PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

I/We, being the person(s) identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow.

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[54] Invention Title: 4- OR 5-SUBSTITUTED PYRIDINE-2-CARBOXYLIC ACIDS, A PROCESS FOR THE PREPARATION THEREOF AND THE USE THEREOF AS PHARMACEUTICALS.

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BASIC CONVENTION APPLICATION(S) DETAILS


P 40 30 999.1 Germany DE 1st October, 1990.

Drawing number recommended to accompany the abstract ...........................................

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

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25th September, 1991 (Date)
1. A 4- or 5-substituted pyridine-2-carboxylic acid of the formula I

\[
R^1 \text{O(O)}C^- \text{NCOOH}
\]

in which

- \( R^1 \) is \( C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, C_2-C_{12}-alkynyl, non-\)
- benzo-fused or benzo-fused \( C_5-C_7-cycloalkyl, ary1 \) or
- heteroaryl, where this radical mentioned for \( R^1 \) is
- unsubstituted or substituted by one or more
equal or different radicals \( R^2 \), where

- \( R^2 \) is halogen, hydroxyl, cyano, nitro, nitroxy, amino,
- carboxyl, \( C_1-C_4-alkoxy, C_1-C_4-alkoxycarbonyl, C_1-C_4-\)
- alkyl- or -dialkylamino, indolyl or phenyl, where the
- indolyl and phenyl radical is unsubstituted or substituted once, twice or three times by halogen,
- nitro, \( C_1-C_4-alkyl \) or \( C_1-C_4-alkoxy \), where in the case of
- multiple substitution the radicals are identical or different, and the physiologically tolerated
- salts, where the 4-methyl and -benzyl esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridine-
- dicarboxylic acid are excepted.
Application Number: 0
Lodged: 

Invention Title: 4- OR 5-SUBSTITUTED PYRIDINE-2-CARBOXYLIC ACIDS, A PROCESS FOR THE PREPARATION THEREOF AND THE USE THEREOF AS PHARMACEUTICALS.

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

4- or 5-substituted pyridine-2-carboxylic acids, a process for the preparation thereof and the use thereof as pharmaceuticals.

Compounds which inhibit the enzymes proline hydroxylase and lysine hydroxylase effect 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 is unable, moreover, to 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 Clq biosynthesis by macrophages (W. Müller et al., FRBS Lett. 90 (1978), 218; Immunobiology 155 (1978), 47). This results in the classical pathway of complement activation becoming inoperative. Hence, inhibitors of proline hydroxylase also act as immunosuppressants, for example in immune complex diseases.

It is known that the enzyme proline hydroxylase is efficiently inhibited by pyridine-2,4- and -2,5-dicarboxylic acids (K. Majamaa 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. 248 (1987) 625-633).
DE-A 34 32 094 describes pyridine-2,4- and -2,5-dicarboxylic diesters with 1-6 carbon atoms in the ester alkyl moiety as pharmaceuticals for 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 relatively little suited for possible administration as pharmaceuticals.

DE-A 37 03 959, DE-A 37 03 962 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 describe 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.

German Patent Application P 40 01 002.3 describes the use of di(nitroxyalkyl)amides of pyridine-2,4- and -2,5-dicarboxylic acids for preparing pharmaceuticals inhibiting proline hydroxylase and lysine hydroxylase.

Both pyridine-2,4- and -2,5-dicarboxamide (Hirakata et al., J. Pharm. Soc. Japan 77 (1957) 219 and Haring et al., Helv. 37 (1954) 147, 153) and pyridine-2,4- and -2,5-dicarbohydrazide (Itai et al., Bl. Nation. Hyg. Labor. Tokyo, 74 (1956) 115, 117 and Shinohara et al., Chem. High Polymers Japan, 15 (1958) 839) have already
been disclosed as agents for tuberculosis.

JP 53/28175 (78/28175) describes N,N'-bis(2-nitroxy-ethyl)pyridine-2,4- and -2,5-dicarboxamides as substances with a vasodilator action.

German Patent Application P . . . . . . . (HOE 90/F 192) describes the use of 2,4- and 2,5-substituted pyridine N-oxides for preparing pharmaceuticals inhibiting proline hydroxylase and lysine hydroxylase.

It has now been found, surprisingly, that 4- or 5-substituted pyridine-2-carboxylic acids of the formula I indicated below, and the physiologically tolerated salts thereof, effectively inhibit lysine hydroxylase and proline hydroxylase in animal models.

