-carboxylic acid (compound B) (sic); 9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (compound C); 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid (compound D); and 1,cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(4-ethyl-1-piperazinyl)-quinoline-3-carboxylic acid.

These substances are known to have powerful antibacterial action and are therefore suitable as medicaments for combating bacterial infections in humans and animals.

The compounds of the formula I are known from: J. Med. Chem. 23 (1980) 1358; DE-OS (German Published Specification) 3,142,854; DE-OS (German Published Specification) 3,033,157; and EP-OS (European Published Specification) 0,067,666.

The compounds of the formula II are known from: EP OS (European Published Specification) 0,047,005; DE-OS (German Published Specification) 3,037,103; and DE-OS (German Published Specification) 2,914,258.

Suitable customary auxiliaries for the solutions according to the invention are non-toxic, pharmaceutical substances. These are, for example, thickeners, absorption accelerators, absorption inhibitors, crystallisation retarders, complexing agents, antioxidants, isotonicity agents or dehydrating agents. They can be solid, semi-solid or liquid in consistency.

Examples of possible acids which do not lead to precipitates are methanesulphonic acid, propionic acid, succinic acid, hydrochloric acid and, in particular, lactic acid.

For various reasons, acid addition salts or alkali metal salts of active compounds are frequently used in pharmacy. Addition salts of the active substances can be prepared from several inorganic and organic acids, such

as, for example, sulphuric acid, nitric acid, hydrochloric acid, citric acid, acetic acid, malic acid, succinic acid, tartaric acid, fumaric acid and methanesulphonic acid.

However, many such salts are unsuitable or very poorly suitable for the preparation of infusion and/or injection solutions, because, for example, the pH and/or the solubility and/or the shelf life, especially in respect of deposits, of the ready-to-use infusion and/or injection solution does not fulfil the pharmaceutical requirements to be imposed on such solutions.

It has now been found that the solutions can be stored if, besides the lactic acid salt of at least one of the active substances and, if appropriate, customary auxiliaries, they additionally contain at least one acid which does not lead to precipitates, in particular lactic acid.

The presence of such acids, in particular lactic acid, or, depending on the pH, a mixture of acid(s) and anion(s) thereof, is essential for the stability of the solution to be administered, in particular in respect of deposits.

Depending on the primary means of packaging used, the concentration of the active substance in the solution, the pH of the solution and the shelf-life requirements imposed, the lactic acid content of the solutions according to the invention can be 0.1 to 90%. The lactic acid content of the solution to be administered can be 0.1 to 10%, preferably 0.5 to 1.4%.

These quantity data relate to the total amount of acid, that is to say non-dissociated and dissociated acid.

Where these acids required for the stability are referred to below, in particular lactic acid, the total amount of acid is meant, that is to say non-dissociated and dissociated acid.

If other acids which do not lead to precipitates are used, such as, for example, methanesulphonic acid, propionic acid, hydrochloric acid or succinic acid, the acid content can be 0.05 to 4%, preferably between 0.3

and 2%, depending on the concentration of the active substance, the shelf-life requirements imposed and the pH of the ready-to-use solutions according to the invention.

The pH of the ready-to-use solutions according to the invention can be between 2.5 and 7, preferably between 3.5 and 4.5.

It was very surprising to discover that by addition of at least one acid which does not lead to precipitates, in particular lactic acid, in amounts such as those given above, it was also possible to stabilise infusion and/or injection solutions of the lactic acid salt of compound B and D, whilst the 1:1 stoichiometric salts of this compound tended to give deposits. This also applies to the formulations, according to the invention, of compound C.

It has furthermore been found that there are several possible processes for the preparation of the solutions according to the invention.

The lactic acid salt of the active substance or a hydrate thereof can be used as the starting substance for the preparation of the solution of the active substance. In this case, it is possible to incorporate the required addition, or some of this addition, of at least one acid which does not lead to precipitates, in particular lactic acid, into the lactic acid salt, for example by freeze-drying.

