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(12) # EUROPEAN PATENT SPECIFICATION

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(54) **N-substituted omega-(2-oxo-4-imidazolin-1-yl) alcanoic acids, salts and esters thereof, process for producing the same and these active agents containing pharmaceutical compounds.**

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**DE-A-2 934 746**
**DE-A-2 950 478**
**US-A-4 238 618**

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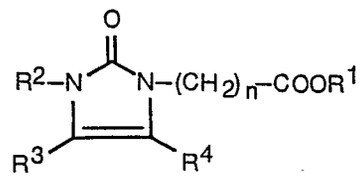
## Description

As described in two own prior, published German patent applications 29 34 746 and 29 50 478, 5- and 4.5- substituted $\omega$-(2-oxo-4-imidazolin-1-yl) alcanoic acids as well as their salts and esters have valuable pharmacological properties such as antithrombotic, antiarteriosclerotic, antiinflammatory and analgetic properties.

The present invention refers to new N-substituted $\omega$-(2-oxo-4-imidazolin-1-yl) alcanoic acid derivatives having the general formula I



I

wherein

n is an integer ranging from 1 to 10, preferably ranging from 6 to 8,

$R^1$ represents hydrogen, an alkali metal ion or a straight or branched hydrocarbon group having from 1 to 6 carbon atoms or the benzyl group,

$R^2$ is $—(CH_2)_m—R$, m being 0, 1 or 2,

R, $R^3$ and $R^4$, which may be identical or different from each other, represent hydrogen (with the exception of R if m is zero), the unsubstituted phenyl group or the phenyl group substituted by one or several identical or differing substituents selected from the group consisting of halogen (in particular chlorine or fluorine), $CH_3$—, $CH_3O$—, —$CH_3$, at least one of R, $R^3$ and $R^4$ being a phenyl group or the phenyl group substituted by one or several identical or differing substituents selected from the group of halogen, —$CH_3$, $CH_3O$—, —$CF_3$.

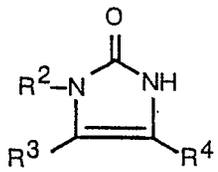
The present invention further refers to processes for producing the same.

The new compounds show interesting pharmacological properties such as antiallergic, antiasthmatic, antithrombotic, antiarteriosclerotic and antiinflammatory properties. They furthermore show antagonistic activity in respect to some physiological processes regulated by PAF (platelet activation factor) as well as excellent compatibility by the stomach and may therefor in particular used for the treatment of thrombotic, allergic, asthmatic and arteriosclerotic as well as inflammatory diseases with at the same time favourable gastrointestinal properties. Futhermore, the compounds of formula I have a low toxicity. They furthermore may be produced in combination with anticoagulantia, in particular with heparin and heparinates.

The new N-substituted $\omega$-(2-oxo-4-imidazolin-1-yl) alcanoic acid derivatives in the form of the free acids or of the salts thereof with pharmacologically compatible bases or as esters thereof may be used as active ingredients in drugs together with usual carrier materials or diluents.

The compounds of general formula I according to the present invention are used in dosages ranging from 0.1 to 100 mg/kg, in particular 1 to 50 mg/kg.

The compounds according to the present invention are produced according to the invention in that a 4-imidazolin-2-one of the general formula II



II

wherein $R^2$, $R^3$ and $R^4$ have the same meaning as in formula I, which may be produced by known processes usual in the chemistry of heterocyclic compounds from isocyanates and $\alpha$-aminoketones or, respectively, from benzoketones with substituted ureas, is subjected to reaction with an alkylating agent of the general formula III

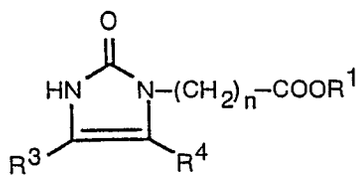
$$X—(CH_2)_n—COOR^1 \qquad III$$

wherein n and $R^1$ have the same meaning as in formula I and X is a halogen atom, in an organic solvent such as acetone, methyl ethyl ketone, dimethylformamide with the addition of an auxiliary base such as sodium hydride, possibly in the presence of alkali metal iodide as catalyst.

The resulting esters of formula I may converted into the corresponding alkali metal salt of formula I ($R^1$ = alkali metal) in usual manner for instance by reaction with an alkali metal hydroxide in an aqueous, alcoholic or alcoholethereal solvent and by subsequent addition of a mineral acid into the acid of formula I ($R^1$ = H).

