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ORIGINAL

COMPLETE SPECIFICATION

STANDARD PATENT

Application Number:

Lodged:

Invention Title: MIXED PYRIDINE-2,4-AND-2,5-DICARBOXAMIDES, A PROCESS FOR PREPARING THEM, THE USE THEREOF AND PHARMACEUTICALS BASED ON THESE COMPOUNDS

The following statement is a full description of this invention, including the best method of performing it known to us :-

Description

Mixed pyridine-2,4- and -2,5-dicarboxamides, a process for preparing them, the use thereof and pharmaceuticals based on these compounds

Compounds which inhibit proline hydroxylase and lysine hydroxylase effect a very selective inhibition of collagen biosynthesis due to influencing collagen-specific hydroxylation reactions. In the course thereof, protein-bound proline or lysine is hydroxylated by the enzymes proline hydroxylase or lysine hydroxylase respectively. If this reaction is suppressed by inhibitors, the resulting collagen molecule is unable to function, is insufficiently hydroxylated and can be released by the cells only in small amounts into the extracellular space. The insufficiently hydroxylated collagen cannot, moreover, be incorporated in the collagen matrix and is very easily broken down by proteolysis. The consequence of these effects is an overall reduction in the amount of collagen deposited in the extracellular space.

It is known that inhibition of proline hydroxylase by known inhibitors such as α,α'-dipyridyl results in inhibition of $C1^q$ biosynthesis by macrophages (W. Müller et al., FEBS Lett. 90 (1978), 218; Immunobiology 155 (1978), 47). This results in the classical pathway of complement activation becoming inoperative. Hence inhibitors of proline hydroxylase act as immunosuppressants, for example in immune complex diseases.

It is known that proline hydroxylase can be effectively inhibited by pyridine-2,4- and -2,5-dicarboxylic acids (K. Mayama et al., Eur. J. Biochem. 138 (1984) 239-245). However, in cell culture, these compounds are effective inhibitors only in very high concentrations (Tschank, G.

et al., Biochem. J. 238 (1987) 625-633).

DE-A 34 32 094 describes pyridine-2,4- and -2,5-dicarboxylic disesters with 1-6 carbon atoms in the ester alkyl moiety as pharmaceuticals for the inhibition of proline hydroxylase and lysine hydroxylase.

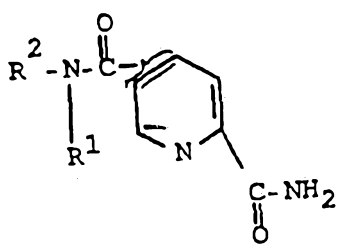
These lower alkylated diesters have the disadvantage, however, that they are too rapidly cleaved in the body to the acids and do not reach their site of action in the cell in sufficiently high concentration and thus are less suitable for possible administration as pharmaceuticals.

DE-A 37 03 959, DE-A 37 03 362 and DE-A 37 03 963 describe in a general form mixed esters/amides, higher alkylated diesters and diamides of pyridine-2,4- and -2,5-dicarboxylic acids which are effective inhibitors of collagen biosynthesis in animal models.

Thus, DE-A 37 03 959 describes, inter alia, the synthesis of N,N'-bis(2-methoxyethyl)pyridine-2,4-dicarboxamide and N,N'-bis(3-isopropoxypropyl)pyridine-2,4-dicarboxamide.

German Patent Applications P 38 26 471.4 and P 38 28 140.6 propose an improved process for preparing N,N'-bis(2-methoxyethyl)pyridine-2,4-dicarboxamide. German Patent Application P 39 24 093.2 proposes novel N,N'-bis(alkoxyalkyl)pyridine-2,4-dicarboxamides.

The object to be achieved was thus to find compounds which are suitable in a much improved manner than those hitherto disclosed for the inhibition of proline hydroxylase and lysine hydroxylase. The object has been achieved by pyridine-2,4- and -2,5-dicarboxamides of the formula I



(I)

in which

R^1 is C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl or C_2-C_{12}-alkynyl, which are unsubstituted or substituted once or, in the case of the C_2-C_{12}-alkyls, C_2-C_{12}-alkenyls and C_2-C_{12}-alkynyls, also several times by

halogen, hydroxyl, cyano, amino, carboxyl, alkoxy, alkoxycarbonyl, alkylcarbonyloxy, alkyl- or dialkylamino, where the alkyl radicals have 1-4 carbon atoms, or by

indolyl or phenyl, which is unsubstituted or substituted once, twice or three times by halogen, nitro, C_1-C_4-alkyl or C_1-C_4-alkoxy, it also being possible in the case of multiple substitutions for the substituents to be independently different from one another,

