

Description

The present invention concerns O-substituted α -ketocarboxylic acid oximes, their physiologically acceptable salts, esters and amides, processes for
5 their preparation, as well as medicaments which contain these compounds.

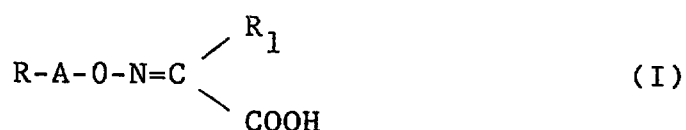
In published German Patent Application 27 26 210, there are described hydrazones of pyruvic acid with hypoglycaemic action which contain phenelzine (2-phenyl-
10 ethyl hydrazine) and similar compounds as hydrazine components. Several of the hydrazines hereby used are known as monoaminoxidase inhibitors. In high dosage, a hypoglycaemia can be brought about by them [Adnitt, P.I.: Hypoglycemic action of monoaminoxidase inhibitors,
15 Diabetes 17: 628-633 (1980) and others]. The task forming the basis of the said published German Patent Application was to strengthen the hypoglycaemic effect of these hydrazines and simultaneously to remove the undesired monoaminoxidase inhibition. The solution of
20 this task was achieved by condensation of the hydrazines with pyruvic acid.

Surprisingly, it has now been found that α -ketocarboxylic acid oximes and their derivatives which, as hydroxylamine components, contain O-alkyld hydroxyl-
25 amines, possess valuable pharmacological properties which are not known of the fundamental hydroxylamines. In comparison with pyruvic acid hydrazones known from the

literature, the α -ketocarboxylic acid oximes according to the invention are characterised by their high chemical stability in physiological media.

The compounds according to the invention especially inhibit the intestinal glucose resorption. Furthermore, a marked hypoglycaemic action can be observed. Therefore, the compounds are outstandingly suitable for the treatment of diseases in which, after ingestion of carbohydrate-containing nutriment, strong long-lasting hyperglycaemias occur. Thus, they can be used as therapeutics for the indications of diabetes, prediabetes, adipositas and atheroscleroses. Furthermore, they show a lipid-sinking action.

Therefore, the subject of the present invention are medicaments containing α -ketocarboxylic acid oximes of the general formula I



in which R signifies hydrogen, a C_3 - C_8 -cycloalkyl, C_1 - C_6 -alkoxy, cinnamyloxy, phenylamino, phenyl-N-alkyl-amino, phenylmercapto, an aryl or aryloxy group, the aryl radical of which can be substituted one or more times by C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, halogen, hydroxyl, trifluoromethyl, amino, acetylamino, nitrile, nitro or a methylenedioxy group, A a straight-chained or branched, saturated or unsaturated alkylene chain with up to 10

C-atoms, which is possibly substituted one or more times by halogen or hydroxyl, whereby, for the case in which T signifies an alkoxy or aryloxy radical, A must possess a straight-chained part of at least 2 carbon atoms by means of which the radical R is connected with the oxygen atom, and R₁ signifies hydrogen, a C₁-C₈-alkyl group which is possibly substituted one or more times by halogen, hydroxyl, nitrile, phenyl or carboxyl, nitrile or formyl, whereby R-A may not be a methyl, ethyl or benzyl group, or their physiologically acceptable salts, carboxylic acid esters and amides, as well as per se known pharmacologically acceptable carrier materials.

For the expert, it is self-evident that for the case in which R signifies an alkoxy or aryloxy radical, A must possess a straight-chained part of at least 2 carbon atoms by means of which the radical R is connected with the oxygen atom. Otherwise, in these cases, acetals would be understood under the formula I which are unstable under physiological conditions.

In connection with the synthesis of α -amino acids, 2-ethoxyiminopropionic acid (general formula I; R = H; A = -CH₂CH₂-) and 2-benzyloxyiminopropionic acid (general formula I; R = phenyl; S = -CH₂-) were prepared as intermediate products [W.E. Weaver et al., J. Org. Chem., 15, 741 (1959)]. 2-Methoxyiminopropionic acid (general formula I; R = H; A = -CH₂-) has been obtained

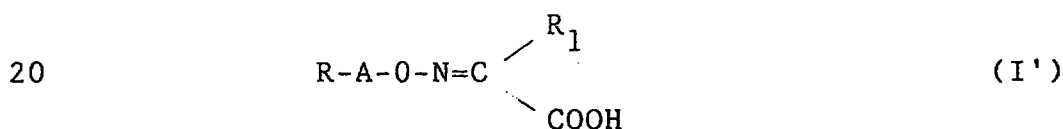
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in the case of the derivatisation of pyruvic acid for analytical purposes [Y. Ishitoya et al., Clin. Chim. Acta, 27, 233 (1970)]. A pharmacodynamic action for these compounds has hitherto not been described for
5 these compounds so that their use as medicaments is new.

Further known compounds are the methyl ester of cyanomethoxyiminoglycoxylic acid, the ethyl ester of cyanoethoxyiminoglycoxylic acid (Beilstein, 31, p.775) and 2-benzyloxyimino-3-phenylpropionic acid (J. Org.
10 Chem., 15, p.741).

Furthermore, from DE-A 28 37 863 are known α -ketocarboxylic acid oxime esters and amides for the protection of plant cultures against aggressive agricultural chemicals. However, a pharmacological
15 action in the case of humans and animals was not yet known.

In comparison therewith, the subject of the present invention are the new α -ketocarboxylic acid oxime derivatives of the general formula I'



in which R signifies hydrogen, a C_3 - C_8 -cycloalkyl, methoxy, cinnamyloxy, phenylamino, phenyl-N-methylamino, phenylmercapto, an aryl or aryloxy group, the aryl radical of which is a phenyl or naphthyl group which can
25 be substituted one or more times by C_1 - C_6 - alkyl,

C_1-C_6 -alkoxy, halogen, hydroxyl, trifluoromethyl, amino, acetylamino, nitrile, nitro or a methylenedioxy group, A a straight-chained or branched saturated or unsaturated alkylene chain with 2 to 8 C-atoms, which is
5 possibly substituted by a halogen or hydroxyl group, whereby, for the case in which R signifies an alkoxy or aryloxy radical, A must possess a straight-chained part of at least 2 carbon atoms by means of which the radical R is connected with the oxygen atom, and R_1 is
10 hydrogen, a C_1-C_6 -alkyl group, which is possibly substituted one or more times by halogen, hydroxyl or phenyl, whereby R-A cannot be an alkyl group with 2 to 4 C-atoms, as well as their physiologically acceptable salts, carboxylic acid esters and amides.