In another way the acids of formula I ($R^1$ = H) and the alkali metal salts thereof of formula I ($R^1$ = alkali metal) may be converted into the esters of formula I ($R^1$ = $C_{1-6}$-alkyl or benzyl) in manners usual in organic chemistry, for instance by the treatment of the compounds of formula I with a solution of hydrochloric acid in the corresponding alcohol or by subjecting the acid or the salt of formula I to reaction with thionyl chloride and subsequent reaction with the corresponding alcohol.

The compounds of formula I may also be produced by subjecting an $\omega$-(2-oxo-4-imidazolin-1-yl)-alcanoic acid or a derivative thereof having the general formula IV




IV

wherein $R^1$, $R^3$ and $R^4$ have the same meaning as in formula I, which may be produced by the synthesis described in the German patent application 29 50 478, to reaction with an alkylating agent of formula V

$$R^2—Y \qquad V$$

wherein Y has the same meaning of X in formula III or Y is another usual favourable group to be split off, for instance the $N_2$-group or the radical or a sulphuric acid ester, in particular of a sulphuric acid lower alkyl ester.

Substituted phenyl groups $R^2$ (or, respectively, R), $R^3$ and $R^4$ are for instance: 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2.5-dimethoxyphenyl, 3.4-dimethoxyphenyl, 3.4.5-trimethoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl.

Alkylating agents of formula III are for instance the esters of the following $\omega$-halogeno alcanoic acids:

chloroacetic acid, bromoacetic acid, iodoacetic acid, 3-chloropropionic acid, 3-bromopropionic acid, 3-iodopropionic acid, 4-chlorobutyric acid, 4-bromobutyric acid, 4-iodobutyric acid, 5-chlorovaleric acid, 5-bromovaleric acid, 5-iodovaleric acid, 6-chlorocapronic acid, 6-bromocapronic acid, 6-iodocapronic acid, 7-chloroenanthic acid, 7-bromoenanthic acid, 7-iodoenanthic acid, 8-chlorocaprylic acid, 8-bromocaprylic acid, 8-iodocaprylic acid, 9-chloropelargonic acid, 9-bromopelargonic acid, 9-iodopelargonic acid, 10-chlorocaprinic acid, 10-bromocaprinic acid, 10-iodocaprinic acid, 11-chloroundecanoic acid, 11-bromoundecanoic acid, 11-iodoundecanoic acid.

Examples for the alkylating agents of formula V are:

Diazomethane, dimethylsulfate, chloromethane, bromoethane, iodomethane, chlorethane, bromoethane, iodoethane, benzylchloride, benzylbromide, benzyliodide, phenylethylchloride, phenylethylbromide, phenylethyliodide as well as those substituted benzyl- and phenylethyl halogenides corresponding to R.

The alcohols $R^1OH$ preferably are such alcohols with straight or secondary branched saturated hydrocarbon groups with 1 to 6 carbon atoms such as methanol, ethanol, propanol, isopropanol, butanol, pentanol, hexanol as well as benzylalcohols.

The new compounds of formula I may be administered orally or by injection or rectally as suitable pharmaceutical products which may be solid or liquid, in the form of suspensions or solutions. Examples for such pharmaceutical products are tablets, powders, capsules, granules, ampoules, sirups and suppositories.

The production of the compounds according to the present invention are further illustrated in the following examples.

The given melting points have been determined on a BÜCHI 510 melting point determination apparatus and are not corrected. The IR-spektra have been determined on a PERKIN ELMER 257 and the mass spektra on a VARIAN MAT—311 A (70 eV).

## Example 1

*[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] acetic acid ethyl ester*

1.5 g of sodium hydride (80% suspension in mineral oil) are washed with n-pentane and added to a mixture of 13.5 g 1-(4-chlorophenyl)-5-phenyl-4-imidazolin-2-one and 100 cc. of anhydrous dimethylformamide (DMF). The mixture is stirred at room temperature and heated to 60°C with continuation of stirring towards the end of hydrogen formation. Thereafter, 6.2 g of chloroacetic acid ethyl ester and 1.5 g of sodium-iodide (NaJ) are added and the mixture is heated to 80°C for 8 hours. After cooling, the reaction product is diluted with water, extracted with ether, the ether phase is washed consequetively with water, with 5% $NaHCO_3$ solution and again with water. The ethereal solution is dried over $Na_2SO_4$, the solvent is distilled off in a vacuum and the residue is purified chromatographically on silicic acid gel using chloroform as eluant.

Yield: 14.5 g. Fp. 96 to 97°C.

IR: (in KBr): 1755 and 1700 $cm^{-1}$.

## Example 2

*7-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] enanthic acid ethyl ester*

The product is obtained as described in example 1 from 1.35 g NaH (80% suspension in mineral oil), 12.2 g of 1-(4-chlorophenyl)-5-phenyl-4-imidazolin-2-one, 100 cc. of DMF, 8.7 g of 7-chloroenanthic acid ethyl ester and 1.35 g of NaJ. Eluant in chromatographic purification: hexane/ethyl acetate.