or R^1 is saturated C_5-C_7-cycloalkyl which is optionally benzo-fused,

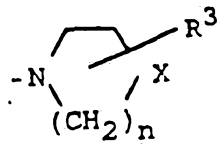
or R^1 is aryl or heteroaryl, which is unsubstituted or in turn substituted once, twice or three times by halogen, nitro, cyano, C_1-C_4-alkyl or C_1-C_4-alkoxy, it also being possible in the case of multiple substitutions for the substituents to be independently different from one another,

or provided that R^2 is H, R^1 is amino which is unsubstituted or mono- or disubstituted by C_1-C_4-alkyl, phenyl or C_1-C_3-alkylcarbonyl,

and

R^2 is hydrogen or R^1, where R^2 and R^1 are identical or different,

or where the radicals R^1 and R^2 form, together with the nitrogen atom, a radical of the formula



in which

n is 1 to 3 and
X is O, S, CH_2 or $N-R^3$,

where

R^3 is hydrogen, phenyl or C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, where these phenyl, alkyl, alkenyl and alkynyl radicals are unsubstituted or substituted one or more times by:
phenyl which in turn is unsubstituted or substituted one or more times by one or more substituents selected from: halogen, nitro, cyano, carboxyl, hydroxyl, methyl, ethyl, methoxy, ethoxy and trifluoromethyl,

or

$N(R^4)_2$, where
R^4 is H or C_1-C_3-alkyl,

or

$COOR^5$, where
R^5 is H or C_1-C_3-alkyl,

or

$CON(R^6)_2$ or $CONHR^6$, where
R^6 is H or C_1-C_3-alkyl, or where $(R^6)_2$ is a C_4-C_6-

alkylene chain in which zero or one CH_2 group which is not directly adjacent to the nitrogen atom is replaced by O, S or N-R^4,

or where

R^3 is C_1-C_4-alkoxycarbonyl or C_3-C_7-cycloalkyl,

and the physiologically tolerated salts, which likewise effectively inhibit lysine hydroxylase and proline hydroxylase in animal models.

The invention particularly relates to pyridine-2,4- and -2,5-dicarboxamides of the formula I in which

R^1 is C_1-C_{12}-alkyl which is unsubstituted or substituted once or, in the case of the C_2-C_{12}-alkyls, also several times by

phenyl, hydroxyl, alkoxy, amino, alkoxycarbonyl, alkyl- or dialkylamino, where the alkyl radicals have 1-3 carbon atoms,

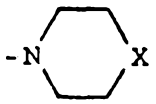
or R^1 is phenyl which is unsubstituted or in turn substituted once by halogen, nitro, cyano, methyl or methoxy,

or, provided that R^2 is H, R^1 is amino which is unsubstituted or monosubstituted by C_1-C_3-alkyl, phenyl or C_1-C_3-alkylcarbonyl,

and

R^2 is hydrogen,

or where the radicals R^1 and R^2 form, together with the nitrogen atom, a radical of the formula



in which

X is O, CH_2 or $N-R^3$,

where

R^3 is hydrogen, or C_1-C_3-alkyl, and the physiologically tolerated salts.

The meanings of halogen are fluorine, chlorine, bromine and iodine, those of aryl are, phenyl and naphthyl, and those of heteroaryl are 5- and 6-membered aromatic rings with 1, 2 or 3 nitrogen and/or oxygen and/or sulfur atoms, which can also be benzo-fused where appropriate; the heteroaryl radicals are, in particular, pyridyl, pyridazyl, pyrimidyl, pyrazyl, 1,3,5-triazyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thienyl, oxazolyl and thiazolyl radicals and, where appropriate, the benzo-fused compounds thereof.

"Substituted several times" means hereinbefore and hereinafter that at least 2, not more than 4, hydrogen atoms present in the alkyl, alkenyl, alkynyl, heteroaryl and aryl radicals are replaced by the substituents mentioned. In the case of multiple substitutions the substituents can also be independently different from one another.

All alkyl and alkenyl radicals mentioned with more than 2 carbon atoms and all alkynyl radicals with more than 3 carbon atoms can be both straight-chain and branched.

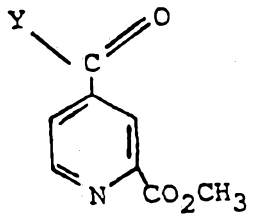
The invention further relates to the compounds of the formula I for use as pharmaceuticals. The invention additionally relates to the compounds of the formula I for use as fibrosuppressants and immunosuppressants and for the inhibition of proline hydroxylase and lysine hydroxylase and for influencing the metabolism of

collagen and collagen-like substances and the biosynthesis of Cl^q. Inhibitors of proline hydroxylase are suitable tools in the therapy of diseases in which the deposition of collagens makes a crucial contribution to the clinical picture. These include, inter alia, fibroses of the lungs, liver and skin (scleroderma) and atherosclerosis.