15 By cycloalkyl groups are to be understood carbocycles with 3 to 8 carbon atoms, preferably the cyclohexyl group.

By aryl radicals of the radical R are understood aromatic hydrocarbons with 6 to 14 carbon atoms,
20 preferably the phenyl and naphthyl group.

By substituted aryl radicals are understood those aromatic hydrocarbons with 6 to 14 carbon atoms which, in one or more positions, carry the hydroxyl group, halogen, the trifluoromethyl group, lower alkyl or lower
25 alkoxy groups, amino, acetylamino, nitrile, nitro or methylenedioxy groups. In particular therefor, there come into question phenyl and naphthyl radicals possibly

substituted by the above-mentioned groups. By halogen, one thereby understands fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine and bromine.

- 5 By lower alkyl groups are to be understood, in all cases, straight-chained or branched radicals with 1 to 6 carbon atoms. This definition also applies to the alkyl radicals of the lower alkoxy groups. As lower alkyl radicals, there preferably find use the methyl and the butyl group and as lower alkoxy radical the methoxy group.
- 10

The aryloxy radical contains aromatic hydrocarbon radicals with 6 to 14 carbon atoms, especially the phenyl radical.

- 15 Amongst unbranched alkylene chains A, there are, in all cases, preferably understood the following:
- $(CH_2)_X$ - with $X = 1$ to 8, $-CH=CH-CH_2-$ and $-C\equiv C-CH_2-$.

As branched groups A are especially preferred the groups: $-CH=C(CH_3)-CH_2-$ and $-C(CH_3)=CH-CH_2-$.

- 20 As physiologically acceptable salts, there come into question especially alkali metal, alkaline earth metal or ammonium salts (as well as possibly salts with blood sugar-lowering biguanides), especially the sodium salts.

- 25 As esters of the carboxylic acids of general formula I, in the meaning of the invention there are

generally to be understood the reaction products of the carboxylic acids with alcohols. Preferred as alcohol components are the lower monohydroxy alcohols, such as methanol, ethanol, propanol or isopropanol.

5 The amides of general formula I according to the invention contain, as amine component, e.g. ammonia, mono- and dialkylamines, e.g. 2-hydroxyethylamine and 1-methylpiperazine, as well as amino acids, whereby p-aminobenzoic acid, anthranilic acid, phenylalanine,
10 α - and β -alanine, serine, valine, glycine, arginine are to be mentioned.

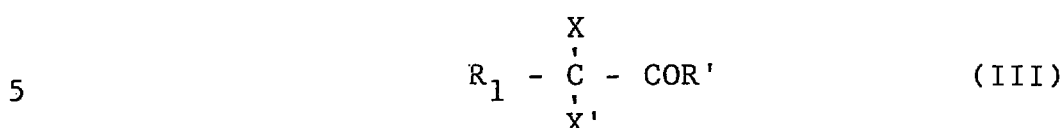
Preferred compound types in the meaning of the invention are 2-cinnamyloxyiminopropionic acid derivatives, whereby the phenyl component can also be substituted.
15 Also preferred are pyruvic acid derivatives which carry a fluorine residue in the 3-position of the propionic acid.

Furthermore, the subject of the invention are all stereoisomeric forms of a compound of general formula I
20 which can occur because of asymmetric carbon atoms or double bonds (C=C or C=N) present in some of the compounds.

Furthermore, the subject of the invention are processes for the preparation of α -ketocarboxylic acid oximes of general formula I', in which R, R₁ and A have
25 the above-given meaning, in that one, for example, a) reacts a hydroxylamine of the general formula II,



in which R and A have the above-given meaning, in per se known manner with a compound of the general formula III,



in which R_1 has the given meaning, X and X' represent halogen or alkoxy groups or together an oxygen atom and R' signifies hydroxyl, a lower alkoxy or a possibly substituted amino group; or

10 b) reacts a compound of the general formula IV



in which R and A have the above given meaning and Y represents a reactive group, in per se known manner with a compound of general formula III, in which X and
 15 X' together represent the =N-OH group and R_1 and R' has the above-given meaning,
 subsequent to the reactions having taken place, the acid derivatives obtained are possibly converted into the free acids of general formula I or, if desired,
 20 the free acid obtained is converted into an ester, into an amide or into a physiologically acceptable salt.

Halogen of the radicals X and X' of the formula III mean fluorine, chlorine, bromine and iodine but preferably chlorine and bromine. Alkoxy groups of the

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radicals X, X' and R' are groups with 1 to 4 carbon atoms, the methoxy and ethoxy group is preferred. As reactive compounds IV, those come especially into question in which Y represents the anion of a strong acid, e.g. of a hydrohalic or sulphonic acid. Compounds of general formula IV are preferably used in which Y signifies a p-toluenesulphonyloxy group, chlorine or bromine.

According to the process mentioned under a), the substituted hydroxylamine II or a corresponding salt is mixed in a suitable polar solvent (e.g. water, a lower alcohol or acetic acid) with a compound of the formula III or preferably with its salts and brought to a weakly acidic pH value, possibly with the help of a buffer, e.g. sodium acetate. The reaction takes place at room temperature but, for the acceleration of the rate of the reaction, can also be carried out with heating. The pyruvic acid oximes I' formed can be filtered off from the reaction medium as sparingly soluble compounds or can be extracted with a suitable non-polar solvent (such as e.g. diethyl ether or methylene chloride).