Yield: 15.7 g (oil)

IR (film): 1735 and 1700 $cm^{-1}$.

## Example 3

*7-(3-ethyl-4.5-diphenyl-2-oxo-4-imidazolin-1-yl) enanthic acid ethyl ester*

The product is obtained as described in example 1 from 2.1 g of NaH (80% suspension in mineral oil), 18.5 g of 1-ethyl-4.5-diphenyl-4-imidazolin-2-one, 140 cc. of DMF, 13.5 g of 7-chloroenanthic acid ethyl ester and 2.1 g of NaJ.

Yield: 14.5 g (oil)

IR (film): 1735 and 1690 $cm^{-1}$.

## Example 4

*8-(3.4-Diphenyl-2-oxo-4-imidazolin-1-yl)-caprylic acid methyl ester*

The product is produced as described in example 1 from 2.34 g of NaH (80% suspension in mineral oil), 18.5 g of 1.5-diphenyl-4-imidazolin-2-one, 160 cc. of DMF, 18.5 g of 8-bromocaprylic acid methyl ester and 2.34 g of NaJ.

Eluant in chromatographic purification: hexane/ethyl acetate.

Yield: 14 g, Fp. 45 to 47°C.

IR (film): 1740 and 1695 $cm^{-1}$.

## Example 5

*8-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid methyl ester*

The product is produced as described in example 1 from 2.4 g of NaH (80% suspension in minera oil), 21.6 g of 1-(4-chlorophenyl)-5-phenyl-4-imidazolin-2-one, 160 cc. of DMF, 19.0 g of 8-bromocaprylic acid methyl ester and 2.4 g of NaJ.

Yield: 33 g (oil)

IR (film): 1740 and 1700 $cm^{-1}$.

Example 6

*8-[2-Oxo-4-phenyl-3-(3-trifluoromethylphenyl)-4-imidazolin-1-yl] caprylic acid methyl ester*

The product is produced as described in example 1 from 1.41 g of NaH (80% suspension in mineral oil), 14.3 g of 5-phenyl-1-(3-trifluoromethylphenyl)-4-imidazolin-2-one, 100 cc. of DMF, 11.1 g of 8-bromocaprylic acid methyl ester and 1.41 g of NaJ.

Eluant in chromatographic purification: hexane/ethyl acetate.

Yield: 7.0 g (oil)

IR (film): 1740 and 1700 $cm^{-1}$.

Example 7

*8-[3-(4-Methoxyphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid methyl ester*

The product is produced as described in example 1 from 2.4 g of NaH (80% suspension in mineral oil), 21.3 g of 1-(4-methoxyphenyl)-5-phenyl-4-imidazolin-2-one, 160 cc. of DMF, 19 g of 8-bromo-caprylic acid methyl ester and 2.4 g of NaJ.

Eluant in chromatographic purification: hexane/ethyl acetate.

Yield: 18.9 g (oil)

IR (film) 1740 and 1695 $cm^{-1}$.

Example 8

*8-[3-(4-Methylphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl]caprylic acid methyl ester*

The product is produced as described in example 1 from 2.25 g of NaH (80% suspension in mineral oil), 18.7 g of 1-(4-methylphenyl)-5-phenyl-4-imidazolin-2-one, 150 cc. of DMF, 17.8 g of 8-bromocaprylic acid methyl ester and 2.25 g of NaJ.

Yield: 18.4 g (oil)

IR (film): 1740 and 1695 $cm^{-1}$.

Example 9

*8-[3-(4-Fluorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid methyl ester*

The product is produced as described in example 1 from 2.16 g of NaH (80% suspension in mineral oil), 18.3 g of 1-(4-Fluorophenyl)-5-phenyl-4-imidazolin-2-one, 150 cc. of DMF, 17.1 g of 8-bromocaprylic acid methyl ester and 2.16 g of NaJ.

Yield: 16.7 g (oil)

IR (film): 1740 and 1700 $cm^{-1}$.

Example 10

*8-[4-(4-Chlorophenyl)-2-oxo-3-phenyl-4-imidazolin-1-yl] caprylic acid methyl ester*

The product is produced as described in example 1 from 1.05 g of NaH (80% suspension in mineral oil), 9.5 g of 5-(4-chlorophenyl)-1-phenyl-4-imidazolin-2-one, 70 cc. of DMF, 8.3 g of 8-bromocaprylic acid methyl ester and 1.05 g of NaJ.

Eluant in chromatographic purification: hexane/ethyl acetate.

