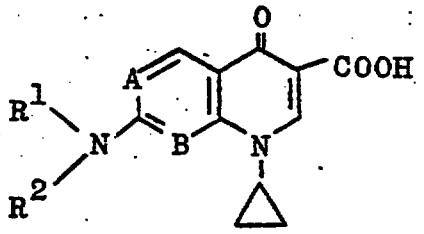
Description

The present invention relates to new 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acids, processes for their preparation and medicaments, in particular antibacterial agents, and feed additives containing these compounds.

It has already been disclosed that 7-amino-1-ethyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acids have antibacterial properties [Eur. J. Med. Chem. 12, 541-547 (1977)]. DE-A1 2,840,910, EP-A1 0,004,279 and EP-A 0,014,393 have disclosed compounds of similar structure, which also have an antibacterial activity. It has now been found that the new 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-napthtyridine-3-carboxylic acids of the formula I



(I)

in which

A can be nitrogen or CR^3,

wherein

R^3 can be hydrogen, nitro, halogen, preferably fluorine or chlorine, or a nitrile, caboxamide (sic), carboxyl or ester group, and

B represents nitrogen or C-H, and A and B cannot simultaneously be nitrogen, and

R^1 and R^2 are identical or different and represent hydrogen or a straight-chain or branched alkyl, alkenyl or alkinyl radical which has 1 - 12 carbon atoms and can optionally be substituted by hydroxyl groups, alkoxy, alkylmercapto or dialkylamino groups with 1 - 3 carbon atoms in each alkyl radical, the nitrile group and an alkoxycarbonyl group with 1 - 4 carbon atoms in

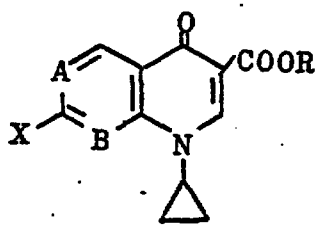
the alcohol part, or R^1 and R^2 furthermore denotes cycloalkyl with 3 - 6 carbon atoms, or further, together with the nitrogen atom which they substitute and, if appropriate, a hetero-atom, such as, for example, oxygen or sulphur, or NR^4, form a 3-membered to 7-membered ring which can be monosubstituted or polysubstituted by alkyl or alkenyl groups with 1 - 6 carbon atoms, hydroxyl groups, alkoxy or alkylmercapto groups with 1 - 3 carbon atoms, an alkoxycarbonyl group with 1 - 4 carbon atoms in the alcohol part, the nitrile group or a phenyl radical and can furthermore possess a double bond, and

R^4 represents hydrogen, or a branched or straight-chain alkyl, alkenyl or alkinyl group which has 1 - 6 carbon atoms and can optionally be substituted by hydroxyl, an alkoxy, alkylmercapto or dialkylamino group with 1 - 3 carbon atoms per alkyl radical or the alkoxycarbonyl group with 1 - 4 carbon atoms in the alcohol part, or represents a phenylalkyl group which is optionally substituted in the phenyl radical and has up to 4 carbon atoms in the aliphatic part, or an optionally substituted phenyl or naphthyl group or a heterocyclic radical, such as, for example, a pyridine, pyrimidine, thiazole or benzothiazole nucleus, or

R^4 furthermore denotes an alkoxycarbonyl group which is optionally substituted by a phenyl radical and has 1 - 4 carbon atoms in the alcohol part, an alkanoyl radical with 1 - 6 carbon atoms, a benzoyl radical, an optionally substituted C1-C6-alkyl- or phenylsulphonyl radical or an optionally substituted aminosulphonyl radical, possible substituents of phenyl and naphthyl groups being halogen, alkyl, alkoxy or alkylenemercapto groups with 1 - 3

carbon atoms, phenyloxy, phenylmercapto, trifluoromethyl, nitro, nitrile or carboxylic ester groups with 1 - 4 carbon atoms in the alcohol part,
and pharmaceutically usable salts thereof have a superior antibacterial action to that of the known quinolone- and azaquinolone-carboxylic acids.

It has furthermore been found that 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acids of the formula I are obtained when quinolone-carboxylic acids of the formula II (R = H)

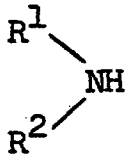


(II)

in which

A and B have the abovementioned meaning and
X represents a halogen atom or an alkylsulphonyl group with 1 - 4 carbon atoms,

are reacted with amines of the formula II



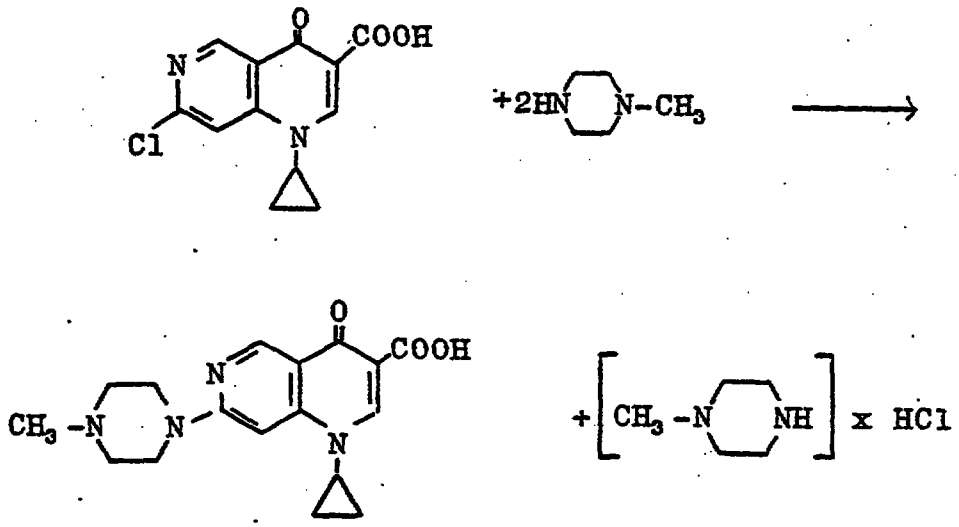
(III)

in which

R^1 and R^2 have the abovementioned meaning.