The pyridine-2,4- and -2,5-dicarboxamides of the formula I which are substituted exclusively in position 4 or 5 in the amide group show a considerable and surprising improved activity in inhibiting proline hydroxylase and lysine hydroxylase in animal experiments compared with the pyridine-2,4-dicarboxamides substituted in position 5 also by carboxamide groups from DE-A-3 707 429 and compared with the pyridine-2,4- and -2,5-dicarboxamides substituted in both amide groups of DE-A 37 039 59.

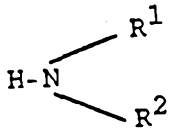
The invention further relates to a process for the preparation of compounds of the formula I, which comprises reacting

a compound of the formula II'



(II')

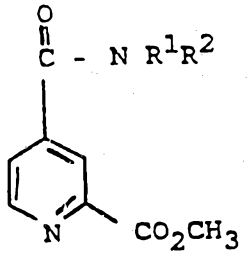
with a compound of the formula III



(III)

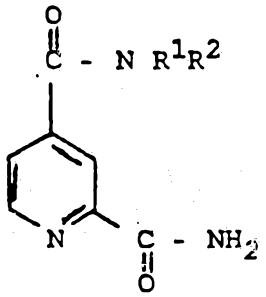
where R^1 and R^2 have the meanings indicated for formula I, and Y is halogen, especially chlorine,

and subsequently converting the resulting compound of the formula IV



(IV)

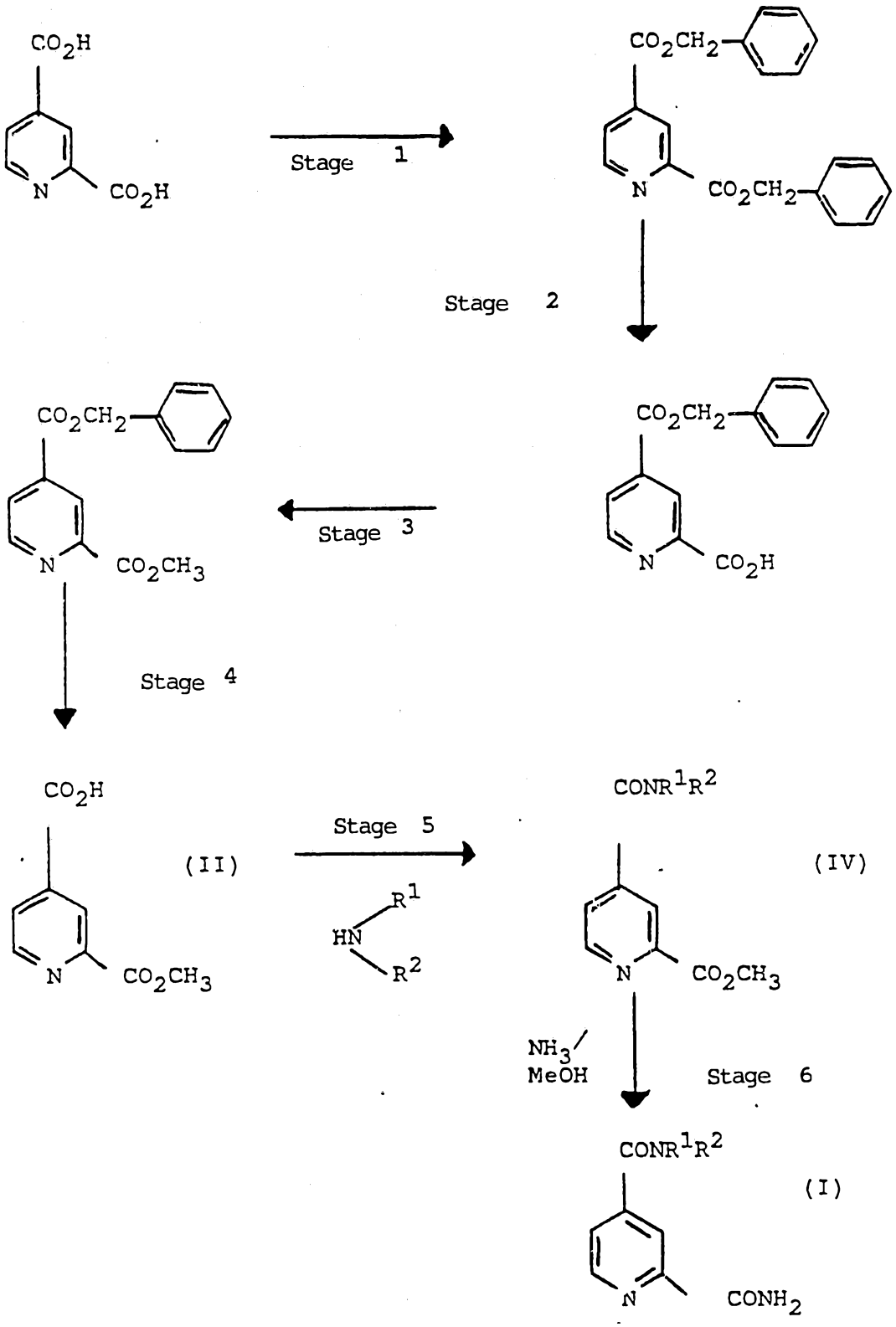
with NH_3 into a compound of the formula I