Yield: 8.3 g, Fp. 83 to 84°C

IR (in KBr): 1740 and 1690 $cm^{-1}$.

Example 11

*8-(3-Benzyl-2-oxo-4-phenyl-4-imidazolin-1-yl) caprylic acid methyl ester*

The product is produced as described in example 1 from 1.8 g of NaH (80% suspension in mineral oil), 15 g of 1-benzyl-5-phenyl-4-imidazolin-2-one, 120 cc. of DMF, 14.2 g of 8-bromocaprylic acid methyl ester and 1.8 g of NaJ.

Yield: 18.8 g (oil)

IR (film): 1735 and 1685 $cm^{-1}$.

Example 12

*8-(2-Oxo-3.4.5-triphenyl-4-imidazolin-1-yl) caprylic acid methyl ester*

The product is produced as described in example 1 from 1.2 g of NaH (80% suspension in mineral oil), 12 g of 1.4.5-triphenyl-4-imidazolin-2-one, 80 cc. of DMF, 9.5 g of 8-bromo-caprylic acid methyl ester and 1.2 g of NaJ.

YieldL 12.9 g (oil)

IR (film): 1740 and 1700 $cm^{-1}$.

Example 13

*8-[4.5-Bis-(2-fluorophenyl)-3-methyl-2-oxo-4-imidazolin-1-yl] caprylic acid methyl ester*

The product is produced as described in example 1 from 0.63 of NaH (80% suspension in mineral oil), 5.9 g of 4.5-bis-(2-fluorophenyl)-1-methyl-4-imidazolin-2-one, 40 cc. of DMF, 5.0 g of 8-bromo caprylic methyl ester and 0.63 g of NaJ.

Eluant in chromatographic purification: hexane/ethyl acetate.

Yield: 5.3 g (oil)

IR (film): 1740 and 1695 $cm^{-1}$.

Example 14

*8-(4.5-Diphenyl-3-methyl-2-oxo-4-imidazolin-1-yl) caprylic acid methyl ester*

The product is produced as described in example 1 from 2.4 g of NaH (80% suspension in mineral oil), 20 g of 4.5-diphenyl-1-methyl-4-imidazolin-2-one, 160 cc of DMF, 19 g of 8-bromo-caprylic acid methyl ester and 2.4 g of NaJ.

Eluant in chromatographic purification: hexane/ethyl acetate.

Yield: 17.5 g (oil)

IR (film): 1740 and 1690 $cm^{-1}$.

Example 15

*9-[3-(4-(Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] pelargonic acid methyl ester*

The product is produced as described in example 1 from 1.35 g of NaH (80% suspension in mineral oil), 12.2 g of 1-(4-chlorophenyl)-5-phenyl-4-imidazolin-2-one, 90 cc. of DMF, 11.3 g of 9-bromo-nonanic acid methyl ester and 1.35 g of NaJ.

Eluant in chromatographic purification: hexane/ethyl acetate.

Yield: 5.4 g, Fp. 54 to 56°C

IR (in KBr): 1740 and 1690 $cm^{-1}$.

Example 16

*11-(3-ethyl-4.5-diphenyl-2-oxo-4-imidazolin-1-yl)undecanoic acid methyl ester*

The product is produced as described in example 1 from 0.45 g of NaH (80% suspension in mineral oil), 4 g of 1-ethyl-4.5-diphenyl-4-imidazolin-2-one, 30 cc. of DMF, 4.2 g of 11-bromo-undecanoic acid methyl ester and 0.45 g of NaJ. Eluant in chromatographic purification: hexane/ethyl acetate.

Yield: 1.5 g (oil)

IR (film): 1740 and 1690 $cm^{-1}$.

11-(3-Ethyl-4.5-diphenyl-2-oxo-4-imidazolin-1-yl)-undecanoic acid:

Example 17

*8-(3-Methyl-2-oxo-5-phenyl-4-imidazolin-1-yl) caprylic acid*

3.2 g of 8-(2-oxo-5-phenyl-4-imidazolin-1-yl) caprylic acid sodium salt (preparation see German patent application P 29 34 746.4) are suspended in 20 cc. of acetone together with 2.8 g of pulverized potassium hydroxide. The mixture is refluxed and converted into a homogenous solution by the addition of some drops of water. Thereafter, 2.8 g of methyl-iodide are added at boiling temperature, the mixture is refluxed for 30 minutes and cooled to room temperature. After cooling, so much of water is added that precipitated solids are dissolved. The solution is stirred at room temperature for 4 hours, is acidified and diluted with water until the crude acid is separated as oil. The oil is dissolved in a small amount of chloroform, the chloroform phase is washed with water several times and is finally extracted with 5% soda lye. The soda lye extract is washed with chloroform, the aqueous solution is acidified with dilute hydrochloric acid and is separated from the acid precipitated as an oil. Purification occurs by chromatography on silicic acid gel using a mixture of chloroform and methanol as eluant.