It is furthermore possible to react 7-halogeno-naphthyridine-3-carboxylic acid esters II (R = alkyl) with III, if appropriate in the presence of an acid-binding agent, such as, for example, triethylamine or pyridine, and then to hydrolyse the resulting 7-amino-naphthyridine-3-carboxylic acid esters under alkaline conditions to give I.

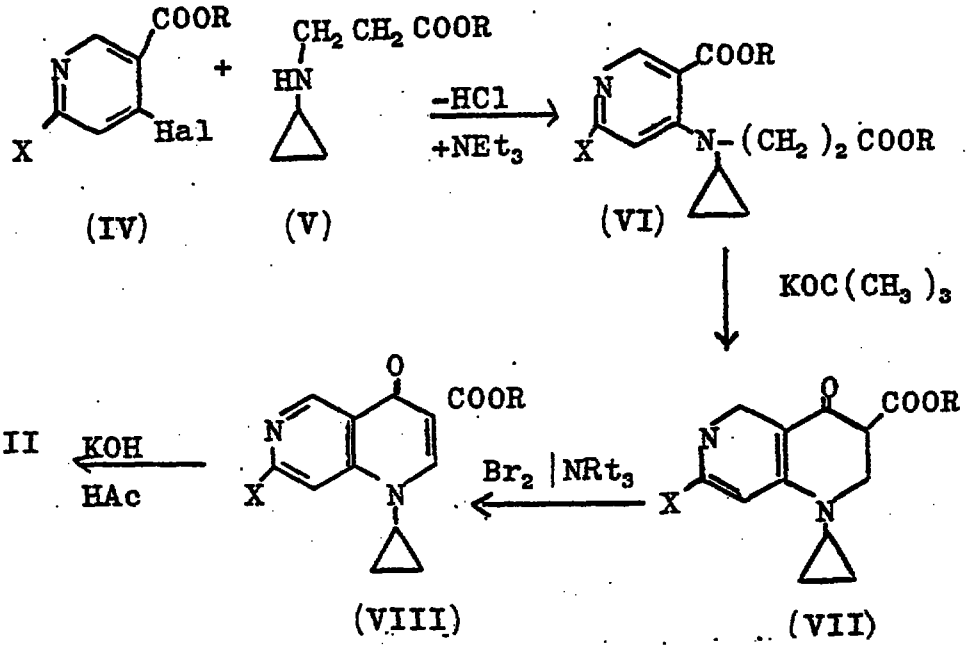
If, for example, 7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid and N-methylpiperazine are used as reactants in the reaction of II with III, the course of the reaction can be represented by the following equation:



The starting compounds II can be prepared in the following manner:

The starting substances used are, for example, 4-halogeno-pyridine-3-carboxylic acid esters of the formula IV, which are substituted by X in the 6-position, and these are largely selectively into the monosubstitution products of the formula VI around, the halogen atom in the 4-position being replaced by the amine radical, with β-cyclopropylamino-propionic acid esters of the formula V, preferably methyl or ethyl esters, which are readily accessible by reaction of corresponding acrylic acid esters with cyclopropylamine. The monosubstitution products of the formula VI are converted into the tetrahydro-naphthyridine-3-carboxylic acid esters of the formula VII by Dieckmann cyclisation in the presence of a strong base, such as, for example, potassium t-butylate or sodium hydride. The carboxylic ester of the formula VIII

is obtained from VII with bromine or sulphuryl chloride and triethylamine or pyridine as the dehydrohalogenating agent, and the compounds of the formula VIII can be saponified with an alkali to give the carboxylic acids of the formula II (R = H, A = N, B = CH).



Preferred possible diluents for the reaction II ⟶ I are ethanol, dioxane, toluene, dimethylformamide and dimethylsulphoxide. Acid-binding agents which can be used are, preferably, alkali carbonates, alkali metal hydroxides or tert.-organic bases, such as, for example, triethylamine, pyridine and the like.

The reaction temperatures can be varied within a substantial range. In general, the reaction is carried out between about 20° and about 180°C, preferably between 60° and 140°C.

The reaction can be carried out under normal pressure, but also under increased pressure, especially in the case of gaseous and low-boiling amines of the formula III. In general, the reaction is carried out under pressures between about 1 and about 100 bars,

preferably between 1 and 10 bars.

In carrying out the process, 1 - 5 mol of amine, preferably 2 - 3 mol of amine, are employed per mol of carboxylic acid.

New antibacterial active compounds which may be mentioned specifically are: 7-methylamino-, 7-benzylamino-, 7-pyrrolidino-, 7-morpholino-, 7-piperidino-, 7-piperazino-, 7-(4-methylpiperazino)-, 7-(4-benzylpiperazino)-, 7-(4-β-hydroxyetylpiperazino)-(sic), 7-(4-γ-hydroxypropylpiperazino)-, 7-(4-formylpiperazino)- or 7-(4-hydroxypiperidino)-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid and pharmaceutically acceptable acid addition salts or alkali metal salts of these compounds.