followed, where appropriate, by conversion into its physiologically tolerated salts.

The following reaction diagram shows the preparation route (stages 5 and 6), including the synthesis of the precursors (1 to 4)

Reaction diagram



In stage 1, commercially available pyridine-2,4-dicarboxylic acid is converted into its dicarbonyl dihalide, preferably its dichloride, and reacted with an optionally substituted benzyl alcohol to give dibenzyl pyridine-2,4-dicarboxylate.

In stage 2, the diester is selectively hydrolyzed in position 2, for example in the presence of a copper salt as described by Delarge, J.: Phar. Acta. Helv. 44 (10), 637 (1969).

The free acid functionality in position 2 is subsequently converted in stage 3 into the corresponding acid chloride and reacted with an alcohol such as, for example, methyl or ethyl alcohol to give the corresponding 2-carboxylic ester.

The remaining benzyl protective group in position 4 is eliminated by hydrogenolysis in stage 4 (for example with H_2/Pd, Houben-Weyl: Vol. IV/1c (1980), pp. 381 - 82).

The free acid in position 4 (formula II) is converted into its acid halide, preferably chloride. The acid chloride can now be converted with the amine of the formula (III) into the mixed pyridine-4-carboxamide-2-carboxylic ester (IV).

The mixed diamide of the formula (I) is prepared from the 2-carboxylic ester (IV) with alcoholic ammonia solution (for example in methanol).

The said process, which has been described in the reaction diagram for the compounds substituted in position 4, also applies to the compounds correspondingly substituted in position 5.

It is possible where appropriate for the products to be worked up, for example, by extraction or by chromatography, for example on silica gel. The isolated products

can be recrystallized and, where appropriate, reacted with a suitable acid to give a physiologically tolerated salt. Examples of suitable acids are:
mineral acids such as hydrochloric and hydrobromic acid and sulfuric, phosphoric, nitric or perchloric acid or organic acids such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, maleic, fumaric, phenylacetic, benzoic, methanesulfonic, toluenesulfonic, oxalic, 4-aminobenzoic, naphthalene-1,5-disulfonic or ascorbic acid.

The starting compounds of the formula (III) which cannot be bought can be synthesized straightforwardly (for example Organikum, Organisch Chemisches Grundpraktikum, 15th edition, VEB Deutscher Verlag der Wissenschaften, 1976; a summary of the various possibilities is to be found in the methods index, p. 822).

The compounds of the formula I according to the invention have valuable pharmacological properties and, in particular, display activity as inhibitors of proline hydroxylase and lysine hydroxylase, as fibrosuppressant and immunosuppressant.

The activity of the fibrogenase can be determined by radioimmunological determination of the N-terminal propeptide of collagen type III or of the N- or C-terminal crosslinking domain of collagen type IV (7s collagen or type IV collagen NC_1) in serum.

For this purpose, the hydroxyproline, procollagen III peptide, 7s collagen and type IV collagen NC_1 concentrations were measured in the liver of

a) untreated rats (control)
b) rats given tetrachloromethane (CCl_4 control)
c) rats given first CCl_4 and then a compound according to the invention

(this test method is described by Rouiller, C., experimental toxic injury of the liver; in The

Liver, C. Rouiller, Vol. 2, pp. 335-476, New York, Academic Press, 1964).

By reason of these pharmacological properties, the compounds according to the invention are suitable for the treatment of disorders of the metabolism of collagen and collagen-like substances and for the treatment of disorders of the biosynthesis of Cl^q.

The invention therefore further relates to the use of the compounds of the formula I according to the invention, and of the physiologically tolerated salts thereof, for the treatment of the abovementioned metabolic disorders.

The compounds can be used as pharmaceuticals either alone or mixed with physiologically tolerated auxiliaries or vehicles. They can be administered for this purpose orally in doses of 0.01 - 25.0 mg/kg/day, preferably 0.01 - 5.0 mg/kg/day or parenterally in doses of 0.001 - 5 mg/kg/day, preferably 0.001 - 2.5 mg/kg/day, especially to 0.005 - 1.0 mg/kg/day. It is also possible to increase the dosage in severe cases. However, lower doses also suffice in many cases. These data relate to an adult weighing about 75 kg.