Yield: 2.6 g (oil)

MS (m/e): 316 (100%), 187 (29%), 174 (65%), 159 (4.8%), 105 (7.7%).

Example 18

*[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] acetic acid*

13.6 g of [3-(4-chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] acetic acid ethyl ester and 1.52 g of NaOH are dissolved in 80 cc. of ethanol and the mixture is stirred at room temperature for 24 hours. The alcohol is distilled off in a vacuum and the residue is dissolved in water. The aqueous solu-

tion is shaken with ether, the aqueous phase is acidified with dilute hydrochloric acid and the precipitated acid is separated and dried.

Yield: 6.0 g, Fp. 214 to 215°C

MS (m/e): 328 (100%), 284 (30%), 269 (2.5%), 214 (14-).

Example 19

*7-[3-(4-Chlorophenyl-2-oxo-4-phenyl-4-imidazolin-1-yl] enanthic acid*

The product is produced as described in example 18 from 13.5 g of 7-[3-(4-chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] enanthic acid ethyl ester, 1.28 g of NaOH in 60 cc. of ethanol.

Yield: 10.0 g, Fp. 141°C

MS (m/e): 398 (100%), 284 (17%), 270 (27%), 214 (22%).

Example 20

*7-(3-Ethyl-4,5-diphenyl-2-oxo-4-imidazolin-1-yl) enanthic acid*

The product is produced as described in example 18 from 12.3 g of 7-(3-ethyl-4,5-diphenyl-2-oxo-4-imidazolin-1-yl) enanthic acid ethyl ester and 1.16 g of NaOH in 60 cc. of ethanol. Further purification by chromatography on silicic acid gel using chloroform as eluant.

Yield: 4.2 g, Fp. 111 to 112°C

MS (m/e): 392 (100%), 277 (8%), 264 (18%), 104 (6%).

Example 21

*8-(3.4-Diphenyl-2-oxo-4-imidazolin-1-yl) caprylic acid*

The product is produced as described in example 18 from 8.2 g of 8-(3.4-diphenyl-2-oxo-4-imidazolin-1-yl) caprylic acid methyl ester and 0.84 g of NaOH in 20 cc. of ethanol. Further purification by chromatography on silicic acid gel using chloroform as eluant.

Yield: 1.4 g, Fp. 108°C

MS (m/e): 378 (100%), 249 (20%), 236 (26%), 180 (24%).

Example 22

*8-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid*

The product is produced as described in example 18 from 20 g of 8-[3-(4-chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid methyl ester and 1.88 g of NaOH in 100 cc. of methanol. Further purification by chromatography on silicic acid gel using a mixture of hexane and ethyl acetate as eluant.

Yield: 8.5 g, Fp. 100 to 101°C

MS (m/e): 412 (100%), 284 (11%), 270 (18%), 214 (16%).

Example 23

*8-[2-Oxo-4-phenyl-3-(3-trifluoromethyl-phenyl)-4-imidazolin-1-yl] caprylic acid*

The product is produced as described in example 18 from 6.9 g of 8-[2-oxo-4-phenyl-3-(3-trifluoromethyl-phenyl)-4-imidazolin-1-yl] caprylic acid methyl ester and 0.66 g of NaOH in 30 cc. of methanol. Further purification by chromatography on silicic acid gel using chloroform as eluant.

Yield: 4.55 g, Fp. 113 to 114°C

MS (m/e): 446 (100%), 318 (10%), 304 (21%), 248 (14%).

Example 24

*8-[3-(4-Methoxyphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid*

The product is produced as described in example 18 from 18.8 g of 8-[3-(4-methoxyphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid methyl ester and 2.12 g of NaOH in 100 cc. of methanol. Further purification by chromatography on silicic acid gel using chloroform as eluant.

Yield: 6.6 g, Fp. 110°C

MS (m/e): 408 (100%), 279 (14%), 266 (18%), 210 (26%).

Example 25

*8-[3-(4-Methylphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid*

The product is produced as described in example 18 from 18.1 g of 8-[3-(4-methylphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid methyl ester and 1.8 g of NaOH in 90 cc. of methanol. Further purification by chromatography on silicic acid gel using chloroform as eluant.

Yield: 6.6 g, Fp. 110 to 101°C

MS (m/e): 392 (100%), 264 (11%), 250 (14%), 194 (12%).

Example 26

*8-[3-(4-Fluorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid*

The product is produced as described in example 18 from 16.4 g of 8-[3-(4-fluorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid methyl ester and 1.6 g of NaOH in 80 cc. of methanol. Further purification by chromatography on silicic acid gel using chloroform as eluant.