Example 1

7-(4-Methylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid (I, R^1R^2N = 4-methylpiperazino, A=N, B=CH).

A suspension of 2.64 g of 7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid and 2.5 g of N-methylpiperazine in 30 ml of ethanol is heated to the boiling point under reflux for 16 hours. The diluent is distilled off in vacuo, the residue is dissolved in 30 ml of 1 N NaOH, the solution is filtered and the filtrate is acidified with 10% strength hydrochloric acid. The precipitate is filtered off with suction and washed with water and ethanol. It can be recrystallised from N-dimethylformamide/ethanol. 3.1 g (94% of the theoretical yield) of 7-(4-methylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid of melting point 326°C (decomposition) (hydrochloride) are obtained.

Examples 2 to 10

The carboxylic acids of Examples 2 to 10 were obtained by a procedure analogous to that in Example 1. They are summarised in Table 1. The labelling of the radicals R^1 and R^2 relate to the formula I of the description.

Table 1

Example No.	A	B	R^1 R^2	Decomposition point (°C)
2	N	CH	$-(CH_2)_2\overset{H}{N}(CH_2)_2-$	322 (hydrochloride)
3	N	CH	$-(CH_2)_2O(CH_2)_2-$	286
4	N	CH	$-(CH_2)_2CH_2(CH_2)_2-$	297
5	N	CH	$-CH_2CH_2CH_2CH_2-$	330
6	N	CH	$-(CH_2)_2N(CH_2)_2-$ CH_2CH_2OH	305 (hydrochloride)
7	N	CH	$-(CH_2)_2N(CH_2)_2-$ $(CH_2)_3OH$	306 (hydrochloride)
8	N	CH	$-(CH_2)_2N(CH_2)_2-$ CHO	300
9	N	CH	$-CH_2-CH-(CH_2)_3-$ OH	302
10	N	CH	$-(CH_2)_2CH(CH_2)_2-$ OH	279
11	CF	CH	$-(CH_2)_2\overset{H}{N}(CH_2)_2-$	256 306 (hydrochloride)
12	CH	N	$-(CH_2)_2N(CH_2)_2-$ CH_3	279
13	CH	N	$-(CH_2)_2\underset{H}{N}(CH_2)_2-$	277
14	CF	CH	$-(CH_2)_2N(CH_2)_2-$ CH_3	249
15	CF	CH	$-(CH_2)_4-$	323
16	C—CN	N	$-(CH_2)_2\overset{H}{N}(CH_2)_2-$	335 (hydrochloride)
17	C—CN	N	$-(CH_2)_2N(CH_2)_2-$ CH_3	295 (hydrochloride)
18	C—CN	N	$-(CH_2)_4-$	290
19	CF	CH	$-(CH_2)_2N(CH_2)_2-$ C_2H_5	306 (hydrochloride)

The 7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid used as the starting material can be prepared in a multi-stage reaction sequence, for example starting from 4,6-dichloro-nicotinic acid methyl ester, which is known (Recueil Trav. chim. Pays-bas. 69, 687 (1950).

1) 6-Chloro-4-(N-2-methoxycarbonylethyl-N-cyclopropyl-amino-pyridine-3-carboxylic acid methyl ester (VI, R = methyl, X = chlorine:

A mixture of 28.6 g of β-cyclopropylamino-propionic acid methyl ester and 21 g of triethylamine is rapidly added dropwise to a solution of 41.2 g of 4,6-dichloro-pyridine-3-carboxylic acid methyl ester in 150 ml of toluene at 10 - 20°C, whilst cooling with ice and stirring. The ice-bath is removed and the mixture is stirred at room temperature for 1/2 hour and heated to the boiling point under reflux for 6 hours. The resulting suspension is washed with water and dried with Na_2SO_4 and the solvent is distilled off in vacuo. 59 g of the title compound are obtained as a brown oil.

The β-cyclopropylaminopropionic acid methyl ester used as a reactant was prepared as follows:

86 g of freshly distilled methyl acrylate which has been cooled to -60°C is added dropwise to a solution, which has been cooled to -60°C to -70°C, of 57 g of cyclopropylamine in 150 ml of ethanol in the course of about 3 hours. The mixture is then allowed to rise slowly to room temperature overnight, the solvent is distilled off in vacuo and the residue is then fractionated. 95 g of β-cyclopropylamino-propionic acid methyl ester pass over at 84 - 86°C/22 mm Hg:

2) 7-Chloro-1-cyclopropyl-4-oxo-1,2,3,4-tetrahydro-1,6-naphthyridine-3-carboxylic acid methyl ester (VII, R = methyl, X = chlorine):

59 g of crude 6-chloro-4-(N-2-methoxycarbonyl-ethyl-N-cyclopropyl)-amino-pyridine-3-carboxylic acid

methyl ester are dissolved in 240 ml of anhydrous toluene, and 23 g of potassium t-butylate are rapidly added, whilst stirring. The mixture is left to stand over After, 20 g of glacial acetic acid and 100 ml of water are added, the phases are separated, the toluene solution is washed again with water and dried with Na_2SO_4 and the toluene is stripped off in vacuo. After recrystallisation from methanol, 18 g of the carbon ester of melting point 155 - 157°C are obtained.

