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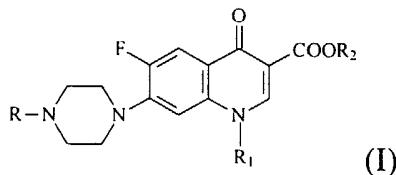
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(54) Title: A PROCESS FOR SYNTHESIS OF FLUOROQUINOLONIC DERIVATIVES

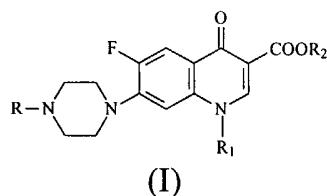


(57) Abstract: A simple and for use convenient procedure for obtaining of antibiotics from the group of fluoroquinolonic derivatives, of general formula (I), is developed where R and R₂ denote hydrogen atom, or alkyl group with C₁-C₄, and R₁ denotes alkyl group with C₁-C₄ or cycloalkyl group (such as cyclopropyl group, for example), and/or salts and hydrates thereof, by reaction of piperazin or piperazin derivatives with the compound of general formula VI in an inert solvent of pharmacopoeic purity, at risen temperature. The lower reaction temperature, work at atmospheric pressure, technical simplicity of the procedure of purification by conversion and isolation in the form of pharmaceutically acceptable salts, yield increase, reducing prices on the procedure for industrial use, as well as pharmacopoeic purity of the product, enabled their use as the antibiotics in human and veterinary medicine.

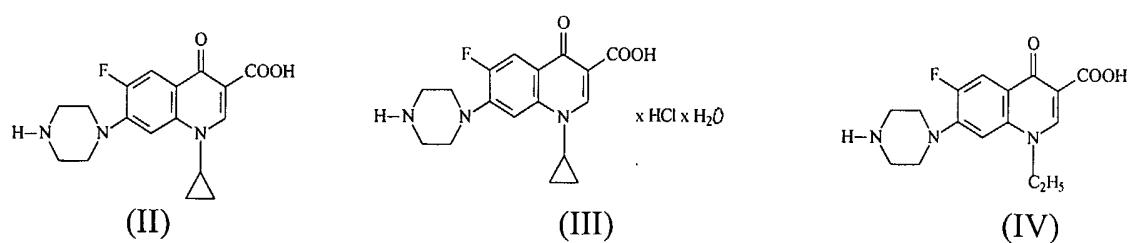
A PROCESS FOR SYNTHESIS OF FLUOROQUINOLONIC DERIVATIVES

The field of technique

The suggested invention is related to the area of organic chemical technology, specifically to the process for obtainig of antibiotics belonging to the group of *fluoroquinolonic* derivatives, with general formula I and salts and hydrates thereof,



wherein R and R₂ denote a *hydrogen* atom, or an *alkyl* group with C₁ – C₄, and R₁ denotes an *alkyl* group with C₁ – C₄ or an *cycloalkyl* group (eg. *cyclopropyl* group). Of special interest, concerning clinical practice are: **ciprofloxacin** (*1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid*) of formula II, **ciprofloxacin hydrochloride monohydrate** (*1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid hydrochloride monohydrate*) of formula III, as well as **norfloxacin** (*1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid*) of formula IV.



These compounds are used in therapy as antibiotics, in human and veterinary medicine. According to the International Classification of patents the invention belongs to the class C 07 D 215/02, 215/04, 215/18, 215/56, C 07 D 241/04, C 07 D 295/04, C 07 D 401/04, 401/10.

Technical problem

There was a need to come to the technically more convenient and economic process for obtaining of antibiotics belonging to the group of *fluoroquinolonic derivatives*. Contemporary pharmaceutical technology sets the more strict demands for increasingly higher purity of the products, in comparison with already existing patents from the eighties, which had lower criteria. The existing patents do not have the product purification phase after evaporation of solvent, and for that reason, the pure product for pharmaceutical use is not obtained, and an additional purification is required. During purification by distillation, degradation of the product occur, for the reason it is heat, moisture, light and oxygen sensitive, and all the secondary products from the phase of synthesis, still stay in the reaction mixture, and side effects of the product are possible.