However, the lactic acid salts can also be prepared directly in the solution, and in particular by addition of the amounts of lactic acid required for salt formation.

It is in this way possible to prepare both ready-to-use solutions of the active substance, filled in suitable containers, for example in ampoules or injection or infusion bottles, as well as precursors, for example concentrates or dry ampoules, suitable for the preparation of such solutions.

The solutions according to the invention, like the compounds of the formulae I and II on which they are based, are to be used as medicaments for combating bacterial infections. Possible uses are as injections and

infusions. The dosages correspond to those of the known compounds A, B, C and D.

Formulations

The solutions according to the invention are prepared by dissolving the active substance or the lactic acid salt thereof and, if appropriate, customary auxiliaries, in a solution of lactic acid or a mixture of lactic acid and, for example, sodium lactate, if necessary with slight warming.

If appropriate, water or a mixture of water and sodium hydroxide solution is also added to adjust the desired concentration of the active substance and/or the pH of the solution.

Example 1

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl-quinolone-3-carboxylic acid (sic) (compound A)	- 150 g
Lactic acid (90% by weight)	- 262 g
2 M sodium hydroxide solution	- 266 g
Water	to 15.0 litres

Example 2

Monolactate of compound A	- 1.27 g
Lactic acid (90% by weight)	- 1.45 g
2 M sodium hydroxide solution	- 1.80 g
Mannitol	- 1.37 g
Water	to 100.0 ml

Example 3

Compound A	- 10.00 g
Lactic acid (90% by weight)	- 4.85 g
Water	to 1000.0 ml

Example 4

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinolone-3-carboxylic acid (compound B)	- 1.00 g
Lactic acid (90% by weight)	- 0.50 g
Glucose	- 3.85 g
Water	to 100.00 ml

Example 5

9-Fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido-[1,2,3-de]-4-benzoxazine-6-carboxylic acid (compound C) - 5.00 g

Lactic acid (90% by weight) - 2.20 g

Water to 100.00 ml

Example 6

Dihydrate of the monolactate of compound A - 69.0 g

Lactic acid (90% by weight) - 24.2 g

Water to 1000.0 ml

Example 7

Compound A - 300.0 g

Lactic acid (90% by weight) - 177.3 g

Water to 6000.0 ml

Example 8

Compound A - 200.0 g

Lactic acid (90% by weight) - 75.0 g

Water to 2000.0 ml

Example 9

Monolactate of compound B - 128.2 g

Lactic acid (90% by weight) - 50.0 g

Water to 1000.0 ml

Example 10

Compound C - 100.0 g

Lactic acid (90% by weight) - 44.4 g

Water to 1000.0 ml

Example 11

Compound A - 30.0 g

Lactic acid (90% by weight) to 100.0 g

Example 12

Compound A 1.00 g

Lactic acid (90% by weight) 0.30 g

Succinic acid 0.71 g

Water to 100.00 ml

Adjusted to pH 3.6 with 2 M sodium hydroxide solution.

Example 13

Monolactate of compound A	1.27 g
Methanesulphonic acid	0.60 g
Water	to 100.00 ml

Adjusted to pH 3.9 with 2 M sodium hydroxide solution.

Example 14

Monolactate of compound A	1.27 g
Lactic acid (90% by weight)	0.56 g
Methanesulphonic acid	1.45 g
Water	to 100.00 ml

Adjusted to pH 3.7 with 2 M sodium hydroxide solution.

Example 15

Compound A	1.00 g
Lactic acid (90% by weight)	0.86 g
Propionic acid	1.12 g
Water	to 100.00 ml

Adjusted to pH 3.8 with 2 M sodium hydroxide solution.

Example 16

Compound B	1.00 g
Lactic acid (90% by weight)	0.87 g
Propionic acid	0.46 g
Water	to 100.00 ml

Example 17

Monolactate of compound B	1.28 g
Lactic acid (90% by weight)	1.11 g
Succinic acid	1.85 g
Water	to 100.00 ml

Adjusted to pH 3.7 with 2 M sodium hydroxide solution.