3) 7-Chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid methyl ester (VIII, R = methyl, X = chlorine):

9.8 g of the tetrahydronaphthyridine-3-carboxylic acid methyl ester prepared according to 2) were dissolved in 200 ml of methylene chloride, and a solution of 5.9 g of bromine in 40 ml of CH_2Cl_2 was rapidly added dropwise at 10 - 15°C, whilst cooling with ice. The mixture is then stirred at ~10°C for a further 10 minutes, 8 g of triethylamine are added and the ice-bath is removed. The mixture is subsequently stirred for 3 hours, washed twice with water and dried with Na_2SO_4, the solvent is distilled off in vacuo and the residue is recrystallised from dimethylformamide/ethanol. 8.8 g of 7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid methyl ester of melting point 272° - 274°C (decomposition) are obtained.

4) 7-Chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid (II, R = H, A = N, B = CH, X = chlorine):

A solution of 5.7 g of potassium hydroxide in 300 ml of water is added to 27.85 g of the ester prepared according to 3). The mixture is heated to 85 - 95°C for 30 minutes, whilst stirring, and the resulting solution is filtered at room temperature and acidified with glacial acetic acid. The precipitate is filtered off with suction, washed with water and dried over calcium chloride in a

vacuum drying cabinet. 20 g of pure 7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid of melting point 226 - 227°C are obtained.

It has furthermore been found that the compounds according to the invention have outstanding antimicrobial properties.

In particular, they have broad bacteriostatic and bactericidal action against Gram-positive bacteria, such as Staphylococci and Streptococci, and Gram-negative bacteria, such as Escherichia, Proteus, Providencia, Enterobacter, Klebsiella, Salmonella and Pseudomonas. The improved antibacterial action of the new compounds according to the invention is particularly clear in Example 1, which, compared with 2-piperazino-8-ethyl-5-oxo-5,8-dihydropyrido[2,3-d]pyrimidine-6-carboxylic acid ("pipemidic acid") or the known compound 1-ethyl-7-methyl-1,8-naphthyrid-4-one-3-carboxylic acid ["nalidixic acid"; Ehrhart/Ruschig, Arzneimittel (Medicaments), Volume 2: Chemotherapeutika (Chemotherapeutics), Verlag Chemie 1968, page 1,568], proved to be far superior in vitro and in vivo on Staphylococci, Escherichia coli, Proteus, Klebsiella and Pseudomonas.

The improved broad antibacterial activity of the compounds according to the invention enable them to be used as active compounds both in human medicine and in veterinary medicine, in which they can be used both for preventing and for the treatment of systemic or local bacterial infections, in particular of the urinary tract. The compounds according to the invention can furthermore also be used as feed additives for promoting growth and for improving feed utilisation in livestock husbandry, in particular in the rearing of animals for fattening. The active compounds are then preferably administered via the feed and/or the drinking water.

The present invention furthermore relates to agents which contain the new compounds according to the

invention. These agents include, for example, feed concentrates, for livestock husbandry, which can also contain, as is customary, vitamins and/or mineral salts, in addition to the active compounds, and pharmaceutical formulations.

The invention preferably relates to antibacterially active agents which contain compounds of the formula I. The invention particularly preferably relates to those antibacterially active agents which contain compounds of the formula I or alkali metal salts or alkaline earth metal salts thereof.

As is customary, the pharmaceutical formulations according to the invention contain non-toxic, inert pharmaceutically suitable excipients, in addition to the new compounds according to the invention. Such pharmaceutically suitable excipients are, for example, fillers and extenders, binders, humectants, solution retarders, absorption accelerators, wetting agents, adsorbents or lubricants, which can have a solid, semi-solid or liquid consistency. Such pharmaceutically suitable excipients are known to the expert.

Tablets, dragees, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays may be mentioned as preferred pharmaceutical formulations. These formulations are prepared by known methods in the customary manner, for example by mixing the new active compound according to the invention with the customary excipients and additives. The active compound should be present in the pharmaceutical formulations listed in a concentration of about 0.1 to 99.5% by weight, preferably about 0.5 to 95% by weight, of the total mixture.

The provision of new bactericides for combating bacteria which are resistant to known bactericides is an enrichment of the state of the art.

36

Minimum inhibitory concentrations mcg/ml in an agar dilution test*)

	Compounds from Example 1	Example 11	Pipemidic acid	Nalidixic acid
Escherichia coli				
T 7	0,25	≤0,015	2	1
455/7	128	1,0	128	>256
103400	0,25		1	2
Salmonella 683	0,5		2	4
Klebsiella 63	1		2	4
Pseudomonas 7167	8	0,5	16	64
Proteus 8228	2		4	8

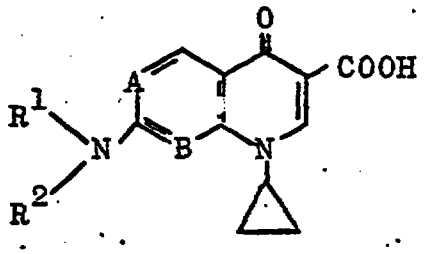
*)Denley multipoint inoculation method

* C L M S *

(37)

Patent Claims

1. 7-Amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acids of the general formula I



(I)

in which

A can be nitrogen or CR^3

wherein

R^3 can be hydrogen, nitro, halogen, preferably fluorine or chlorine, or a nitrile, carboxamide, carboxyl or ester group, and