The suggested original invention solves the problem of obtaining of pure product, introducing the purification phase, which enables obtaining of entire palette of pharmaceutically acceptable salts with pharmacological purity. This technical problem is solved by precipitation of the product with an inorganic acid (e.g. concentrated *hydrochloric acid*), as well as with an organic acid (e.g. *acetic acid*) and use of active charcoal, which enables higher yield and avoids energy loss with distillation during subsequent purification. The problem of stability of the product is also solved within one working phase, without previous drying, preventing degradation of the product and unwanted secondary reactions, and the secondary products are removed from the reaction mixture.

Background of the invention

In professional and patent literature, there are number of ways for obtaining of antibiotics belonging to the group of *fluoroquinolonic derivatives* of general formula I.

It is known from before that the compounds of *1-ethyl-6-fluoro-4-oxo-piperazino-quinoline-3-carboxylic acid* (**Eur. J. Med. Chem.**, 12,541-547, 1977), as well as of *1-ethyl-6-fluor-4-oxo-piperazino-quinoline-3-carboxylic acid* (**J. Med. Chem.**, 23,1358,1980) possess antibiotic properties.

According to the process described in Eastern-Germany patent **DE 202, 560**, European patent **EP 2, 078, 362**, as well as in Israeli patent and **IL 66243**, *ciprofloxacin* of formula II is obtained in reaction between *piperazine* and *7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid*, in the presence of *dimethylsulphoxide*, at rised temperature, and the product is isolated from the reaction mixture by distillation under extremely low vacuum, while the residue is rinsed in *water* and *ethanol* and dried, and obtained product is, in the next phase, converted, using 10% *HCl*, into *ciprofloxacin hydrochloride*. A deficit of the processes in the mentioned patents was the way of isolation, ie. purification of *ciprofloxacin* from the reaction mixture, which contributes to the obtaining of the product in lower yield and purity, as well as to the rising of production costs. The product obtained in such way, is not pure enough for pharmaceutical use, so, instead of vacuum distillation, the phase of additional purification is introduced.

Obtaining of *ciprofloxacin hydrochloride monohydrate* of formula III, is described in Spanish patents **ES 2, 006, 098** and **ES 2, 006, 099**.

According to the process described in Spanish patent **ES 2, 006, 098** *ciprofloxacin hydrochloride monohydrate* of formula III, is obtained when previously synthetized and dried *ciprofloxacin hydrate* with 2,5 mol of hydration *water*, is in the next phase suspended and isolated from *isopropanol* and *isobutanol*. Here mentioned *ciprofloxacin hydrate* with 2,5 mol of hydration *water* is obtained

by decomposition of previously synthetized and dried compound *1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(4-ethoxycarbonyl-1-piperazino-quinoline-3-carboxylate ethylate* using *concentrated hydrochloric acid* and appropriate isolation from the corresponding solvent.

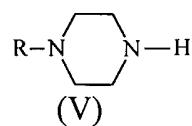
According to the process described in Spanish patent ES 2, 006, 099 *ciprofloxacin hydrochloride monohydrate* of formula III, is obtained by decomposition of previously synthetized and dried *p-toluol sulphonyl compound of ciprofloxacin* into *ciprofloxacin hydrate* with 2,5 mol of hydration *water*, and formed dried *ciprofloxacin hydrate* with 2,5 mol of hydration *water* is in the next phase suspended in the mixture of solvents, through which the gas *hydrogen chloride* at suitable flow rate, until wanted concentration in the solution is achieved, and formed product *ciprofloxacin hydrochloride monohydrate* is isolated from the mixture of solvents. Disadvantages of the described patent are use of gaseous hydrogen chloride, which increases the risk and requires special equipment for performing of the synthesis.

Description of technical problem solution with examples

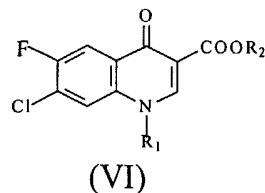
The stated invention avoids the disadvantages of the known processes, primarily given in Eastern-Germany patent **DE 202, 560**, European patent **EP 2, 078, 362**, Israeli patent **IL 66243/3**, as well as in Spanish patents **ES 2, 006, 098** and **ES 2, 006, 099**. In the quoted patents, during purification, degradation of the product, which is heat, moisture, light and air oxygen sensitive, occurs, and all the secondary products from the synthesis phase, still remains in reaction mixture, and unwanted reactions with the product are also possible, so, what is obtained, is not the pure product for pharmaceutical use, and the additional purification is required.