The invention also embraces the use of the compounds according to the invention for preparing pharmaceuticals which are employed for the treatment and prophylaxis of the abovementioned metabolic disorders.

The invention additionally relates to pharmaceuticals which contain one or more compounds of the formula I according to the invention and/or their physiologically tolerated salts.

The pharmaceuticals are producing by processes known per se and familiar to the person skilled in the art. As pharmaceuticals, the pharmacologically active compounds (= active substance) according to the invention are

employed either as such or, preferably, in combination with suitable pharmaceutical auxiliaries or vehicles in the form of tablets, coated tablets, capsules, suppositories, emulsions, suspensions or solutions, where the content of active substance is up to 95 % advantageously between 10 to 75 %.

Suitable auxiliaries and vehicles for the required pharmaceutical formulation are, for example, besides solvents, gel formers, suppository bases, tableting auxiliaries and other active substance vehicles, also antioxidants, dispersants, emulsifiers, form suppressants, flavorings, preservatives, solubilizers or colorants.

The active substances can be administered orally, parenterally or rectally.

The active compounds are mixed with the additives suitable for this, such as vehicles, stabilizers or iner diluents, and converted by the usual methods into suitable dosage forms such as tablets, coated tablets, hard gelatin capsules, aqueous alcoholic or oily suspensions or aqueous or oily solutions. Examples of inert vehicles which can be used are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose or starch, especially corn starch. The preparation can be carried out either as dry or as wet granules. Examples of suitable oily vehicles or solvents are vegetable or animal oils, such as sunflower oil or fish liver oil.

For subcutaneous or intravenous administration, the active compounds are, if required, converted into a solution, suspension or emulsion with the substances suitable for this purpose, such as solubilizers, emulsifiers or other auxiliaries. Examples of suitable solvents are physiological saline or alcohols, for example ethanol, propanol, glycerol, as well as sugar

solutions such as glucose or mannitol solutions, or else a mixture of the various solvents mentioned.

The invention is explained in more detail hereinafter by means of examples.

General procedure for the preparation of the compounds

1 mmol of methyl pyridine-4-carboxamide-2-carboxylate (IV) is dissolved in 30 ml of saturated methanolic ammonia solution and stirred at room temperature for 2 hours. The solution is concentrated and the residue is stirred with diisopropyl ether and filtered off with suction.

Example 1

4-N-Ethylpyridine-2-carboxamide-4-carboxamide

Melting point: 197°C

Example 2

4-Morpholinocarbonylpyridine-2-carboxamide

Melting point: 128°C

Example 3

4-N,N-Diethylpyridine-2-carboxamide-4-carboxamide

Oil, MS = 222 ($M + H^+$) molecular mass C11H15N3O2 (221)

Example 4

4-N-(2-methoxypropyl)pyridine-2-carboxamide-4-carboxamide

Melting point: 116 - 120°C

Example 5

4-N-(3-methoxypropyl)pyridine-2-carboxamide-4-carboxamide

Melting point: 149°C

Example 6

4-N-(3-hydroxypropyl)pyridine-2-carboxamide-4-carboxamide

Melting point: 154 - 156°C

Example 7

4-N-alanylpyridine-2-carboxamide-4-carboxamide

Melting point: 124 - 125°C

Example 8

4-N-(O-benzylalanyl)pyridine-2-carboxamide-4-carboxamide

Melting point: 138 - 140°C

COMPARATIVE EXAMPLE 1

Comparison tests have been carried out between the compound of Example 4 of the instant application (4-N-(2-methoxyethyl)-pyridine-2-carboxamide-4-carboxamide) and the compound of Example 19 of AU-B-599746 (N,N'-Bis (2-methoxyethyl) pyridine 2,4 dicarboxamide).

A further comparison was carried out between the compound of Example 5 of the instant application (4-N- (3-methoxypropyl) -pyridine-2-carboxamide-4-carboxamide) and N,N' -Bis (3-methoxypropyl) -pyridine-2, 4-dicarboxamide, called Example 0 hereinafter.

The compounds of the instant invention have to be taken up by the liver. Compounds which are slowly taken up from the liver (high $t_{1/2}$-value) have a longer duration of action than those with a fast up-take (low $t_{1/2}$-value). In the following it is shown that the compounds of the instant invention surprisingly have higher $t_{1/2}$-values than the compounds disclosed by AU-B-599746.

Method: The isolated perfused rat liver; Uptake of prolylhydroxylase proinhibitors.