B represents nitrogen or C-H, and A and B cannot simultaneously be nitrogen, and

R^1 and R^2 are identical or different and represent hydrogen or a straight-chain or branched alkyl, alkenyl or alkinyl radical which has 1 - 12 carbon atoms and can optionally be substituted by hydroxyl groups, alkoxy, alkylmercapto or dialkylamino groups with 1 - 3 carbon atoms in each alkyl radical, the nitrile group, an alkoxycarbonyl group with 1 - 4 carbon atoms in the alcohol part, or R^1 and R^2 furthermore denotes cycloalkyl with 3 - 6 carbon atoms, or further, together with the nitrogen atom which they substitute and, if appropriate, a hetero-atom, such as, for example, oxygen or sulphur, or NR^4, form a 3-membered to 7-membered ring which can be monosubstituted or polysubstituted by alkyl or alkenyl groups with 1 - 6 carbon atoms, hydroxyl groups, alkoxy or alkylmercapto groups with 1 - 3 carbon atoms, an

alkoxycarbonyl group with 1 - 4 carbon atoms in the alcohol part, the nitrile group or a phenyl radical and can furthermore possess a double bond, and

R^4 represents hydrogen, or a branched or straight-chain alkyl, alkenyl or alkinyl group which has 1 - 6 carbon atoms and can optionally be substituted by hydroxyl, an alkoxy, alkylmercapto or dialkylamino group with 1 - 3 carbon atoms per alkyl radical or the alkoxycarbonyl group with 1 - 4 carbon atoms in the alcohol part, or represents a phenylalkyl group which is optionally substituted in the phenyl radical and has up to 4 carbon atoms in the aliphatic part, or an optionally substituted phenyl or naphthyl group or a heterocyclic radical, such as, for example, a pyridine, pyrimidine, thiazole or benzothiazole nucleus, or

R^4 furthermore denotes an alkoxycarbonyl group which is optionally substituted by a phenyl radical and has 1 - 4 carbon atoms in the alcohol part, an alkanoyl radical with 1 - 6 carbon atoms, a benzoyl radical, an optionally substituted C1-C6-alkyl- or rhenylsulphonyl radical or an optionally substituted aminosulphonyl radical, possible substituents of phenyl and naphthyl groups being halogen, alkyl, alkoxy or alkylenemercapto groups with 1 - 3 carbon atoms, phenyloxy, phenylmercapto, trifluoromethyl, nitro, nitrile or carboxylic ester groups with 1 - 4 carbon atoms in the alcohol part,

and pharmaceutically usable salts thereof.

2. 6-Fluoro-7-piperazino-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

3. 7-(4-Methylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid.

4. 7-Piperazino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid.

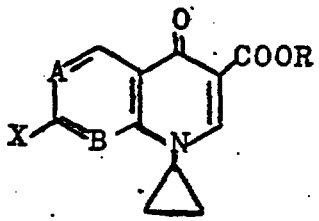
5. 7-(4-Hydroxyethylpiperazino)-1-cyclopropyl-4-oxo-

1,4-dihydro-naphthyridine-3-carboxylic acid.

6. 7-(4-Formylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid.

7. Process for the preparation of 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acids of the general formula I in Claim 1, characterised in that

(a) naphthyridone-3-carboxylic acids of the general formula II (R=H)



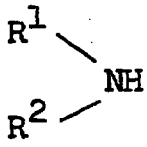
(II)

in which

A and B have the abovementioned meaning and

X represents a halogen atom or an alkylsulphonyl group with 1 - 4 carbon atoms,

are reacted with amines of the general formula III



(III)

in which

R^1 and R^2 have the abovementioned meaning,

or

(b) 7-halogeno-naphthyridone-3-carboxylic acid esters of the general formula II (R=alkyl) are reacted with amines of the general formula III, if appropriate in the presence of an acid-binding agent, such as, for example, triethylamine or pyridine, and the resulting 7-amino-naphthyridine-3-carboxylic acid esters are then hydrolysed under alkaline conditions.

8. Medicaments, characterised in that they contain 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acids according to Claim 1.

9. Process for the preparation of antibacterial agents, characterised in that 7-amino-1-cyclopropyl-4-

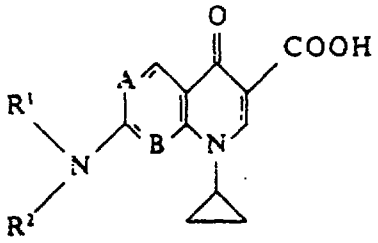
* C L M S *

oxo-1,4-dihydro-naphthyridine-3-carboxylic acids according to Claim 1 are mixed with inert, non-toxic pharmaceutically suitable excipients.