Thus the invention claims compounds of the formula I

\[
R^1\text{O(O)C-} \quad \text{COOH}
\]  

(I)

in which

- \( R^1 \) is \( C_1-C_{12} \)-alkyl, \( C_2-C_{12} \)-alkenyl, \( C_2-C_{12} \)-alkynyl, non-benzo-fused or benzo-fused \( C_5-C_7 \)-cycloalkyl, aryl or heteroaryl, where this radical mentioned for \( R^1 \) is unsubstituted or substituted by one or more identical or different radicals \( R^2 \), where
- \( R^2 \) is halogen, hydroxyl, cyano, nitro, nitroxy, amino, carboxyl, \( C_1-C_4 \)-alkoxy, \( C_1-C_4 \)-alkoxycarbonyl, \( C_1-C_4 \)-alkyl- or -dialkylamino, indolyl or phenyl, where the indolyl and phenyl radical is unsubstituted or substituted once, twice or three times by halogen, nitro, \( C_1-C_4 \)-alkyl or \( C_1-C_4 \)-alkoxy, where in the case of multiple substitution the radicals are identical or different, and the physiologically tolerated salts, where the 4-methyl and -benzyl esters of
2,4-and the 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid are excepted.

Particularly preferred compounds of the formula I are those in which

$R^1$ is $C_1$-$C_5$-alkyl, $C_2$-$C_6$-alkenyl, $C_2$-$C_6$-alkynyl, $C_5$-$C_7$-cycloalkyl, aryl or heteroaryl, where these radicals mentioned for $R^1$ are unsubstituted or substituted by one or two identical or different radicals $R^2$, where

$R^2$ is halogen, hydroxyl, cyano, amino, carboxyl, $C_1$-$C_5$-alkoxy, $C_1$-$C_4$-alkoxycarbonyl, $C_1$-$C_5$-alkyl- or dialkyl-amino, or phenyl, where the phenyl radical is unsubstituted or substituted once by halogen, $C_1$-$C_5$-alkyl or $C_1$-$C_2$-alkoxy, and the physiologically tolerated salts, where the 4-methyl and -benzyl esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid are excepted.

Especially preferred compounds of the formula I are those in which

$R^1$ is $C_1$-$C_5$-alkyl, $C_6$-cycloalkyl, phenyl or pyridyl, where these radicals mentioned for $R^1$ are unsubstituted or substituted by one or two identical radicals $R^2$, where

$R^2$ is hydroxyl, amino, carboxyl, $C_1$-$C_4$-alkoxy, $C_1$-$C_4$-alkoxycarbonyl or phenyl, where the phenyl radical is unsubstituted or substituted once by methyl or methoxy, and the physiologically tolerated salts, where the 4-methyl and -benzyl esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid are excepted.

Said 4-methyl and -benzyl esters of 2,4- and 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid are described by Thums, L: J. Pharm. Biolog. 24(1-2), 3-21 (1969) and Delarge, J: Pharm. Acta. Helv. 44(10), 637-43 (1969). The corresponding 4-benzyl esters are disclosed in P ........... (HOE 89/F 241) and the 5-benzyl esters are disclosed in DE-A 37 03 963.
Halogen means fluorine, chlorine, bromine and iodine, aryl means phenyl and naphthyl, and heteroaryl means 5- and 6-membered aromatic rings with 1, 2 or 3 nitrogen and/or oxygen and/or sulphur atoms, which can also optionally be benzo-fused; the heteroaryl radicals are, in particular, pyridyl, pyridazyl, pyrimidyl, pyrazyl, 1,3,5-triazyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thienyl, oxazolyl and thiazolyl radicals and optionally their benzo-fused compounds.

"Substituted more than once" means hereinbefore and hereinafter that at least 2 and at most all of the hydrogen atoms present in the alkyl radicals are replaced by said substituents. In this connection there is preferably one substituent per methyl or methylene group.

In the case of multiple substitutions, the substituents can also be different independently of one another.

The invention also relates to the use of compounds of the formula I plus the 4-methyl and -benzyl esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid and the physiologically tolerated salts thereof for producing a pharmaceutical inhibiting proline hydroxylase and lysine hydroxylase.

Finally, the invention relates to the compounds of the formula I plus the 4-methyl and -benzyl esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid for use as pharmaceuticals.

The invention particularly relates to the compounds of the formula I plus the 4-methyl and -benzyl esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid for use as fibrosuppressants and immunosuppressants and for inhibiting proline hydroxylase and lysine hydroxylase and for influencing the metabolism of collagen and collagen-like substances and the biosynthesis of Clq.
All said alkyl radicals with more than 2 carbon atoms can be either straight-chain or branched.