The suggested original invention solves the problem of obtaining of pure product, by introducing of purification phase, which enables obtaining of entire palette of pharmaceutically acceptable salts, with pharmacological purity, by precipitation with an inorganic acid (e.g. concentrated *hydrochloric acid*) as well as with an organic acid (e.g. *acetic acid*) and using active charcoal. Higher yield is achieved, and higher stability of the product, carrying out the process within one work phase, without previous drying, which avoids energy loss that occurs with distillation, prevents degradation and unwanted secondary reactions, and possibly formed secondary products are removed from the reaction mixture.

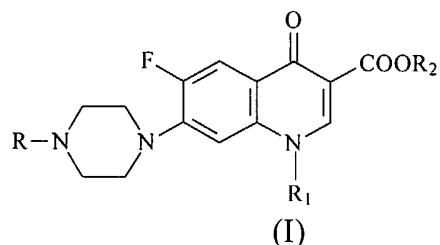
The suggested invention shows simplified reaction procedure of *piperazine* or *piperazine derivatives*, of general formula V:



wherein R denotes *hydrogen* atom, or *alkyl* group with C₁ – C₄, with a compound of general formula VI:



wherein R₁ denotes *alkyl* group with C₁ – C₄ or *cycloalkyl* group (e.g. *cyclopropyl* group), and R₂ denotes *hydrogen* atom, or *alkyl* group with C₁ – C₄. The reaction is carried out in an inert solvent of pharmacopoeic purity – p.a. quality, belonging to the group of organic solvents such as *alcohols*, *ethers*, as well as *acetonitrile*, *benzene*, *dimethylsulphoxide*, *pyridine*, *dimethylformamide*, at atmospheric pressure and at temperature of reaction mixture in range between 20 and 200° C. To a cooled reaction mixture at temperature of 20 to 70°C, with stirring and cooling, a quantity of an inorganic acid (e.g. *hydrochloric acid*), or organic acid (e.g. *acetic acid*), 3 to 5 times greater than starting number of mols of the *compound* of general formula VI, is added, obtainig *fluoroquinolonic* derivatives of general formula I

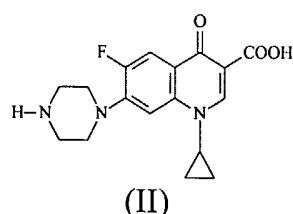


wherein R and R₂ denote *hydrogen* atom, or *alkyl* group with C₁ – C₄, and R₁ denotes *alkyl* or *cycloalkyl* group (e.g. *cyclopropyl* group). *Fluoroquinolonic* compounds of general formula I have acid- and base-centers, which, according to the suggested invention enables purification using acids and bases. The product is isolated in the range of pH between 4 and 8, and is further purified suspending of the precipitate into 5 to 15 time greater quantity of *water* in regard to the starting volume of solvent used in the phase of synthesis. Precipitate of the compound of general formula I is purified from the secondary products by addition of active charcoal, converting with suitable inorganic acid such as *hydrochloric* and *sulphuric* or organic acid (such as *acetic*, *lactic*, *tartaric*, *maleic*, *citric*) with stirring and cooling and isolating in the forms of salts *chlorides*, *sulphates*, *lactates*, *acetates*,

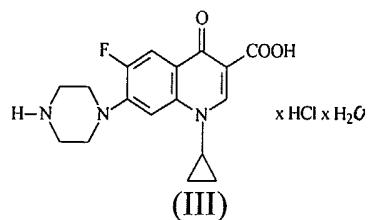
tartarates, maleates. Then, by alkalization, with alkaline aqueous solution such as *ammonium hydroxide, sodium carbonate, sodium hydroxide or potassium hydroxide*, with stirring and cooling, the compound of general formula I is obtained.

Obtained product is further hydrochlorated by instillation of *hydrochloric acid* aqueous solution. The reaction mixture is heated at 40-80°C, afterwards, it is effluxed into an organic solvent belonging to the group of alcohols such as *methanol, absolute ethanol, isopropanol*. Cooled mixture is filtrated, and the precipitate is rinsed with mentioned solvent. The product is dried using vacuum, which gives the compound of general formula I in the form of pharmaceutically acceptable salt (*chloride, sulphate, lactate, citrate, acetate, tartarate, maleate*) and/or hydrate of pharmacological purity.