* C L M S *

Patentansprüche (as printed)

1. 7-Amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridin-3-carbonsäuren der allgemeinen Formel I



(I)

in welcher

A Stickstoff oder CR^3 sein kann, wobei R^3 Wasserstoff, Nitro, Halogen, bevorzugt Fluor oder Chlor, oder eine Nitril-, Carbonamid-, Carboxyl- oder Estergruppe sein kann und

B Stickstoff oder C-H darstellt und A und B nicht gleichzeitig Stickstoff sein können sowie

R^1 und R^2 gleich oder verschieden sind und für Wasserstoff, einen verzweigten oder unverzweigten Alkyl-, Alkenyl- oder Alkinylrest mit 1—12 Kohlenstoffatomen stehen, der gegebenenfalls durch Hydroxylgruppen, Alkoxy-, Alkylmercapto- oder Dialkylamino-Gruppen mit 1—3 Kohlenstoffatomen in jedem Alkylrest, die Nitril- sowie eine Alkoxycarbonyl-Gruppe mit 1—4 Kohlenstoffatomen im Alkoholteil substituiert sein kann, ferner Cycloalkyl mit 3—6 Kohlenstoffatomen bedeutet und weiterhin gemeinsam mit dem Stickstoffatom, das sie substituieren und gegebenenfalls einem Heteroatom wie z. B. Sauerstoff, Schwefel oder NR^4 einen 3—7-gliedrigen Ring bilden, der ein- oder mehrfach durch Alkyl- oder Alkenylgruppen mit 1—6 Kohlenstoffatomen, Hydroxyl-, Alkoxy- und Alkylmercaptogruppen mit 1—3 Kohlenstoffatomen, eine Alkoxycarbonylgruppe mit 1—4 Kohlenstoffatomen im Alkoholteil, die Nitrilgruppe sowie einen Phenylrest substituiert sein kann und ferner eine Doppelbindung besitzen kann und

R^4 Wasserstoff, eine verzweigte oder unverzweigte Alkyl-, Alkenyl- oder Alkinylgruppe mit 1—6 Kohlenstoffatomen, die gegebenenfalls durch Hydroxyl, Alkoxy-, Alkylmercapto- und Dialkylaminogruppe mit 1—3 Kohlenstoffatomen für einen Alkylrest, die Alkoxycarbonylgruppe mit 1—4 Kohlenstoffatomen im Alkoholteil substituiert sein kann, eine gegebenenfalls im Phenylrest substituierte Phenylalkylgruppe mit bis zu 4 Kohlenstoffatomen im aliphatischen Teil, sowie eine gegebenenfalls substituierte Phenyl- oder Naphthylgruppe oder ein heterocyclischer Rest wie beispielsweise einen Pyridin-, Pyrimidin-, Thiazol- oder Benzthiazolkern darstellt, ferner eine gegebenenfalls durch einen Phenylrest substituierte Alkoxycarbonylgruppe mit 1—4 Kohlenstoffatomen im Alkoholteil, ein Alkanoylrest mit 1—6 Kohlenstoffatomen, ein Benzoylrest, ein gegebenenfalls substituierter C1—C6-Alkyl- oder Rhenylsulfonylrest sowie ein gegebenenfalls substituierter Aminosulfonylrest bedeutet, wobei als Substituenten von Phenyl- und Naphthylgruppen Halogen, Alkyl-, Alkoxy- oder Alkylmercaptogruppen mit 1—3 Kohlenstoffatomen, Phenyloxy-, Phenylmercapto, Trifluormethyl-, Nitro-, Nitril- oder Carbonestergruppen mit 1—4 Kohlenstoffatomen im Alkoholteil in Frage kommen,

und deren pharmazeutisch verwendbaren Salze.

2. 6-Fluor-7-piperazino-1-cyclopropyl-4-oxo-1,4-diphydro-chinolin-3-carbonsäure.

3. 7-(4-Methylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridin-3-carbonsäure.

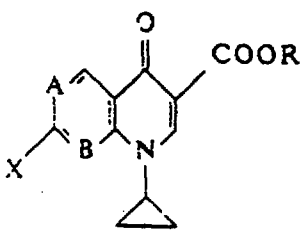
4. 7-Piperazino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridin-3-carbonsäure.

5. 7-(4-Hydroxyethylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridin-3-carbonsäure.

6. 7-(4-Formylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridin-3-carbonsäure.

7. Verfahren zur Herstellung von 7-Amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridin-3-carbonsäuren der allgemeinen Formel I in Anspruch 1, dadurch gekennzeichnet, daß man

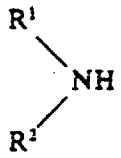
(a) Naphthyridon-3-carbonsäuren der allgemeinen Formel II (R = H)



(II)

in welcher
A und B die oben angegebene Bedeutung haben und
X für ein Halogenatom oder eine Alkylsulfonylgruppe mit 1—4 Kohlenstoffatomen steht,

mit Aminen der allgemeinen Formel III



(III)

in welcher
R^1 und R^2 die oben angegebene Bedeutung haben,

umsetzt, oder

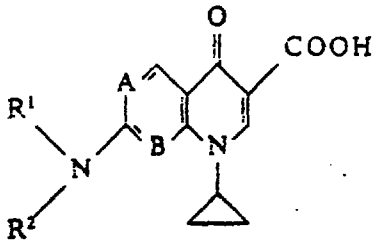
(b) 7-Halogen-naphthyridon-3-carbonsäureester der allgemeinen Formel II (R = Alkyl) mit Aminen der allgemeinen Formel III gegebenenfalls in Gegenwart eines Säurebinders, wie z. B. Triethylamin oder Pyridin, umsetzt und anschließend die erhaltenen 7-Amino-naphthyridin-3-carbonsäureester alkalisch verseift.

8. Arzneimittel, gekennzeichnet durch einen Gehalt an 7-Amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridin-3-carbonsäuren gemäß Anspruch 1.

9. Verfahren zur Herstellung von antibakteriellen Mitteln, dadurch gekennzeichnet, daß man 7-Amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridin-3-carbonsäuren gemäß Anspruch 1 mit inerten, nicht-toxischen pharmazeutisch geeigneten Trägerstoffen vermischt.