Non-fasted female rats, 200-300 g, (number: N) were anaesthetized with pentobarbital (5 mg/100 g i.p.). After cannulation of the portal vein, the liver was washed with 100 ml heparinized (5 IU/ml) saline of 37°C for 3 minutes while the outflow occurred via the incised caudal vena cava. Subsequently, the organ was excised and connected to the perfusion apparatus and perfused with recirculating medium (100 ml) for 2 hours, 30 ml/min. Perfusion medium was KRB* with bovine erythrocytes. Bovine blood was mixed with a citrate solution 1:1 immediately in the slaughterhouse. This mixture was centrifuged 10 minutes (6000 U/min) and the supernatant removed. The same procedure was repeated once with saline and twice with KRB. The final perfusion medium contained 33.3% of the erythrocyte sediment and 66.7% of KRB (ref.: 1).

Composition of the solutions used:

Citrate solution:

Glucose monohydrate	22.6 g
Tri-sodium citrate	4.0 g
Citric acid	5.5 g
NaCl	4.2 g

add 1000 ml distilled water

* Krebs-Ringer-Buffer	(KRB)
NaCl	8.0 g
KCl	0.2 g
$NaHCO_3$	1.0 g
$NaH_2PO_4.H_20$	0.1 g
$CaCl_2$	0.2 g
$MgCl_2.6H_20$	0.1 g
Bovine Albumin	16.0 g

add 898 ml distilled water and adjust to pH 7.4

Perfusion apparatus (ref.: 2): Central element of the apparatus was a thermostatized cylinder, with an insertable base as support of the organ. The discharge tube was elongated and the lower end of this tube was connected to a peristaltic pump. On the return of the perfusate to the organ, it passed through a heat exchanger (glass spiral) which maintained the temperature of the perfusate at 370C. The perfusate in the bottom of the cylinder was bubbled with 70 ml gas/minute, CO_2/O_2 mixture (5:95%). To avoid foam formation, 14 µl/ml 0.1% Genapol PF-10 had been added to the perfusate. Samples for analysis were withdrawn from the perfusate at a location before the perfusate entered the liver at the time points given below.

Treatments: The test compounds were added to the liver perfusate 10 minutes before mounting the liver into the perfusion apparatus in a concentration of 50 µg/ml, 3 to 5 livers were perfused for each compound.

After 0, 15, 30, 45, 60, 90 and 120 minutes, aliquots of 0.5 ml were withdrawn from the perfusate, and the erythrocytes were removed by centrifugation. The supernatant (100 µl) was mixed with 50 µl meta-phosphoric acid, centrifuged, and the supernatant analyzed by HPLC (C_o and C_t values).

Statistical methods: Analysis of linear regression was performed after log-transformation of the concentration of the compounds found in the perfusate. Half-life times were calculated from the regression lines (ref.: 3), according to the formula:

$$t_{1/2} = ((\log(10^{CO/2}))-C_O)/A_1 \quad \text{[minutes]}$$

References :

(1) Schimassek, H., "Metabolite des Kohlenhydratstoffwechsels der isoliert-perfundierten Rattenleber, " Biochem. Z., 336:460-467 (1963).

(2) Ryoo, H., and Tarver, H., "Studies on Plasma Protein Synthesis With a New Liver Perfusion Apparatus," P.S.E.B.M., 128:760-772 (1968).

(3) Tallarida and Murray, R.B., Manual of Pharmacological Calculations. Springer, New York (1981).

The results are summarized in Table 1 and Fig. 1.