According to the process mentioned under b), a reactive compound IV is reacted in a suitable polar solvent (e.g. a lower alcohol) with a compound of the formula III, in which X and X' together signify the group =N-OH, with addition of a basic condensation

agent (e.g. alkali metal hydroxide or alkali metal alcoholate), preferably with heating. The pyruvic acid oximes can, possibly after neutralisation of excess condensation agent, be extracted by suitable solvents
5 directly from the reaction mixture (e.g. by polar solvents, such as lower alcohols.

The preparation of salts of the carboxylic acids of general formula I' takes place in per se known manner, for example by reaction with the corresponding
10 free bases, carbonates or alcoholates.

The esters occurring as intermediates in the case of the above-described processes can be isolated and possibly directly saponified to the corresponding carboxylic acids. On the other hand, the carboxylic
15 acids obtained can, again according to per se known methods, be reacted to the desired esters. The saponifications of the esters are preferably carried out in alkaline medium.

The amides of general formula I' according to the
20 invention can be prepared according to per se known methods from the carboxylic acids or their reactive derivatives by reaction with amines.

The substituted hydroxylamines and their salts are, in part, new compounds. In general, a pure preparation is not necessary so the crude products obtained
25 can be employed. They can be prepared by per se known processes, for example by reaction of compounds of

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general formula IV with N-hydroxyphthalimide and subsequent splitting off of the phthalic acid protective group, e.g. by means of hydrazine, or with hydroxycarbamic acid esters and subsequent saponification of
5 the O-alkylated derivatives.

As anti-diabetic compositions according to the invention, there come into question all usual oral and parenteral forms of administration, for example, tablets, capsules, dragees, syrups, solutions, suspensions, drops, suppositories etc. For this purpose, one
10 mixes the active material with solid or liquid carrier materials and subsequently brings them into the desired form. Solid carrier materials are e.g. starch, lactose, methyl cellulose, talc, highly dispersed silicic acid,
15 high molecular fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high molecular polymers (such as polyethylene glycols).
Compositions suitable for oral administration can, if
20 desired, contain flavouring and sweetening agents.

As injection medium, there is preferably used water which contains the additives usual in the case of injection solutions, such as stabilising agents, solubilising agents and/or buffers. Such additives
25 are e.g. acetate or tartrate buffers, ethanol, complex formers (such as ethylenediamine-tetraacetic acid and its non-toxic salts) or high molecular polymers (such

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as liquid polyethylene oxide) for viscosity regulation.

For combating of diseases in which, after the ingestion of carbohydrate-containing nutriments, strong and long-lasting hyperglycaemias occur, the pharmacologically active compounds of general formula I are administered in individual doses of 10 to 600, preferably 50 to 200 mg., whereby these individual doses can, according to need, be administered one or more times per day.

Preferred in the sense of the present invention are, apart from the compounds mentioned in the Examples and the compounds derivable by combination of all meanings of the substituents mentioned in the claims, also, in particular, the following acids and their salts, as well as corresponding esters and amides:

2-(3,5-di-tert.-butyl-4-hydroxycinnamyloxyimino)-propionic acid

2-(2-n-propoxycinnamyloxyimino)-propionic acid

2-(5-chloro-3-methylcinnamyloxyimino)-propionic acid.

The following Examples show some of the numerous process variants which can be used for the synthesis of the compounds according to the present invention:-

Example 1.

Sodium 2-(2-methallyloxyimino)-propionate.

10.3 g. (0.1 mol) Pyruvic acid oxime are first introduced, with stirring, into a solution of 13.6 g. (0.2 mol) sodium ethylate in 200 ml. ethanol. Subse-

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quently, at boiling temperature, one slowly adds dropwise, 18.1 g. (0.2 mol) β -methallyl chloride and maintains at this temperature for 14 h. A further 9.0 g. (0.1 mol) β -methallyl chloride and 6.8 g.

5 (0.1 mol) sodium ethylate are again added thereto and the heating continued a further 7 h. Thereafter, one filters off hot with suction from the resultant precipitate and evaporates the filtrate. One recrystallises the evaporation residue from ethanol.

10 Yield: 7.3 g. (61% of theory); m.p. 240°C. (decomp.).

In analogous way, one obtains from pyruvic acid oxime and

a) 2-methoxyethyl bromide

sodium 2-(2-methoxyethyloxyimino)-propionate

15 m.p. 185°C. (decomp.)

b) 3-phenylpropyl bromide

sodium 2-(3-phenylpropyloxyimino)-propionate

m.p. 234°C. (decomp.) (ethanol-water)

c) 2-phenoxyethyl bromide

20 sodium 2-(2-phenoxyethyloxyimino)-propionate

m.p. 209°C. (decomp.) (ethanol)

d) 2-cyclohexylethyl bromide

sodium 2-(2-cyclohexylethyloxyimino)-propionate

m.p. 234 - 235°C. (decomp.) (ethanol)

25 Example 2.

2-(2-p-Tolyloxyimino)-propionic acid.

One reacts 2-p-tolyloethyl bromide and pyruvic

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acid oxime according to the process described in
Example 1 and evaporates the reaction mixture after
completion of the reaction. One takes up the residue
in a little water, washes with ether and acidifies the
5 aqueous solution. The precipitate obtained is filtered
off with suction and dried.

Yield: 41% of theory; m.p. 106 - 108°C.

In analogous way, one obtains from pyruvic acid
oxime and

- 10 a) 2-phenylethyl bromide
2-(2-phenylethyloxyimino)-propionic acid
m.p. 74°C.
- b) hexyl bromide
2-hexyloxyimino propionic acid
15 m.p. 41°C.
- c) octyl bromide
2-octyloxyiminopropionic acid
m.p. 42°C. (ligroin)
- d) 3-phenylpropargyl bromide
20 2-(3-phenyl-2-propynyloxyimino)-propionic acid
m.p. 84 - 85°C.

Example 3.