Yield: 3.6 g, Fp. 110°C

MS (m/e): 396 (100%), 268 (11%), 254 (18%), 198 (16%).

Example 27

*8-[4-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid*

The product is produced as described in example 18 from 6.1 g of 8-[4-(4-chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid ethyl ester and 0.56 g of NaOH in 30 cc. of methanol. The product is finally boiled in a small amount of ether, filtered off with suction and dried.

Yield: 3.6 g, Fp. 156 to 157°C

MS (m/e): 412 (100%), 284 (14%), 270 (23%), 214 (16%).

Example 28

*8-(3-Benzyl-2-oxo-4-phenyl-4-imidazolin-1-yl) caprylic acid*

The product is produced as described in example 18 from 20.3 g of 8-(3-benzyl-2-oxo-4-phenyl-4-imidazolin-1-yl) caprylic acid methyl ester. Further purification by chromatography on silicic acid gel using chloroform as eluant.

Yield: 9.5 g, Fp. 95°C

MS (m/e): 392 (82%), 173 (13%), 159 (10%), 91 (100%).

Example 29

*8-(2-Oxo-3.4.5-triphenyl-4-imidazolin-1-yl)-caprylic acid*

The product is prepared as described in example 18 from 7.5 g of 8-(2-oxo-3.4.5-triphenyl-4-imidazolin-1-yl)-caprylic acid methyl ester and 0.64 g of NaOH in 30 cc. of methanol. Further purification by chromatography on silicic acid gel using chloroform as eluant.

Yield: 3.5 g, FP. 142 to 143°C

MS (m/e): 454 (100%), 325 (14%), 312 (23%), 180 (11%).

Example 30

*8-[4.5-Bis-(2-fluorophenyl)-3-methyl-2-oxo-4-imidazolin-1-yl] caprylic acid*

The product is produced as described in example 18 from 5.2 g of 8-[4.5-bis-(2-fluorophenyl)-3-methyl-2-oxo-4-imidazolin-1-yl] caprylic acid methyl ester and 0.53 g of NaOH in 25 cc. of methanol. Recrystallization from ether/hexane.

Yield: 3.9 g, Fp, 130 to 131°C

MS (m/e): 428 (100%), 299 (24%), 286 (53%).

Example 31

*8-(4.5-Diphenyl-3-methyl-2-oxo-4-imidazolin-1-yl) caprylic acid*

The product is produced as described in example 18 from 17.5 g of 8-(4.5-diphenyl-3-methyl-2-oxo-4-imidazolin-1-yl) caprylic acid methyl ester and 2.1 g of NaOH in 100 cc. of methanol. Further purification by chromatography on silicic acid gel using chloroform as eluant.

Yield: 10.2 g, Fp. 112 to 114°C

MS (m/e): 392 (100%), 263 (10%), 250 (33%).

Example 32

*9-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] pelargonic acid*

The product is produced as described in example 18 from 4.4 g of 9-[3-(4-chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] pelargonic acid methyl ester and 0.4 g of NaOH in 20 cc. of methanol. Further purification by chromatography on silicic acid gel using chloroform as eluant.

Yield: 2.8 g, Fp. 143 to 144°C

MS (m/e): 426 (100%), 284 (11%), 270 (20%), 214 (17%).

Example 33

*[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] acetic acid sodium salt*

5 g of [3-(4-chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] acetic acid are dissolved in ethanol, the solution is neutralized with the equivalent amount of alcoholic soda lye and the resulting solution is evaporated to dryness in a vacuum. The solid residue is pulverized.

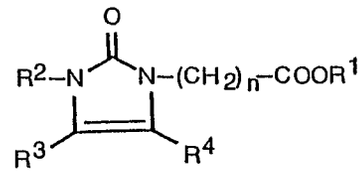
Yield: 100%

IR (in KBr): 1675 and 1600 $cm^{-1}$.

As described in example 33, examples 34 to 47 (see table 1 have been executed.