Claims (as printed)

1. 7-Amino-1-cyclopropyl-4-oxo-1,4-diphydro-naphthyridine-3-carboxylic acids of the general formula I



(I)

in which

A can be nitrogen or CR^3

wherein

R^3 can be hydrogen, nitro, halogen, preferably fluorine or chlorine, or a nitrile, carboxamide, carboxyl or ester group, and

B represents nitrogen or C—H, and A and B cannot simultaneously be nitrogen, and

R^1 and R^2 are identical or different and represent hydrogen or a branched or straight-chain alkyl, alkenyl or alkinyl radical which has 1—12 carbon atoms and can optionally be substituted by hydroxyl groups, alkoxy, alkylmercapto or dialkylamino groups with 1—3 carbon atoms in each alkyl radical, the nitrile group or an alkoxy-carbonyl group with 1—4 carbon atoms in the alcohol part of furthermore denotes cycloalkyl with 3—6 carbon atoms, or, together with the nitrogen atom which they substitute and, if appropriate, a hetero-atom, such as, for example, oxygen or sulphur, or NR^4, form a 3-membered to 7-membered ring which can be monosubstituted or polysubstituted by alkyl or alkenyl groups with 1—6 carbon atoms, hydroxyl groups, alkoxy or alkylmercapto groups with 1—3 carbon atoms, an alkoxycarbonyl group with 1—4 carbon atoms in the alcohol part, the nitrile group or a phenyl radical and can furthermore possess a double bond, and

R^4 represents hydrogen, or a branched or straightchain alkyl, alkenyl or alkinyl group which has 1—6 carbon atoms and can optionally be substituted by hydroxyl, an alkoxy, alkylmercapto or dialkylamino group with 1—3 carbon atoms per alkyl radical or the alkoxycarbonyl group with 1—4

* C L M S *

carbon atoms in the alcohol part, or represents a phenylalkyl group which is optionally substituted in the phenyl radical and has up to 4 carbon atoms in the aliphatic part, or an optionally substituted phenyl or naphthyl group or a heterocyclic radical, such as, for example, a pyridine, pyrimidine, thiazole or benzothiazole nucleus, or denotes an alkoxycarbonyl group which is optionally substituted by a phenyl radical and has 1—4 carbon atoms in the alcohol part, an alkanoyl radical with 1—6 carbon atoms, a benzoyl radical, an optionally substituted C1—C6-alkyl or phenylsulphonyl radical or an optionally substituted aminosulphonyl radical, possible substituents of phenyl and naphthyl groups being halogen, alkyl, alkoxy or alkylmercapto groups with 1—3 carbon atoms, phenyloxy, phenylmercapto, trifluoromethyl, nitro, nitrile or carboxylic ester groups with 1—4 carbon atoms in the alcohol part,

and pharmaceutically usable salts thereof.

2. 6-Fluoro-7-piperazino-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

3. 7-(4-Methylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid.

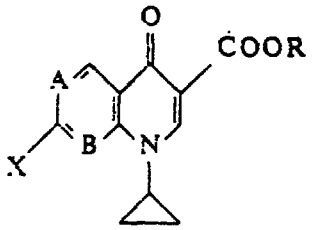
4. 7-Piperazino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid.

5. 7-(4-Hydroxyethylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid.

6. 7-(4-Formylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid.

7. Process for the preparation of 7-amino-1-cycloprophyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acids of the general formula I in Claim 1, characterised in that

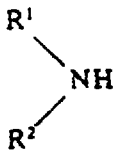
(a) naphthyridone-3-carboxylic acids of the general formula II (R = H)



(II)

in which
A and B have the abovementioned meaning and
X represents a halogen atom or an alkylsulphonyl group with 1—4 carbon atoms,

are reacted with amines of the general formula III



(III)

in which
R^1 and R^2 have the abovementioned meaning,
or

(b) 7-halogeno-naphthyridone-3-carboxylic acid esters of the general formula II (R = alkyl) are reacted with amines of the general formula III, if appropriate in the presence of an acid-binding agent, such as, for example, triethylamine or pyridine, and the resulting 7-amino-naphthyridine-3-caroxylic acid esters are then hydrolysed under alkaline conditions.

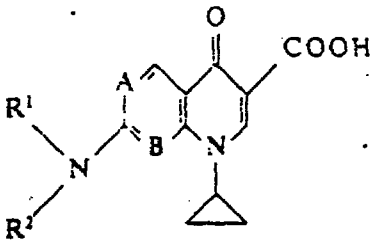
8. Medicaments, characterised in that they contain 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acids according to Claim 1.

9. Process for the preparation of antibacterial agents, characterised in that 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acids according to Claim 1 are mixed with inert, non-toxic pharmaceutically suitable excipients.