2-(γ-Methylcinnamyloxyimino)-propionic acid

A suspension of 4.2 g. (21 mmol) O-(γ-methyl-
25 cinnamyl)-hydroxylamine hydrochloride in 50 ml. water
is covered with 50 ml. methylene chloride and subse-
quently mixed, while stirring, with a solution of

2.73 g. (31 mmol) pyruvic acid and 2.54 g. (31 mmol) sodium acetate in 10 ml. water. The precipitate thereby largely dissolves. One further stirs for 1 h., separates off the methylene chloride phase and extracts 5 the aqueous phase with methylene chloride. The combined organic extracts are dried and evaporated. One recrystallises the residue from ligroin. Yield: 3.3 g. (67% of theory); m.p. 56 - 58°C.

In analogous way, one obtains from pyruvic acid and 10

a) 0-cinnamylhydroxylamine hydrochloride

2-cinnamyloxyiminopropionic acid

m.p. 89 - 91°C.

b) 0-(β -methylcinnamyl)-hydroxylamine hydrochloride

15 2-(β -methylcinnamyloxyimino)-propionic acid

m.p. 139°C.

Example 4.

2-(3-Chlorocinnamyloxyimino)-propionic acid.

One adds dropwise at room temperature a solution 20 of 5.6 g. (64 mmol) pyruvic acid in 100 ml. water at room temperature, while stirring, into a solution of 7.8 g. (42 mmol) 0-(3-chlorocinnamyl)-hydroxylamine in 100 ml. methylene chloride. One further stirs for 15 min., separates off the organic phase and again 25 extracts the aqueous part with methylene chloride. The combined methylene chloride solutions are dried and evaporated. One recrystallises the residue from a

mixture of ethyl acetate and ligroin.

Yield: 8.4 g. (78% of theory); m.p. 99 - 101°C.

In analogous way, one obtains from pyruvic acid
and

- 5 a) 0-(2-chlorocinnamyl)-hydroxylamine
2-(2-chlorocinnamyloxyimino)-propionic acid
m.p. 88 - 90°C. (methanol-water)
- b) 0-(4-chlorocinnamyl)-hydroxylamine
2-(4-chlorocinnamyloxyimino)-propionic acid
10 m.p. 114 - 116°C. (ethyl acetate-ligroin)
- c) 0-allylhydroxylamine
2-(allyloxyimino)-propionic acid
m.p. 38 - 39°C.

Example 5.

- 15 2-(4-Fluorocinnamyloxyimino)-propionic acid.

One reacts 8.2 g. (49 mmol) 0-(4-fluorocinnamyl)-
hydroxylamine with 5.2 g. (59 mmol) pyruvic acid
according to the process described in Example 4.
Yield: 6.2 g. (53% of theory); m.p. 98 - 100°C. (ethyl
20 acetate and ligroin).

In analogous way, one obtains from pyruvic acid
and

- a) 0-(3-trifluoromethylcinnamyl)-hydroxylamine
2-(3-trifluoromethylcinnamyloxyimino)-propionic
25 acid
m.p. 103 - 105°C.

- b) 0-(3-methylcinnamyl)-hydroxylamine
2-(3-methylcinnamyloxyimino)-propionic acid
sodium salt: m.p. 240°C. (decomp.)
- 5 c) 0-(4-tert.-butylcinnamyl)-hydroxylamine
2-(4-tert.-butylcinnamyloxyimino)-propionic acid
m.p. 114 - 116°C.
- d) 0-(3-methoxycinnamyl)-hydroxylamine
2-(3-methoxycinnamyloxyimino)-propionic acid
m.p. 91 - 92°C.
- 10 e) 0-(2-methoxycinnamyl)-hydroxylamine
2-(2-methoxycinnamyloxyimino)-propionic acid
m.p. 84 - 86°C.
- f) 0-(5-chloro-2-methylcinnamyl)-hydroxylamine
2-(5-chloro-2-methylcinnamyloxyimino)-propionic acid
15 m.p. 112°C.
- g) 0-(5-chloro-2-methoxycinnamyl)-hydroxylamine
2-(5-chloro-2-methoxycinnamyloxyimino)-propionic
acid
m.p. 124 - 126°C.
- 20 h) 0-[3-(1-naphthyl)-2-propenyl]-hydroxylamine
2-[3-(1-naphthyl)-2-propenyloxyimino]-propionic
acid
m.p. 85 - 87°C.
- i) 0-(3,5-dichlorocinnamyl)-hydroxylamine
25 2-(3,5-dichlorocinnamyloxyimino)-propionic acid
m.p. 101 - 104°C.

- j) 0-(5-chloro-2-methoxy- β -methylcinnamyl)-hydroxyl-
amine
2-(5-chloro-2-methoxy- β -methylcinnamyloxyimino)-
propionic acid
5 m.p. 108 - 110°C.
- k) 0-(5-bromo-2-methoxycinnamyl)-hydroxylamine
2-(5-bromo-2-methoxycinnamyloxyimino)-propionic
acid
m.p. 118 - 120°C.
- 10 l) 0-(5-fluoro-2-methoxycinnamyl)-hydroxylamine
2-(5-fluoro-2-methoxycinnamyloxyimino)-propionic
acid
m.p. 114 - 116°C.
- 15 m) 0-(2-methoxy-5-trifluoromethylcinnamyl)-hydroxyl-
amine
2-(2-methoxy-5-trifluoromethylcinnamyloxyimino)-
propionic acid
m.p. 120 - 123°C.
- 20 n) 0-(2,5-dimethoxycinnamyl)-hydroxylamine
2-(2,5-dimethoxycinnamyloxyimino)-propionic acid
m.p. 74 - 76°C.
- o) 0-(2-methoxy-5-methylcinnamyl)-hydroxylamine
2-(2-methoxy-5-methylcinnamyloxyimino)-propionic
acid
25 m.p. of the sodium salt 218°C.

Example 6.

2-(Cinnamyloxyimino)-propionic acid ethyl ester.

One heats a mixture of 2.2 g. (10 mmol) 2-cinnamyloxyimino)-propionic acid, 16 ml. chloroform, 1.78 g. (15 mmol) thionyl chloride and 2 drops of dimethylformamide for 2 hours at reflux temperature.