Example 18

Compound B	1.00 g
Lactic acid (90% by weight)	0.42 g
Methanesulphonic acid	1.50 g
Water	to 100.00 ml

Adjusted to pH 3.8 with 2 M sodium hydroxide solution.

Example 19

Compound C	1.00 g
Lactic acid (90% by weight)	0.39 g
Methanesulphonic acid	0.53 g
Water	to 100.00 ml

Adjusted to pH 3.9 with 2 M sodium hydroxide solution.

Example 20

Monolactate of compound C	1.25 g
Lactic acid (90% by weight)	0.56 g
Propionic acid	1.03 g
Water	to 100.00 ml

Example 21

Compound C	1.00 g
Lactic acid (90% by weight)	1.39 g
Succinic acid	0.64 g
Water	to 100.00 ml

Adjusted to pH 3.7 with 2 M sodium hydroxide solution.

Example 22

Compound A	1.00 g
Lactic acid (10% by weight)	0.33 g
1 M hydrochloric acid	1.20 g
Water	to 100.00 ml

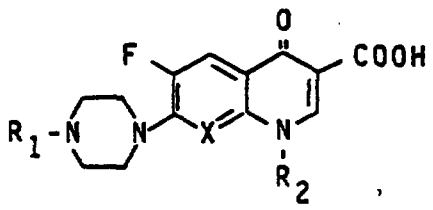
Example 23

Compound A	1.00 g
Lactic acid (90% by weight)	0.41 g
Water	to 100.00 ml

Adjusted to pH 4.0 with 1 M hydrochloric acid.

Patent Claims

1. Solutions of lactic acid salts of piperazinyl-quinolone- and piperazinyl-azaquinoline-carboxylic acids of the general formulae I and II



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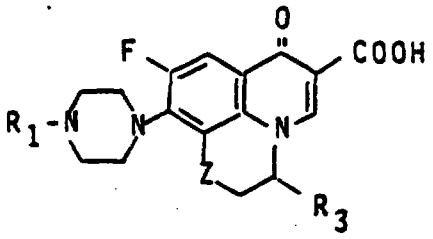


(II)

in which

X denotes N, C-H or C-F,

Z denotes O or CH_2,

R_1 denotes hydrogen, methyl, ethyl or β-hydroxy-ethyl,

R_2 denotes cyclopropyl or ethyl and

R_3 denotes hydrogen, methyl or ethyl,

which, besides the lactic acid salts mentioned and, if appropriate, customary auxiliaries, additionally contain at least one acid which does not lead to precipitates.

2. Solutions according to Claim 1, which contain lactic acid as the acid which does not lead to precipitates.

3. Solutions according to Claim 1, which contain the lactate of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinoline-3-carboxylic acid as the lactic acid salt.

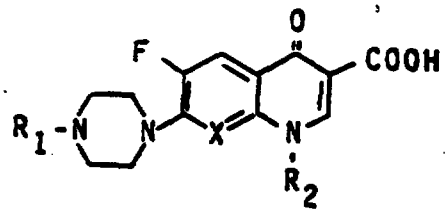
4. Solutions according to Claim 1, in which the

* C L M S *

lactic acid content is 0.1 to 90%.

5. Ready-to-use solutions according to Claim 1, in which the lactic acid content is 0.1 to 10%, preferably 0.5 to 1.4%.

6. Process for the preparation of solutions of lactic acid salts of piperazinyl-quinolone- and piperazinyl-azaquinoline-carboxylic acids of the general formulae I or II



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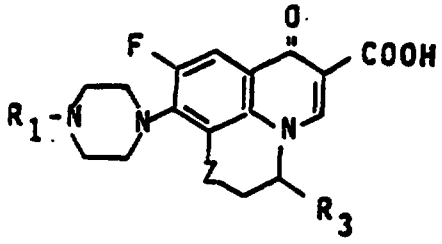

(II)

in which

X denotes H, C-H or C-F,

Z denotes O or CH_2,

R_1 denotes hydrogen, methyl, ethyl or β-hydroxy-ethyl,-

R_2 denotes cyclopropyl or ethyl and

R_3 denotes hydrogen, methyl or ethyl,

characterised in that solutions of lactic acid salts of the acids of the formulae (I) or (II) are reacted with 0.1 to 90% of lactic acid or with 0.1 to 10% of at least one acid which does not lead to precipitation, with warming.