The invention also relates to a process for preparing compounds of the formula I plus the 4-methyl and -benzyl esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid, which comprises reacting a compound of the formula II

\[
\text{II} \\
\text{C-Z} \\
\text{O} \\
\text{N-C-Z} \\
\text{O}
\]

in which Z is halogen, especially chlorine or bromine, hydroxyl or alkoxy, especially \((\text{C}_1-\text{C}_6)\)-alkoxy, with a compound of the formula III

\[
\text{III} \\
\text{HO-R}^1 \\
\text{C-Z} \\
\text{O}
\]

in which \(R^1\) has the meaning indicated in claim 1, and, in a second reaction stage, selectively hydrolyzing in position 2 the diester of the formula IV

\[
\text{IV} \\
\text{R}^1\text{OOC} \\
\text{C-Z} \\
\text{O}
\]

resulting therefrom.

The selective hydrolysis of an ester, for example in the presence of a copper catalyst, is described by Delarge, J. in: Pharm. Acta. Helv. 44 (10), 637 (1969).

Said process is disclosed for the preparation of the corresponding benzyl esters in DE-A 37 03 963.

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

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 NC1) in serum.

For this purpose, the hydroxyproline, procollagen III peptide, 7s collagen and type IV collagen NC1 concentrations were measured in the liver of

a) untreated rats (control)
b) rats given tetrachloromethane (CCl₄ control)
c) rats given first CCl₄ and then a compound according to the invention (this test method is described by Roullier, C., experimental toxic injury of the liver; in The Liver, C. Roullier, Vol. 2, pp. 335-476, New York, Academic Press, 1964).

The compounds of the formula I plus the 4-methyl and -benzyl esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid can be used as medicaments in the form of pharmaceutical products which contain them where appropriate together with tolerated pharmaceutical vehicles. The compounds can be used as medicines, for example in the form of pharmaceutical products which contain these compounds mixed with a pharmaceutical, organic or inorganic vehicle suitable for enteral, percutaneous or parenteral administration, such as, for example, water, gum arabic, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, poly-alkylene glycols, vaseline etc.

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 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, plus the 4-methyl and -benzyl esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridine-dicarboxylic acid.

The pharmaceuticals are produced 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 excipients in the form of tablets, coated tablets, capsules, suppositories, emulsions, suspensions or solutions, where the content of active substance is up to about 95 %, advantageously between 10 and 75 %.

Suitable auxiliaries and excipients 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, foam 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 excipients, stabilizers or inert 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 excipients 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 excipients 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 compounds according to the invention.

0.1 mol of copper nitrate (X 3 H₂O) is introduced into 700 ml of methanol, and 0.1 mol of a pyridine-2,4- or -2,5-dicarboxylic ester of the formula IV is added. The mixture is heated under reflux for 3 hours, cooled, and the resulting copper complex is filtered off with suction and washed with diethyl ether. 0.1 mol of the copper complex is introduced into 400 ml of dioxane. Hydrogen sulfide is passed in at room temperature over a period of
2 hours. The precipitated copper sulfide is filtered off and the filter is washed with a little dioxane. The filtrate is concentrated, the residue is triturated with petroleum ether and the crystalline residue is filtered off.

Example 1
Benzyl 2-carboxypyridine-4-carboxylate
Yield: 77% melting point: 113-115°C

Example 2
Benzyl 2-carboxypyridine-5-carboxylate
Yield: 75% melting point: 132°C

Example 3
Ethyl 2-carboxypyridine-4-carboxylate
Yield: 96% melting point: 149-153°C

Example 4
Methyl 2-carboxypyridine-5-carboxylate
Yield: 60% melting point: 185°C

Example 5
Butyl 2-carboxypyridine-4-carboxylate
Yield: 41% melting point: 102°C

Example 6
Butyl 2-carboxypyridine-5-carboxylate
Yield: 51% melting point: 104°C

Example 7
3-Methoxybutyl 2-carboxypyridine-4-carboxylate
Yield: 63% melting point: 77°C

Example 8
3-Methoxybutyl 2-carboxypyridine-5-carboxylate
Yield: 25% melting point: 163°C
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A 4- or 5-substituted pyridine-2-carboxylic acid of the formula I

\[
\text{R}^1\text{O(O)C-} \quad \text{N COOH} \quad \text{(I)}
\]

in which

- \( \text{R}^1 \) is \( \text{C}_1-\text{C}_{12}-\text{alkyl}, \text{C}_2-\text{C}_{12}-\text{alkenyl}, \text{C}_2-\text{C}_{12}-\text{alkynyl}, \text{non-benzo-fused or benzo-fused C}_2-\text{C}_7-\text{cycloalkyl}, \text{aryl or heteroaryl}, \) where this radical mentioned for \( \text{R}^1 \) is unsubstituted or substituted by one or more identical or different radicals \( \text{R}^2 \), where