- 5 One then evaporates off the chloroform and excess thionyl chloride in a vacuum. One mixes the oil remaining behind with 20 ml. ethanol and leaves to stand for 12 hours at room temperature. Thereafter, one evaporates off the ethanol in a vacuum and takes up the
- 10 residue in ether. The solution is washed twice with saturated sodium hydrogen carbonate solution, dried and evaporated in a vacuum. One dissolves the residue in ligroin, clarifies with charcoal and again evaporates. As residue, one obtains 2.4 g. (97% of theory) 2-
- 15 cinnamyloxyimino)-propionic acid ethyl ester, colourless oil; $n_D^{20} = 1.5390$.

Example 7.

2-(Cinnamyloxyimino)-propionamide.

- One prepares 2-(cinnamyloxyimino)-propionyl
- 20 chloride from 4.38 g. (20 mmol) 2-(cinnamyloxyimino)-propionic acid and 3.57 g. (30 mmol) thionyl chloride as described in Example 6. The crude acid chloride is dissolved in 20 ml. chloroform and added dropwise, while stirring, to an ice-cooled solution of ammonia
- 25 in 40 ml. chloroform. One leaves the reaction mixture to stand overnight at room temperature and then shakes

up with 100 ml. water. Subsequently, one washes the organic phase first with 0.5N hydrochloric acid, then with a saturated sodium hydrogen carbonate solution, dries over sodium sulphate and evaporates in a vacuum.

- 5 One recrystallises the residue from a mixture of ethyl acetate and ligroin. One obtains 2.9 g. (66% of theory) 2-(cinnamyloxyimino)-propionamide; m.p. 120 - 121°C.

In analogous way, one obtains from 2-(cinnamyloxy-
10 imino)-propionyl chloride and ethanolamine

a) 2-cinnamyloxyimino)-propionic acid N-(2-hydroxy-ethylamide);

m.p. 74 - 76°C.

Example 8.

- 15 4-[2-(Cinnamyloxyimino)-propionyl]-1-methylpiperazine.

One adds dropwise 4.8 g. (20 mmol) 2-(cinnamyloxy-
imino)-propionyl chloride (prepared according to
Example 6) while stirring at 0°C., to a solution of
2.0 g. (20 mmol) 1-methylpiperazine in 40 ml. dry
20 pyridine, further stirs for 1 hour at 0°C. and pours
on to ice. The mixture is extracted with ether, the
ether extracts are dried over sodium sulphate and
evaporated.

Yield 4.3 g. (71% of theory), colourless oil.

- 25 The hydrochloride melts at 162 - 164°C. (from isopropanol).

In analogous way, from β -alanine ethyl ester

hydrochloride and 2-(cinnamyloxyimino)-propionyl chloride, one obtains 3-[2-(cinnamyloxyimino)-propionylamido]-propionic acid ethyl ester, colourless oil.

- 5 13.7 g. (43 mmol) of the crude ester are dissolved in 250 ml. methanol and mixed with 90 ml. 1N aqueous potassium hydroxide solution. One heats the mixture, while stirring, for 2 hours at 40°C. and subsequently distils off the methanol in a vacuum.
- 10 The aqueous residue is clarified with charcoal and neutralised with 90 ml. of 1N hydrochloric acid. The precipitated crystals are filtered off with suction and recrystallised from a mixture of ethyl acetate and ligroin. One obtains 7.3 g. (58% of theory) 3-[2-
- 15 (cinnamyloxyimino)-propionylamido]-propionic acid; m.p. 111 - 113°C.

Example 9.

2-(Cinnamyloxyimino)-3-fluoropropionic acid.

- One drops, with stirring, a solution of 4.82 g. (33 mmol) sodium 3-fluoro-2-oxopropionate hydrate in 50 ml. water to a solution of 4.1 g. (27.5 mmol) O-cinnamylhydroxylamine in 50 ml. methylene chloride. One then mixes the mixture with 33 ml. (33 mmol) 1N hydrochloric acid, further stirs for 30 minutes and
- 20 separates off the organic phase. One washes with water, dries over sodium sulphate and evaporates. One recrystallises the residue twice from ethyl acetate and
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ligroin. One obtains 3.1 g. (48% of theory) 2-(cinnamyloxyimino)-3-fluoropropionic acid; m.p. 81 - 83°C.

In analogous way, one obtains from

- 5 a) 3-chloro-2-oxopropionic acid and 0-cinnamyl-
hydroxylamine
3-chloro-2-cinnamyloxyiminopropionic acid
m.p. 95 - 98°C.

Example 10.

Cinnamyloxyiminoacetic acid.

- 10 One mixes, with stirring, a solution of 3.73 g.
(25 mmol) 0-cinnamylhydroxylamine in 50 ml. methylene
chloride with a solution of 2.22 g. (30 mmol)
glyoxylic acid in 50 ml. water and stirs up the
reaction mixture for 30 minutes at room temperature.
- 15 One then separates the phases and washes the organic
part with water, dried it with sodium sulphate and
evaporates. One recrystallises the residue from ethyl
acetate and ligroin. One obtains 2.7 g. (53% of theory)
cinnamyloxyiminoacetic acid; m.p. 85 - 88°C.

- 20 In analogous way, one obtains from 0-cinnamyl-
hydroxylamine and

- a) 2-oxobutyric acid

2-cinnamyloxyiminobutyric acid

m.p. 75 - 77°C.

- 25 b) 3-methyl-2-oxobutyric acid

2-cinnamyloxyimino-3-methylbutyric acid

sodium salt: m.p. 220°C. (decomp.)