7. Antibacterial medicaments, characterised in that they contain at least one solution according to Claim 1.

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Revendications

1. Solutions de sels lactiques d'acides pipérazinyl-quinolone- et d'acide pipérazinyl-azaquinolone-carboxyliques de formules générales I et II

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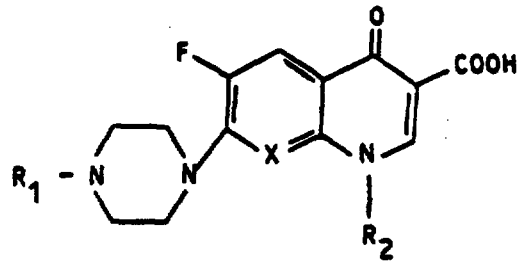

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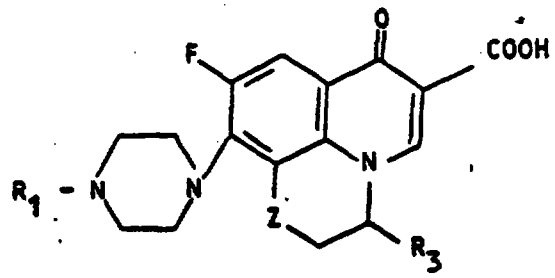


(II)

dans lesquelles

X représente N, C-H ou C-F,
Z représente O ou CH_2,
R_1 représente l'hydrogène ou un groupe méthyle, éthyle ou β-hydroxyéthyle,
R_2 représente un groupe cyclopropyle ou éthyle et
R_3 représente l'hydrogène ou un groupe méthyle ou éthyle,

qui, outre les sels lactiques cités et éventuellement des substances auxiliaire habituelles, contiennent en outre au moins un acide ne conduisant pas à des précipitations.

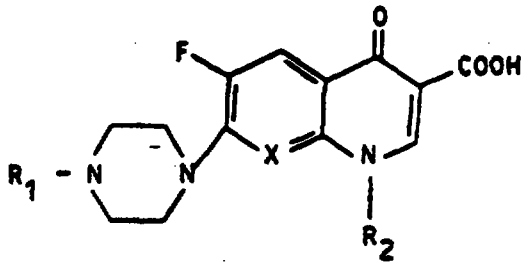
2. Solutions selon la revendication 1, qui contiennent de l'acide lactique comme acide ne conduisant pas à des précipitations.

3. Solutions selon la revendication 1, qui contiennent comme sel lactique le lactate de l'acide 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-pipérazinyl)-quinoléine -3-carboxylique.

4. Solutions selon la revendication 1, dont la teneur en acide lactique est de 0,1 à 90 %.

5. Solutions prêtes à l'emploi selon la revendication 1, dont la teneur en acide lactique est de 0,1 à 10 %, de préférence de 0,5 à 1,4 %.