TABLE 1

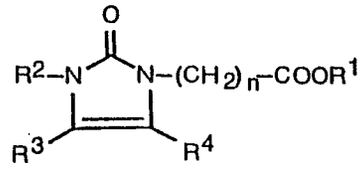
Sodium salt of N-substituted ω-(2-oxo-4-imidazolin-1-yl) alcanoic acids




| Example No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | n | IR maxima in KBr in $cm^{-1}$ | corresponding acid |
|---|---|---|---|---|---|---|---|
| 34 | Na | Cl–⟨⟩– | ⟨⟩– | H | 6 | 1690, 1570 | 7-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] enanthic acid |
| 35 | Na | $C_2H_5$ | ⟨⟩– | ⟨⟩– | 6 | 1690, 1575 | 7-(3-Ethyl-4.5-diphenyl-2-oxo-4-imidazolin-1-yl) enanthic acid |
| 36 | Na | ⟨⟩– | ⟨⟩– | H | 7 | 1690, 1570 | 8-(3.4-Diphenyl-2-oxo-4-imidazolin-1-yl) caprylic acid |
| 37 | Na | Cl–⟨⟩– | ⟨⟩– | H | 7 | 1690, 1570 | 8-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid |
| 38 | Na | $CF_3$–⟨⟩– | ⟨⟩– | H | 7 | 1695, 1570 | 8-[2-Oxo-4-phenyl-3-(3-trifluoromethylphenyl)-4-imidazolin-1-yl] caprylic acid |

TABLE 1 (Continued)

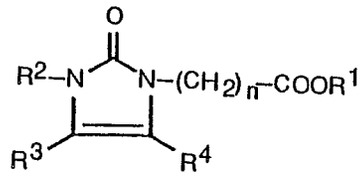
Sodium salt of N-substituted $\omega$-(2-oxo-4-imidazolin-1-yl) alcanoic acids



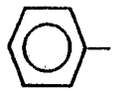
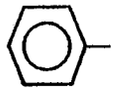
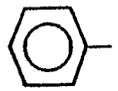
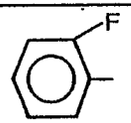
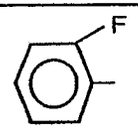
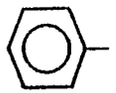
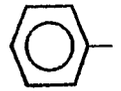
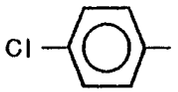
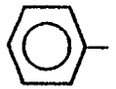

| Example No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | n | IR maxima in KBr in $cm^{-1}$ | corresponding acid |
|---|---|---|---|---|---|---|---|
| 39 | Na | $CH_3O$– | | H | 7 | 1690, 1570 | 8-[3-(4-Methoxyphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid |
| 40 | Na | $CH_3$– | | H | 7 | 1690, 1570 | 8-[3-(4-Methylphenyl)-2-oxo-4-phenyl-3-imidazolin-1-yl] caprylic acid |
| 41 | Na | F– | | H | 7 | 1690, 1570 | 8-[3-(4-Fluorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid |
| 42 | Na | | Cl– | H | 7 | 1685, 1565 | 8-[4-(4-Chlorophenyl)-2-oxo-3-phenyl-4-imidazolin-1-yl] caprylic acid |
| 43 | Na | –$CH_2$– | | H | 7 | 1690, 1570 | 8-(3-Benzyl-2-oxo-4-phenyl-4-imidazolin-1-yl) caprylic acid |

TABLE 1 (Continued)

Sodium salt of N-substituted $\omega$-(2-oxo-4-imidazolin-1-yl) alcanoic acids



I

| Example No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | n | IR maxima in KBr in $cm^{-1}$ | corresponding acid |
|---|---|---|---|---|---|---|---|
| 44 | Na |  |  |  | n | 1700, 1565 | 8-(2-Oxo-3.4.5-triphenyl-4-imidazolin-1-yl)-caprylic acid |
| 45 | Na | $CH_3$– |  |  | 7 | 1690, 1570 | 8-[4.5-Bis-(2-fluorophenyl)-3-methyl-2-oxo-4-imidazolin-1-yl] caprylic acid |
| 46 | Na | $CH_3$– |  |  | 7 | 1690, 1570 | 8-(4.5-Diphenyl-3-methyl-2-oxo-4-imidazolin-1-yl) caprylic acid |
| 47 | Na |  |  | H | 8 | 1695, 1570 | 9-[3-4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] pelargonic acid |

Example 48

*[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] acetic acid hexyl ester*

1 g of [3-(4-chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] acetic acid are dissolved in a small amount of anhydrous chloroform. 0.7 g of thionylchloride are added thereto and the mixture is stirred at about 50°C for 2 hours. The mixture is evaporated in a vacuum, the residue is mixed with a small amount of chloroform and 0.31 g of hexanol are added to the mixture. After stirring for one hour at room temperature, the $CHCl_3$-solution is first extracted with an $NaHCO_3$-solution and then with water. It finally is dried over $Na_2SO_4$. The $CHCl_3$-solution is evaporated, remaining hexanol is distilled off a high vacuum and the residue is further purified chromatographically on silicic acid gel using $CHCl_3$ as eluant.

Yield: 0.5 g (oil)

IR (film): 1750 and 1710 $cm^{-1}$.