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- c) 2-oxovaleric acid
2-cinnamyloxyiminovaleric acid
m.p. 53 - 55°C.
- d) 4-methyl-2-oxovaleric acid
5 2-cinnamyloxyimino-4-methylvaleric acid
m.p. 60 - 62°C.
- e) 3-methyl-2-oxovaleric acid
2-cinnamyloxyimino-3-methylvaleric acid
m.p. 57 - 59°C.
- 10 f) 2-oxooctanoic acid
2-cinnamyloxyiminooctanoic acid
m.p. 56 - 58°C.
- g) phenylpyruvic acid
2-cinnamyloxyimino-3-phenylpropionic acid
15 m.p. 84 - 86°C.
- h) oxalacetic acid
2-cinnamyloxyiminosuccinic acid
m.p. 124 - 126°C.
- i) α -ketoglutaric acid
20 2-cinnamyloxyiminoglutaric acid
m.p. 121 - 123°C.

Example 11.

Sodium 2-(4-phenylbutoxyimino)-propionate.

A solution of 5.0 g. (30 mmol) O-(4-phenylbutyl)-
25 hydroxylamine in 60 ml. methylene chloride is mixed
dropwise, while stirring, with a solution of 9.2 g.
(36 mmol) pyruvic acid in 60 ml. water. One further

stirs for 30 minutes and separates the phases. The organic phase is dried over sodium sulphate and evaporated in a vacuum. As residue, there remain 7.1 g. of colourless oil which, in the case of treating with a solution of 2.3 g. (27.5 mmol) sodium hydrogen carbonate in 50 ml. water, dissolves with foaming. The aqueous solution is washed with ether, clarified with charcoal and evaporated in a vacuum. One triturates the residue under acetone. One obtains 4.0 g. (52% of theory) sodium 2-(4-phenylbutoxyimino)-propionate; m.p. 215 - 216°C.

In analogous way, one obtains from pyruvic acid and

- a) 0-(5-phenylpentyl)-hydroxylamine
15 sodium 2-(5-phenylpentoxyimino)-propionate
 m.p. 209 - 212°C.
- b) 0-(2-phenoxypropyl)-hydroxylamine
 sodium 2-(2-phenoxypropoxyimino)-propionate
 m.p. 204 - 206°C.

20 Example 12.

2-(3-Phenoxypropoxyimino)-propionic acid.

One reacts 5.0 g. (30 mmol) 0-(3-phenoxypropyl)-hydroxylamine with 3.2 g. (36 mmol) pyruvic acid according to the process described in Example 11 and 25 recrystallises the evaporation residue from ethyl acetate and ligroin. One obtains 6.1 g. (86% of theory) 2-(3-phenoxypropoxyimino)-propionic acid; m.p. 86-88°C.

In an analogous way, one obtains from pyruvic acid and

- a) 0-[2-(4-chlorophenoxy)-propyl]-hydroxylamine
2-[2-(4-chlorophenoxy)-propoxyimino]-propionic
5 acid
m.p. 70 - 73°C.

Example 13.

2-Cinnamyloxyiminopropionic acid.

One adds 4.0 g. (28 mmol) 0-cinnamylhydroxylamine
10 to a solution of 3.5 g. (24 mmol) 2,2-dichloro-
propionic acid and 3.45 g. (25 mmol) potassium
carbonate in 40 ml. water, heats, while stirring, to
90°C., adds dropwise, within 30 minutes, a solution of
a further 3.5 g. (25 mmol) potassium carbonate in
15 15 ml. water and stirs for 1 hour at 90°C. One then
cools, shakes out with ether and acidifies with hydro-
chloric acid. The precipitate is filtered off with
suction and recrystallised from a mixture of ligroin
and ethyl acetate.

20 Yield: 3.0 g. (57% of theory); m.p. 89 - 91°C.

The mixed melting point with the product des-
cribed in Example 3a shows no depression.

Example 14.

2-Cinnamyloxyiminopropionic acid methyl ester.

25 2.8 g. (15 mmol) 0-cinnamylhydroxylamine hydro-
chloride in 20 ml. water are added to 2.8 g. (19 mmol)
2,2-dimethoxypropionic acid methyl ester in 100 ml.

water. One leaves the mixture to stand for 2 days, with occasional shaking, then extracts the resultant oil with methylene chloride. The extracts are dried and evaporated. As residue, there are obtained 3.3 g. 5 (94% of theory) 2-cinnamyloxyiminopropionic acid methyl ester, colourless oil.

The ester can be saponified by means of potassium hydroxide solution in methanol to 2-cinnamyloxyimino-propionic acid; m.p. 89 - 91°C.

10 Example 15.

2-(3-Fluorocinnamyloxyimino)-pyruvic acid.

One reacts 6.2 g. (37 mmol) 0-(3-fluorocinnamyl)-hydroxylamine with 3.9 g. (44 mmol) pyruvic acid according to the process described in Example 4.

15 Yield: 5.4 g. (61% of theory), m.p. 88 - 90°C. (ethyl acetate and ligroin).

By suitable choice of the starting components, in analogous manner there can be prepared:

- 2-[3-(3-methylphenyl)-propoxyimino]-propionic acid
- 20 2-[3-(4-methylphenyl)-propoxyimino]-propionic acid
- 2-[3-(3-chlorophenyl)-propoxyimino]-propionic acid
- 2-[3-(4-chlorophenyl)-propoxyimino]-propionic acid
- 2-[3-(3-methoxyphenyl)-propoxyimino]-propionic acid
- 2-[3-(4-methoxyphenyl)-propoxyimino]-propionic acid
- 25 2-(2-methyl-3-phenylpropoxyimino)-propionic acid
- 2-[5-(3-chlorophenyl)-pentyloxyimino]-propionic acid
- 2-[5-(4-chlorophenyl)-pentyloxyimino]-propionic acid