- \( \text{R}^2 \) is halogen, hydroxyl, cyano, nitro, nitroxy, amino, carboxyl, \( \text{C}_1-\text{C}_4-\text{alkoxy}, \text{C}_1-\text{C}_4-\text{alkoxycarbonyl}, \text{C}_1-\text{C}_4-\text{alkyl- or -dialkylamino}, \text{indolyl or phenyl}, \) where the indolyl and phenyl radical is unsubstituted or substituted once, twice or three times by halogen, nitro, \( \text{C}_1-\text{C}_4-\text{alkyl or C}_1-\text{C}_4-\text{alkoxy}, \) where in the case of multiple substitution the radicals are identical or different, and the physiologically tolerated salts, where the 4-methyl and -benzyl esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid are excepted.

2. A compound as claimed in claim 1, in which

- \( \text{R}^1 \) is \( \text{C}_1-\text{C}_6-\text{alkyl}, \text{C}_2-\text{C}_6-\text{alkenyl}, \text{C}_2-\text{C}_6-\text{alkynyl}, \text{C}_5-\text{C}_7-\text{cycloalkyl}, \text{aryl or heteroaryl}, \) where these radicals mentioned for \( \text{R}^1 \) are unsubstituted or substituted by one or two identical or different radicals \( \text{R}^2 \), where

- \( \text{R}^2 \) is halogen, hydroxyl, cyano, amino, carboxyl, \( \text{C}_1-\text{C}_4-\text{alkoxy}, \text{C}_1-\text{C}_4-\text{alkoxycarbonyl}, \text{C}_1-\text{C}_4-\text{alkyl- or dialkylamino}, \text{or phenyl}, \) where the phenyl radical is unsubstituted or substituted once by halogen, \( \text{C}_1-\text{C}_2-\text{alkyl} \) or \( \text{C}_1-\text{C}_2-\text{alkoxy}, \) and the physiologically tolerated salts, where the 4-methyl and -benzyl
esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid are excepted.

3. A compound as claimed in claim 1, in which
   \( R^1 \) is \( C_1-C_2 \)-alkyl, \( C_6 \)-cycloalkyl, phenyl or pyridyl, where these radicals mentioned for \( R^1 \) are unsubstituted or substituted by one or two identical radicals \( R^2 \), where
   \( R^2 \) is hydroxyl, amino, carboxyl, \( C_1-C_4 \)-alkoxy, \( C_1-C_4 \)-alkoxycarbonyl or phenyl, where the phenyl radical is unsubstituted or substituted once by methyl or methoxy, and the physiologically tolerated salts, where the 4-methyl and -benzyl esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid are excepted.

4. A process for preparing 4- or 5-substituted pyridine-2-carboxylic acids of the formula I and their physiologically tolerated salts plus the 4-methyl and -benzyl esters of 2,4- and the 5-methyl and -benzyl esters of 2,5-pyridinedicarboxylic acid, which comprises reacting a compound of the formula II

\[
\begin{align*}
\text{II} & \\
\text{(II)} & \\
\end{align*}
\]

in which \( Z \) is halogen, especially chlorine or bromine, hydroxyl or alkoxy, especially \( (C_1-C_6) \)-alkoxy, preferably \( (C_1-C_4) \)-alkoxy, with a compound of the formula III

\[
\begin{align*}
\text{III} & \\
\text{(III)} & \\
\end{align*}
\]

in which \( R^1 \) has the meaning indicated in claim 1, and, in a second reaction stage, selectively hydrolyzing in position 2 the diester of the formula IV

\[
\begin{align*}
\text{IV} & \\
\text{(IV)} & \\
\end{align*}
\]
resulting therefrom.

5. A compound as claimed in claim 4 for inhibiting proline hydroxylase and lysine hydroxylase.

6. A compound as claimed in claim 4 for use as fibrosuppressant and immunosuppressant.

7. A pharmaceutical containing a compound as claimed in claim 4 and/or its physiologically tolerated salts for the treatment of disturbances of the biosynthesis of collagen and collagen-like substances and of the biosynthesis of Clq.

8. A process for producing pharmaceuticals for influencing the biosynthesis of collagen and collagen-like substances and the biosynthesis of Clq, which comprises incorporating into the pharmaceutical a compound of the formula I as claimed in claim 4 and/or a physiologically tolerated salt of this compound.

DATED THIS 25th day of September, 1991

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