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Revendications (as printed)

1. Acides 7 amino 1 cyclopropyl 4 oxo 1,4 dihydro naphtyridine 3 carboxyliques de formule générale I:



(I)

dans laquelle

A peut être un atome d'azote ou CR^3, R^3 pouvant être un atome d'hydrogène, un groupe nitro, un atome d'halogène, de préférence, un atome de fluor ou un atome de chlore, ou encore un groupe nitrile, carbonamide, carboxy ou ester, et

B représente un atome d'azote ou CH, A et B ne pouvant être simultanément un atome d'azote, et

R^1 et R^2 sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle, un groupe alcényle ou un groupe alcynyle ramifié ou non ramifié, contenant 1 à 12 atomes de carbone et pouvant être éventuellement substitué par des groupes hydroxy, des groupes alcoxy, alkylmercapto ou dialkylamino contenant 1 à 3 atomes de carbone dans chaque groupe alkyle, le groupe nitrile, ainsi que par un groupe alcoxy-carbonyle contenant 1 à 4 atomes des carbone dans la fraction alcool; ils représentent également un groupe cycloalkyle contenant 3 à 6 atomes de carbone et, en outre, ensemble avec l'atome d'azote qu'ils substituent et éventuellement un hétéro-atome tel que, par exemple, un atome d'oxygène, un atome de soufre ou NR⁵, ils forment un noyau triangulaire à heptagonal qui peut être substitué une ou plusieurs fois par des groupes alkyle ou alcényle contenant 1 à 6 atomes de carbone, par des groupes hydroxy-, alcoxy- et alkyl-mercapto contenant 1 à 3 atomes de carbone, par un groupe alcoxycarbonyle contenant 1 à 4 atomes de carbone dans la fraction alcool, par le groupe nitrile, ainsi que par un groupe phenyle et, en outre, ils peuvent comporter une double liaison, et

R^4 représente un atome d'hydrogène, un groupe alkyle, alcényle ou alcynyle ramifié ou non ramifié contenant 1 à 6 atomes de carbone et qui peut éventuellement être substitué par un groupe hydroxy, alcoxy, alkyl-mercapto et dialkylamino contenant 1 à 3 atomes de carbone pour un radical alkyle, et par un groupe alcoxycarbonyle contenant 1 à 4 atomes de carbone dans la fraction alcool, un groupe phénylalkyle éventuellement substitué dans le radical phényle et contenant jusqu'à 4 atomes de carbone dans la fraction aliphatique, ainsi qu'un groupe phényle ou naphtyle éventuellement substitué ou un radical hétérocyclique tel que, par exemple, un noyau pyridine, pyrimidine, thiazole ou benzthiazole, de même qu'un groupe alcoxycarbonyle éventuellement substitué par un groupe phényle et contenant 1 à 4 atomes de carbone dans la fraction alcool, un radical alcanoyle contenant 1 à 6 atomes de carbone, un radical benzoyle, un radical alkyl en C_1-C_6-ou phénylsulfonyle éventuellement substitué, de même qu'un radical aminosulfonyle éventuellement substitué et, comme substituants des groupes phényle et naphtyle, on envisage les atomes d'halogènes, les groupes alkyle-, alcoxy- ou alkylène-mercapto contenant 1 à 3 atomes de carbone, les groupes phényloxy, phényl-mercapto, trifluorométhyle, nitro, nitrile ou ester carboxylique contenant 1 à 4 atomes de carbone dans la fraction alcool,

ainsi que leurs sels pharmaceutiquement utiles.

2. L'acide 6-fluoro-7-pipérazino-1-cyclopropyl-4-oxo-1,4-dihydro-quinoléine-3-carboxylique.

3. L'acide 7-(4-méthylpipérazino)-1-cyclopropyl-4-oxo-1,4-diphydro-naphtyridine-3-carboxylique.

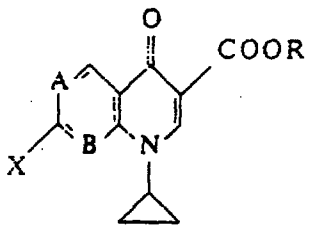
4. L'acide 7-piperazino-1-cyclopropyl-4-oxo-1,4-dihydro-naphtyridine-3-carboxylique.

5. L'acide 7-(4-hydroxyéthylpipérazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphtyridine-3-carboxylique.

6. L'acide 7-(4-formylpipérazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphtyridine-3-carboxylique.

7. Procédé de préparation d'acides 7-amino-1-cyclopropyl-4-oxo-1,4-dihydronaphtyridine-3-carboxyliques de formule générale I suivant la revendication 1, caractérisé en ce que:

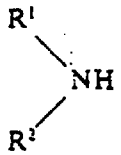
(a) on fait réagir des acides naphtyridone-3-carboxyliques de formule générale II (R = H):



(II)

dans laquelle
A et B ont les significations indiquées ci-dessus et
X représente un atome d'halogène ou un groupe alkylsulfonyle contenant 1 à 4 atomes de carbone,

avec des amines de formule générale III:



(III)

dans laquelle
R^1 et R^2 ont les significations indiquées ci-dessus,
ou

(b) on fait réagir des esters d'acides 7-halogéno-naphtyridone-3-carboxyliques de formule générale II (R = alkyle) avec amines de formule générale III éventuellement en présence d'un fixateur d'acide tel que, par exemple, la triéthylamine ou la pyridine, puis on saponifie, par voie alcaline, les esters d'acides 7-amino-naphtyridine-3-carboxyliques obtenus.

8. Médicaments, caractérisés en ce qu'ils contiennent des acides 7-amino-1-cyclopropyl-4-oxo-1,4 dihydro-naphtyridine-3-carboxyliques suivant la revendication 1.

9. Procédé de préparation d'agents antibactériens, caractérisé en ce qu'on mélange des acides 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphtyridine-3-carboxyliques suivant la revendication 1 avec des substances supports inertes, non toxiques et pharmaceutiquement appropriées.