6. Procédé pour la fabrication de solutions de sels lactiques d'acides pipérazinyl-quinolone- et pipérazinyl-azaquinolone-carboxyliques de formules générales I et II



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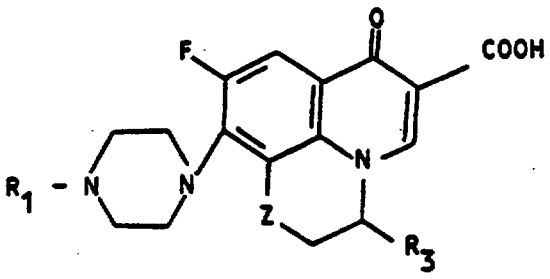


(II)

dans lesquelles

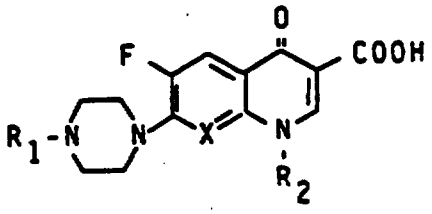
X	représente N, C-H ou C-F,
Z	représente O ou CH_2,
R_1	représente l'hydrogène ou un groupe méthyle, éthyle ou β-hydroxyéthyle,
R_2	représente un groupe cyclopropyle ou éthyle et
R_3	représente l'hydrogène ou un groupe méthyle ou éthyle,

caractérisé en ce que l'on fait réagir en chauffant des solutions de sels lactiques des acides de formules I ou II avec 0,1 à 90 % d'acide lactique ou avec 0,1 à 10 % d'au moins un acide ne conduisant pas à des précipitations.

7. Médicament antibactérien, caractérisé en ce qu'il contient au moins une solution selon la revendication 1.

Claims

1. Solutions of lactic acid salts of piperazinyl-quinolone- and piperazinyl-azaquinolone-carboxylic acids of the general formulae I or II



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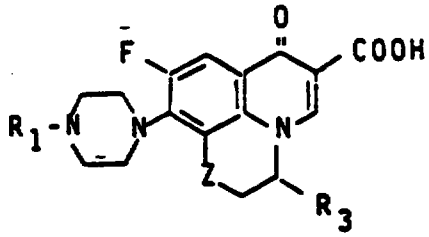


(II)

in which

X	denotes N, C-H or C-F,
Z	denotes O or CH_2,
R_1	denotes hydrogen, methyl, ethyl or β-hydroxyethyl,
R_2	denotes cyclopropyl or ethyl and
R_3	denotes hydrogen, methyl or ethyl,

which, besides the lactic acid salts mentioned and, if appropriate, customary auxiliaries, additionally contain at least one acid which does not lead to precipitates.

As printed

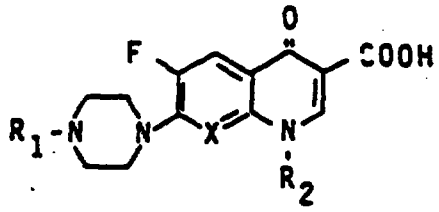
2. Solutions according to claim 1, which contain lactic acid as the acid which does not lead to precipitates.

3. Solutions according to claim 1, which contain the lactate of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinoline-3-carboxylic acid as the lactic acid salt.

4. Solutions according to claim 1, in which the tactic acid content is 0.1 to 90 %.

5. Ready-to-use solutions according to claim 1, in which the lactic acid content is 0.1 to 10 %, preferably 0.5 to 1.4 %.

6. Process for the preparation of solutions of lactic acid salts of piperazinyl-quinolone- and piperazinylazaquinolone-carboxylic acids of the general formulae I or II



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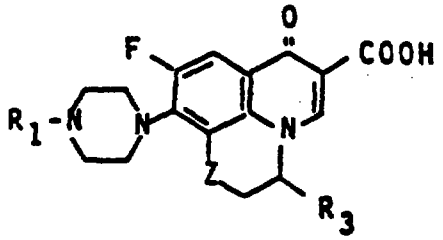

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R_1 denotes hydrogen, methyl, ethyl or β-hydroxyethyl,

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R_3 denotes hydrogen, methyl or ethyl,

characterised in that solutions of lactic acid salts of the acids of the formulae (I) or (II) are reacted with 0.1 to 90 % of lactic acid or with 0.1 to 10 % of at least one acid which does not lead to precipitation, with warming.

7. Antibacterial medicaments, characterised in that they contain at least one solution according to claim 1.

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