Table 1

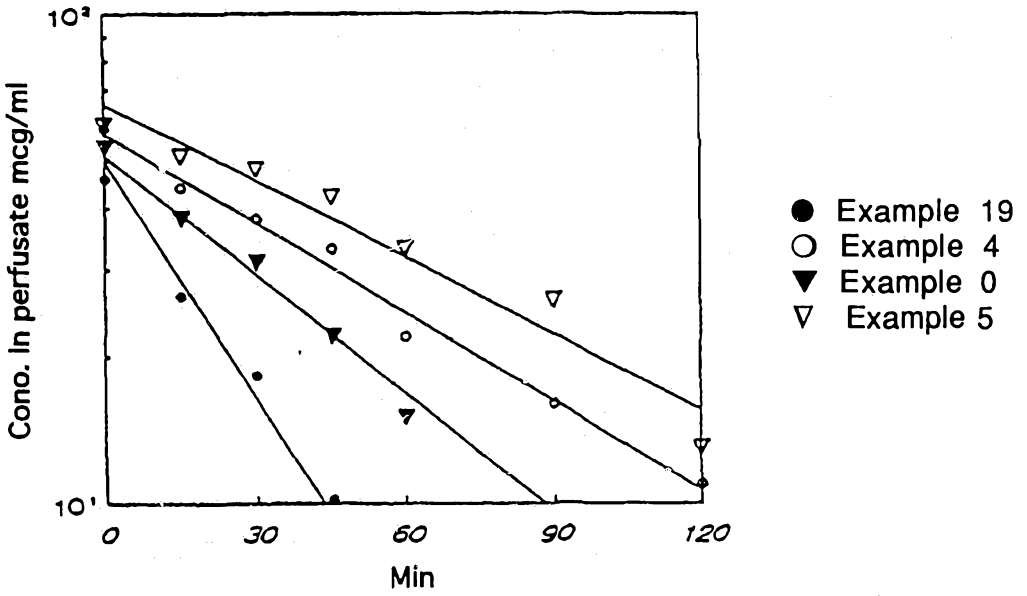
Treatment	Dose µg/ml	N	C_o Intercept (X)	a_1 Slope	$t_{1/2}$ min	r Coefficent of regression
Example 19 of AU-B-599746	50	4	1,69	-0,016	19	0,997
Example 4	50	4	1,75	-0,006	50 (+163%)	0,994
Example 0	50	5	1,70	-0008	37	0,997
Example 5	50	3	1,81	-0,005	60 (+62%)	0,974

Parameter of the regression lines

$LogC_t = C_o - a_1 . t$

Fig. 1

Uptake of 2,4-pyridine dicarboxylate derivatives in the perfused rat liver

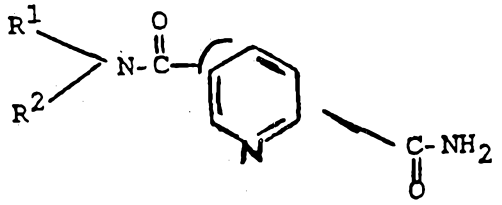


The comparison results show that the compounds of the claimed invention have $t_{1/2}$-value which is about 163% higher than the corresponding compound of Example 19 of AU-B-599746.

Patent Claims

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A pyridine-2,4- or -2,5-dicarboxamide of the formula I



(I)

in which

R^1 is C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl or C_2-C_{12}-alkynyl, which are unsubstituted or substituted once or, in the case of the C_2-C_{12}-alkyls, C_2-C_{12}-alkenyls and C_2-C_{12}-alkynyls, also several times by

halogen, hydroxyl, cyano, amino, carboxyl, alkoxy, alkoxycarbonyl, alkylcarbonyloxy, alkyl- or dialkylamino, where the alkyl radicals have 1-4 carbon atoms, or

indolyl or phenyl, which is unsubstituted or substituted once, twice or three times by halogen, nitro, C_1-C_4-alkyl or C_1-C_4-alkoxy, it also being possible in the case of multiple substitutions for the substituents to be independently different from one another,

or R^1 is saturated C_5-C_7-cycloalkyl which is optionally benzo-fused,

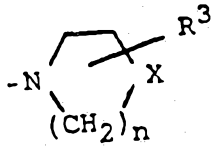
or R^1 is aryl or heteroaryl, which is unsubstituted or in turn substituted once, twice or three times by halogen, nitro, cyano, C_1-C_4-alkyl or C_1-C_4-alkoxy, it also being possible in the case of multiple substitutions for the substituents to be independently different from one another,

or provided that R^2 is H, R^1 is amino which is unsubstituted or mono- or disubstituted by C_1-C_4-alkyl, phenyl or C_1-C_3-alkylcarbonyl,

and

R^2 is hydrogen or R^1, where R^2 and R^1 are identical or different,

or where the radicals R^1 and R^2 form, together with the nitrogen atom, a radical of the formula



in which

n is 1 to 3 and

X is O, S, CH_2 or N-R^3,

where

R^3 is hydrogen, phenyl or C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, where the phenyl, alkyl, alkenyl and alkynyl radicals are unsubstituted or substituted one or more times by:

phenyl which in turn is unsubstituted or substituted one or more times by one or more substituents selected from: halogen, nitro, cyano, carboxyl, hydroxyl, methyl, ethyl, methoxy, ethoxy and trifluoromethyl,

or

$N(R^4)_2$, where

R^4 is H or C_1-C_3-alkyl,

or

$COOR^5$, where
R^5 is H or C_1-C_3-alkyl,

or

$CON(R^6)_2$ or $CONHR^6$, where
R^6 is H or C_1-C_3-alkyl, or where $(R^6)_2$ is a C_4-C_6-alkylene chain in which zero or one CH_2 group which is not directly adjacent to the nitrogen atom is replaced by O, S or N-R^4,

or where

R^3 is C_1-C_4-alkoxycarbonyl or C_3-C_7-cycloalkyl,
and the physiologically tolerated salts.