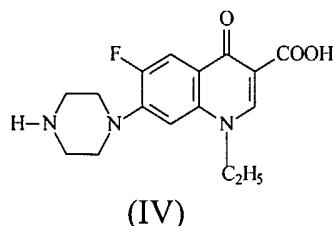
Special interest in clinical practice in human and veterinary medicine, as antibiotics belonging to the group of *fluoroquinolonic derivatives* have: **ciprofloxacin** (*1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid*) of formula II,



ciprofloxacin hydrochloride monohydrate (*1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid hydrochloride monohydrate*) of formula III,



as well as ***norfloxacin*** (*1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid*) of formula IV,



or the pharmaceutically acceptable salts thereof (*chlorides, sulphates, lactates, cutrates, acetates, tartarates, maleates*) and/or pharmacologically pure hydrates thereof.

In such way processed compounds can be used in pharmaceutical form of tablets, pills, dragees, capsules, ampullas or suppositories, with usual pharmaceutical additives, for obtaining of pharmaceutical preparations for use as antibiotics in human and veterinary medicine, and as a food additive.

The procedure is in more details described in the following examples, but should not be considered as restrictive.

EXAMPLE 1: Synthesis of ***ciprofloxacin hydrochloride monohydrate*** (*1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid hydrochloride monohydrate*) of formula III

Mixture of 49,25gr of *7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid*, 72,25gr of *piperazine* and 250cm³ of *dimethylsulphoxide* is heated for 1,5 to 2 hours at temperature of 140°C. To the cooled reaction mixture at temperature of 70°C, 985cm³ of *distilled water* is added. With stirring and cooling, to the reacting mixture 62,5cm³ of *concentrated hydrochloric acid* is instilled. Formed suspension is filtered, and the precipitate is rinsed with *distilled water*. Crude precipitate is suspended in *water* and dissolved, by addition of 2mol/dm³ of *hydrochloric acid*. The solution is, after addition of *active charcoal*, heated with stirring at 50°C and filtered. To the filtrate, with

stirring and cooling, 2mol/dm³ of *sodium hydroxide* is added. Formed suspension is filtered, and the precipitate is rinsed with *distilled water*.

Crude precipitate is, with stirring suspended in *water* and 60 cm³ of 2mol/dm³ *hydrochloric acid* is instillated. The reaction mixture is heated for 30 minutes at 75-80°C, and afterwards, it is effluxed into 1750cm³ of *absolute ethanol*. The mixture cooled to 0-5°C is filtered, and the precipitate is rinsed three times with 30cm³ of *absolute ethanol* each time. The product is dried in vacuum drier at 80°C. 49,46gr of *ciprofloxacin hydrochloride monohydrate* (*1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid hydrochloride monohydrate*) of formula III is obtained, in the form of white crystals, melting point 308-310°C with decomposition (73% yield).

EXAMPLE 2: Synthesis of *ciprofloxacin* (*1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid*)

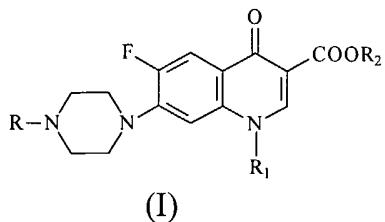
Mixture of 49,25 gr of *7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid*, 72,25 gr of *piperazin* and 400 cm³ of *pyridine* is heated for 1,5 to 2 hours at 110°C. Into cooled reaction mixture 985 cm³ of *distilled water* is added. With stirring and cooling, 62,5 cm³ of *concentrated hydrochloric acid* is instillated into the reaction mixture. The formed suspension is filtered, and the precipitate is rinsed with *distilled water*. Crude precipitate is suspended in *water* and dissolved by addition of 2 mol/dm³ *sodium hydroxide*. The solution is, after addition of *active charcoal*, heated to 50°C and filtered. Into filtrate, with stirring and cooling, 2 mol/dm³ of *hydrochloric acid* is added. The formed suspension is filtered, and the precipitate is rinsed with *distilled water*, and then, three times with 30 cm³ of *absolute ethanol* each time. The product is dried in vacuum drier at 100°C. 50gr of *ciprofloxacin* (*1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid*) is obtained, in the form of white crystals, melting point 255-257°C (86% yield). Obtained product can be further hydrochlorated in the way, already described in example 1.