- 2-[5-(4-methoxyphenyl)-pentyloxyimino]-propionic acid
2-(3-cyclohexyl-2-propenyloxyimino)-propionic acid
2-(4-methylcinnamyloxyimino)-propionic acid
2-(3-t-butylcinnamyloxyimino)-propionic acid
5 2-(3-bromocinnamyloxyimino)-propionic acid; m.p. 107-109°C.
2-(3-cyanocinnamyloxyimino)-propionic acid
2-(3,4-methylenedioxycinnamyloxyimino)-propionic acid
2-(3-nitrocinnamyloxyimino)-propionic acid; m.p. 131-10 132°C.
2-(3-aminocinnamyloxyimino)-propionic acid
2-(3-acetamidocinnamyloxyimino)-propionic acid
2-[3-(3-methylphenyl)-2-propynyloxyimino]-propionic acid
2-[3-(4-methylphenyl)-2-propynyloxyimino]-propionic acid
15 2-[3-(3-chlorophenyl)-2-propynyloxyimino]-propionic acid
2-[3-(4-chlorophenyl)-2-propynyloxyimino]-propionic acid
2-[3-(4-methoxyphenyl)-2-propynyloxyimino]-propionic acid
acid
2-(3-hydroxy-3-phenylpropoxyimino)-propionic acid
20 2-(2-hydroxy-3-phenylpropoxyimino)-propionic acid
2-(2-chloro-3-phenylpropoxyimino)-propionic acid
2-(β -chlorocinnamyloxyimino)-propionic acid; m.p. 116-118°C.
2-(3-oxo-3-phenylpropoxyimino)-propionic acid
25 2-(2-oxo-3-phenylpropoxyimino)-propionic acid
2-[2-(3-chlorophenoxy)-propoxyimino]-propionic acid
2-[2-(4-methoxyphenoxy)-propoxyimino]-propionic acid

- 2-[3-(3-chlorophenoxy)-propoxyimino]-propionic acid
2-[3-(4-chlorophenoxy)-propoxyimino]-propionic acid
2-[3-(4-methoxyphenoxy)-propoxyimino]-propionic acid
2-(2-hydroxy-3-phenoxypropoxyimino)-propionic acid
5 2-(3-anilinopropoxyimino)-propionic acid
2-[3-(N-methylanilino)-propoxyimino]-propionic acid
2-(3-anilino-2-hydroxypropoxyimino)-propionic acid
2-(3-phenylthiopropoxyimino)-propionic acid
2-(2-cinnamyloxyethoxyimino)-propionic acid
10 3-fluoro-2-(2-propenyloxyimino)-propionic acid
2-(2-propenyloxyimino)-butyric acid
3-fluoro-2-hexyloxyiminopropionic acid
2-(2-hexyloxyimino)-butyric acid; m.p. 236-237°C.
(Na salt)
15 3-hydroxy-2-(3-phenylpropoxyimino)-propionic acid
3-fluoro-2-(3-phenylpropoxyimino)-propionic acid
2-(3-phenylpropoxyimino)-butyric acid
2-[3-(3-chlorophenyl)-propoxyimino]-3-fluoropropionic
acid
20 2-[3-(3-chlorophenyl)-propoxyimino]-butyric acid
3-fluoro-2-[3-(3-methylphenyl)-propoxyimino]-propionic
acid
2-[3-(3-methylphenyl)-propoxyimino]-butyric acid
3-oxo-2-cinnamyloxyimino-propionic acid
25 2-cinnamyloxyimino-3,3-dichloropropionic acid
2-cinnamyloxyimino-3-cyanopropionic acid
2-cinnamyloxyimino-4-cyanobutyric acid

(B)

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- 2-cinnamyloxyimino-3-hydroxypropionic acid
2-(3-chlorocinnamyloxyimino)-3-fluoropropionic acid;
m.p. 92-94°C.
2-(3-chlorocinnamyloxyimino)-butyric acid; m.p. 91-93°C.
- 5 3-fluoro-2-(3-methylcinnamyloxyimino)-propionic acid
2-(3-methylcinnamyloxyimino)-butyric acid
3-hydroxy-2-(3-phenylpropyn-2-yloxyimino)-propionic acid
3-fluoro-2-(3-phenylpropyn-2-yloxyimino)-propionic acid
2-(3-phenylpropyn-2-yloxyimino)-butyric acid
- 10 2-[3-(3-chlorophenyl)-propyn-2-yloxyimino]-3-fluoro-
propionic acid
2-[3-(3-chlorophenyl)-propyn-2-yloxyimino]-butyric acid
3-fluoro-2-[3-(3-methylphenyl)-propyn-2-yloxyimino]-
propionic acid
- 15 2-[3-(3-methylphenyl)-propyn-2-yloxyimino]-butyric acid
3-fluoro-2-(2-phenoxypropoxyimino)-propionic acid
2-(2-phenoxypropoxyimino)-butyric acid.

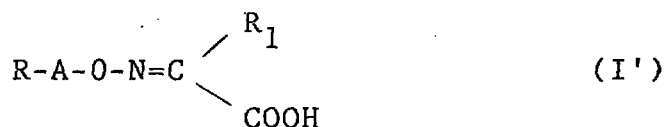


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Claims

1. α -Ketocarboxylic acid oximes of the formula I'



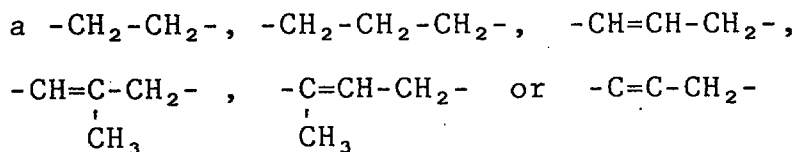
in which R signifies hydrogen, a C₃-C₈ cycloalkyl,
5 methoxy, cinnamyloxy, phenylamino, phenyl-N-methyl-
amino, phenylmercapto, an aryl or aryloxy group, the
aryl radical of which is a phenyl or naphthyl group
which can be substituted one or more times by C₁₋₆
alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, trifluoromethyl,
10 amino, acetylamino, nitrile, nitro or a methylenedioxy
group, A signifies a straight-chained or branched,
saturated or unsaturated alkylene chain with 2 to 8
C-atoms, which is optionally substituted by a halogen
or hydroxyl group, whereby for the case in which R
15 signifies an alkoxy or aryloxy radical, A must possess
a straight-chained part of at least 2 carbon atoms,
through which the radical R is connected with the
oxygen atom, and R₁ signifies hydrogen, a C₁-C₆ alkyl
group, which is optionally substituted once or twice by
20 halogen, hydroxyl or phenyl, whereby R-A cannot be an
alkyl group with 2 to 4 C-atoms; as well as their
physiologically acceptable salts, carboxylic acid
esters and amides.