2. A pyridine-2,4- or -2,5-dicarboxamide of the formula I as claimed in claim 1, in which

R^1 is C_1-C_{12}-alkyl which is unsubstituted or substituted once or, in the case of the C_2-C_{12}-alkyls, also several times by

phenyl, hydroxyl, alkoxy, alkoxycarbonyl, or dialkylamino, where the alkyl radicals have 1-3 carbon atoms,

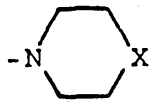
or R^1 is phenyl which is unsubstituted or in turn substituted once by halogen, nitro, cyano, methyl or methoxy,

or, provided that R^2 is H, R^1 is amino which is unsubstituted or monosubstituted by C_1-C_3-alkyl, phenyl or C_1-C_3-alkylcarbonyl,

and

R^2 is hydrogen,

or where the radicals R^1 and R^2 form, together with the nitrogen atom, a radical of the formula



in which

X is O, CH_2 or $N-R^3$,

where

R^3 is hydrogen, or C_1-C_3-alkyl, and the physiologically tolerated salts.

3. A pyridine-2,4- or -2,5-dicarboxamide of the formula I as claimed in claim 1, in which

R^1 is C_1-C_{12}-alkyl which is unsubstituted or substituted once or, in the case of the C_2-C_{12}-alkyls, also several times by

phenyl, hydroxyl, alkoxy, alkoxycarbonyl, or dialkylamino, where the alkyl radicals have 1-3 carbon atoms,

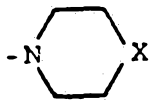
or R^1 is phenyl,

or, provided that R^2 is H, R^1 is amino which is unsubstituted or monosubstituted by methylcarbonyl,

and

R^2 is hydrogen,

or where the radicals R^1 and R^2 form, together with the nitrogen atom, a radical of the formula



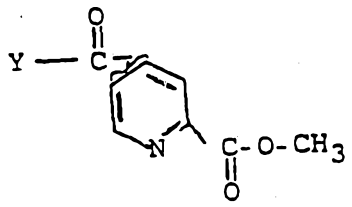
in which

X is O, CH_2 or $N-R^3$,

where

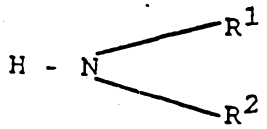
R^3 is hydrogen, or methyl, and the physiologically tolerated salts.

4. A process for the preparation of compounds of the formula I, which comprises reacting a compound of the formula II'



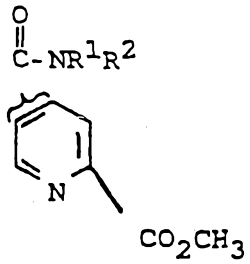
(II')

with a compound of the formula III



(III)

where R^1 and R^2 have the meanings indicated for formula I, and Y is halogen, especially chlorine, and subsequently converting the resulting compound of the formula IV



(IV)

with NH_3 into a compound of the formula I and into its physiologically tolerated salts.

5. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 3 in adjunct with pharmaceutically acceptable carriers and/or excipients.

6. A method of inhibition of proline hydroxylase and lysine hydroxylase comprising administering to a patient requiring such treatment, an effective amount of a compound as claimed in any one of claims 1 to 3.

7. A method of fibrosuppression and immunosuppression comprising administering to a patient requiring such treatment, an effective amount of a compound as claimed in any one of claims 1 to 3.

8. A method of influencing the metabolism of collagen and collagen-like substances and the biosynthesis of Clq comprising administering to a patient requiring such treatment, an effective amount of a compound of the formula I as claimed in any one of claims 1 to 3.

9. A method of treatment of disorders of the metabolism of collagen and collagen-like substances and of the biosynthesis of Clq comprising administering to a patient requiring such treatment an effective amount of a compound of the formula I as claimed in any one of claims 1 to 3.

10. A process for the production of pharmaceuticals for influencing the metabolism of collagen and collagen-like substances and the biosynthesis of Clq, comprising admixing in a pharmacologically effective ratio, a compound of the formula I as claimed in any one of claims 1 to 3 and pharmaceutically acceptable carriers and/or excipients.

DATED this 2nd day of August, 1993.

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Abstract of the disclosure

Mixed pyridine-2,4- and -2,5-dicarboxamides, a process for preparing them, the use thereof and pharmaceuticals based on these compounds

The invention relates to mixed pyridine-2,4- and -2,5-dicarboxamides where the carboxamide group in position 2 is a primary amide.

The said compounds are suitable for the inhibition of proline hydroxylase and lysine hydroxylase and are used as fibrosuppressants and immunosuppressants.