EXAMPLE 3: Synthesis of *norfloxacin* (*1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid*)

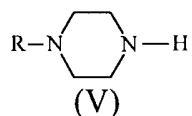
The synthesis is carried out analogously to the procedure explained in example 2, with the difference that instead of the compound *7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid*, compound *7-chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid* is used, when *norfloxacin* (*1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid*) is obtained in the yield of 68% in the form of crystals with melting point 220-221°C.

PATENT CLAIMS

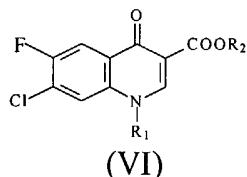
1. The procedure for obtaining of antibiotics, *fluoroquinolonic derivatives*, of general formula I



wherein R and R₂ denote *hydrogen* atom, or *alkyl* group with C₁ – C₄, and R₁ denotes *alkyl* or *cycloalkyl* group, such as *cyclopropyl* group, by reaction of *piperazin*, or *piperazin derivatives*, of general formula V:



wherein R denotes *hydrogen* atom, or *alkyl* group with C₁ – C₄, with compound of general formula VI:



wherein R₁ denotes *alkyl* or *cycloalkyl* group, such as *cyclopropyl* group, and R₂ denotes *hydrogen* atom, or *alkyl* group with C₁ – C₄, in an inert solvent, of pharmacopoeic purity – p.a. quality, belonging to the group of organic solvents such as *alcohols*, *ethers*, as well as *acetonitrile*, *benzene*, *dimethylsulphoxide*, *pyridine*, *dimethylformamide*, at atmospheric pressure and temperature of the reaction mixture in range between 20 and 200°C, **denoted by the fact**, that into the cooled reaction mixture, at temperature of 20 to 70°C, with stirring and cooling, 3 to 5 times greater quantity of an inorganic acid, such as *hydrochloric acid*, or an organic acid, such as *acetic acid*, is added, in relation to the starting number of mols of the compound of general formula VI, while, with stirring and cooling *fluoroquinolonic derivative* of

general formula I is precipitated, and the precipitate is suspended in 5 to 15 times greater quantity of *water*, in relation to the volume of used solvent from the phase of synthesis and with *active charcoal*, is further purified from the secondary products by conversion, using inorganic acids such as: *hydrochloric*, *sulphuric* or organic acids, such as: *acetic*, *lactic*, *tartaric*, *maleic*, *citric*, with stirring and cooling and by isolation in the forms of salts *chlorides*, *sulphates*, *lactates*, *citrates*, *acetates*, *tartarates*, *maleates*, and afterwards, using alkalization with alkali aqueous solution such as *ammonium hydroxide*, *sodium hydroxide*, *potassium hydroxide* or *sodium carbonate* and with the corresponding acid, purified *fluoroquinolonic derivative* of general formula I is obtained, and it is further hydrochlorated by instillation of *hydrochloric acid* aqueous solution at temperature between 40 and 80°C and effluxed into an organic solvent such as *methanol*, *absolute ethanol*, *isopropanol*, which gave the compound of general formula I in the form of the pharmaceutically acceptable salt and/or hydrate of pharmacological purity.

2. A procedure, according to the patent claim 1, **denoted by the fact**, that the precipitate is isolated in pH range between 4 and 8.
3. Antibiotic, *ciprofloxacin* (*1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid*) obtained according to the procedure according to the patent claims 1 and 2.
4. Antibiotic *ciprofloxacin hydrochloride monohydrate* (*1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid hydrochloride monohydrate*) obtained according to the procedure according to the patent claims 1 and 2.

5. Antibiotic ***norfloxacin*** (*1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid*) obtained according to the procedure according to the patent claims 1 and 2.
6. Pharmaceutical preparation for use in human and veterinary medicine, as an antibiotic in the form of tablets, pills, dragees, capsules, ampullas or suppositories, and as food additives, **denoted by the fact**, that it contains the compound obtained according to the patent claims 1 to 5, with usual pharmaceutical additives.