2. Compounds according to claim 1, characterised in
25 that R and R₁ have the given meanings and A represents



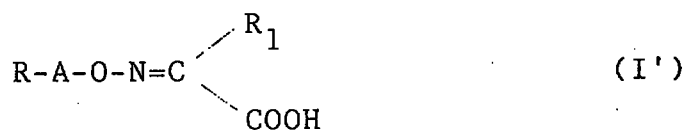
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3. Compounds according to claim 2, characterised in that R and A have the given meanings and R_1 represents
5 a methyl, ethyl or fluoromethyl group.

4. Process for the preparation of α -ketocarboxylic acid oximes of the general formula I'



in which R signifies hydrogen, a C_3-C_8 cycloalkyl,
10 methoxy, cinnamyloxy, phenylamino, phenyl-N-methylamino, phenylmercapto, an aryl or aryloxy group, the aryl radical of which is a phenyl or naphthyl group which can be substituted one or more times by C_{1-6} alkoxy, halogen, hydroxyl, trifluoromethyl, amino, acetylamino,
15 nitrile, nitro or a methylenedioxy group, A signifies a straight-chained or branched, saturated or unsaturated alkylene chain with 2 to 8 C-atoms, which is optionally substituted by a halogen or hydroxyl group, whereby, for the case in which R signifies an alkoxy or aryloxy
20 radical, A must possess a straight-chained part of at least 2 carbon atoms through which the radical R is connected with the oxygen atom, and R_1 signifies hydrogen, a C_1-C_6 alkyl group, which is optionally substituted once or twice by halogen, hydroxyl or phenyl,



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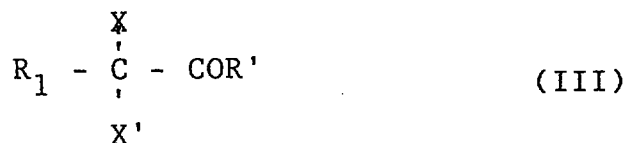
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whereby R-A cannot be an alkyl group with 2 to 4 C-atoms, as well as of their physiologically acceptable salts, carboxylic acid esters and amides, characterised in that, in per se known manner, one

5 a) reacts a hydroxylamine of the general formula II,

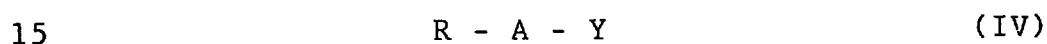


in which R and A have the above-given meaning, with a compound of the general formula III



10 in which R_1 has the given meaning, X and X' signify halogen or alkoxy groups or together represent an oxygen atom and R' signifies hydroxyl, a lower alkoxy or an optionally substituted amino group; or

b) reacts a compound of general formula IV



in which R and A have the above-given meaning and Y represents a reactive group, with a compound of general formula III, in which X and X' together represent the group =N-OH and R_1 and R' have the above-given meaning,

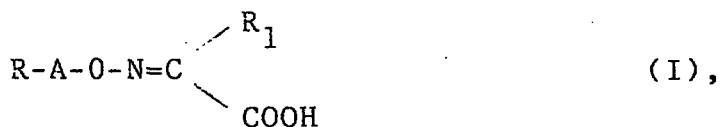
20 subsequent to the reaction having taken place, one optionally converts the acid derivatives obtained into the free acids of the general formula I or, if desired, converts the free acid obtained into an ester, into an amide or into a physiologically acceptable salt.



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5. Medicaments for humans and animals, containing α -ketocarboxylic acid oximes of the formula I



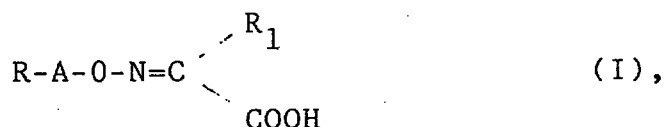
- in which R signifies a C₃-C₈ cycloalkyl, C₁-C₆ alkoxy, cinnamyloxy, phenylamino, phenyl-N-alkylamino, phenyl-mercapto, an aryl or aryloxy group the aryl radical of which can be substituted one or more times by C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, hydroxyl, trifluoromethyl, amino, acetylamino, nitrile, nitro or a methylenedioxy group,
- 10 A signifies a straight-chained or branched, saturated or unsaturated alkylene chain with up to 10 C-atoms, which is optionally substituted one or more times by halogen or hydroxyl, whereby, for the case in which R signifies an alkoxy or aryloxy radical, A must possess
- 15 a straight-chained part through which the radical R is connected with the oxygen atom, and R₁ signifies hydrogen, a C₁-C₈ alkyl group, which is optionally substituted one or more times by halogen, hydroxyl, nitrile, phenyl or carboxyl, nitrile or formyl, whereby
- 20 R-A cannot be a benzyl group, or their physiologically acceptable salts, carboxylic acid esters and amides, as well as per se known pharmacologically acceptable carrier materials.

6. Agents containing α -ketocarboxylic acid oximes of the formula I



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in which R signifies hydrogen, A signifies a straight-chained or branched, saturated or unsaturated alkylene chain with up to 10 C-atoms, which is optionally substituted one or more times by halogen or hydroxyl, and R₁ signifies hydrogen, a C₁-C₈ alkyl group which is optionally substituted one or more times by halogen, hydroxyl, nitrile, phenyl or carboxyl, nitrile or formyl, whereby R-A cannot be a methyl or ethyl group; or their physiologically acceptable salts, carboxylic acid esters and amides, as well as per se known pharmacologically acceptable carrier materials for use in a therapeutic treatment of the human or animal body.

7. α -Ketocarboxylic acid oximes according to claim 5 or 6 for use in the combating of diabetes, prediabetes, adipositas and atherosclerosis.

8. Compounds according to claims 1 to 3 for use in the combating of diabetes, prediabetes, adipositas or atherosclerosis.