Example 49

*8-(4.5-Diphenyl-3-methyl-2-oxo-4-imidazolin-1-yl) caprylic acid benzyl ester*

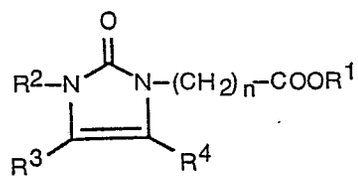
The product is prepared as described in Example 48 from 1.5 g of 8-(4.5-diphenyl-3-methyl-2-oxo-4-imidazolin-1-yl) caprylic acid, 0.55 g of thionyl chloride and 0.37 g of benzyl alcohol.

Yield: 1.4 g (oil)

IR (film): 1740 and 1700 $cm^{-1}$.

**Claims for the Contracting States: BE FR GB NL SE CH IT LU LI**

1. N-substituted $\omega$-(2-oxo-4-imidazolin-1-yl) alcanoic acids and their derivatives having the general formula I



I

wherein

n is an integer ranging from 1 to 10,

$R^1$ is hydrogen, an alkali metal ion or a straight or branched hydrocarbon group having from 1 to 6 carbon atoms or the benzyl group,

$R^2$ is —$(CH_2)_m$—R wherein m is 0, 1 or 2,

R, $R^3$ and $R^4$, which may be identical or different from each other, represent hydrogen (with the exception of R if m is zero), the unsubstituted phenyl group or the phenyl group substituted by one or several equal or differing substituents selected from the group of halogen, $CH_3$—, $CH_3O$—, —$CF_3$, at least one of R, $R^3$ and $R^4$ representing the unsubstituted phenyl or the phenyl group substituted by one or several identical or differing substituents selected from the group of halogen, —$CH_3$, $CH_3O$—, —$CF_3$.

2. [3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] acetic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

3. 7-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] enanthic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

4. 7-(3-ethyl-4.5-diphenyl-2-oxo-4-imidazolin-1-yl)enanthic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

5. 8-(3.4-Diphenyl-2-oxo-4-imidazolin-1-yl)caprylic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

6. 8-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

7. 8-[2-Oxo-4-phenyl-3-(3-trifluoromethyl-phenyl)-4-imidazolin-1-yl] caprylic acid and the pharmaceutically compatible salts and with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

8. 8-[3-(4-Methoxyphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid and the pharma-

ceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

9. 8-[3-(4-Methylphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

10. 8-[3-(4-Fluorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] carpylic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

11. 8-[4-(4-Chlorophenyl)-2-oxo-3-phenyl-4-imidazolin-1-yl] caprylic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

12. 8-(3-Benzyl-2-oxo-4-phenyl-4-imidazolin-1-yl) caprylic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

13. 8-(2-Oxo-3.4.5-triphenyl-4-imidazolin-1-yl) caprylic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

14. 8-[4.5-Bis-(2-fluorophenyl)-3-methyl-2-oxo-4-imidazolin-1-yl] caprylic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

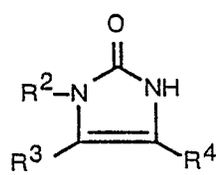
15. 8-(4.5-Diphenyl-3-methyl-2-oxo-5-imidazolin-1-yl) caprylic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

16. 8-(3-Methyl-2-oxo-5-phenyl-4-imidazolin-1-yl) caprylic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

17. 9-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] pelargonic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

18. 11-(3-Ethyl-4.5-diphenyl-2-oxo-4-imidazolin-1-yl) undecanoic acid and the pharmaceutically compatible salts and esters with hydrocarbyl alcohols having 1 to 6 carbon atoms in the hydrocarbyl group or with benzyl alcohol.

19. Process for producing the compounds of formula I according to claims 1 to 18, characterized in that a 4-imidazolin-2-one having the general formula II

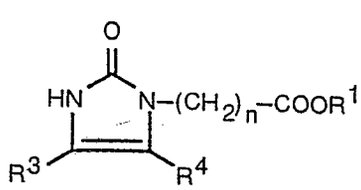



II

wherein $R^2$, $R^3$ and $R^4$ have the same meaning as in formula I, is subjected to reaction with an alkylating agent having the general formula III

$$X—(CH_2)_n—COOR^1 \qquad III$$

wherein n and $R^1$ have the same meaning as in formula I and X is halogen, in an organic solvent with the addition of an additional base, possibly in the presence of an alkali metal iodide as catalyst or an $\omega$-(2-oxo-4-imidazolin-1-yl) alcanoic acid, an ester thereof or an alkali metal salt of formula IV




IV

wherein $R^1$, $R^3$ and $R^4$ have the same meaning as in formula I, are subjected to reaction with an alkylating agent having the general formula V

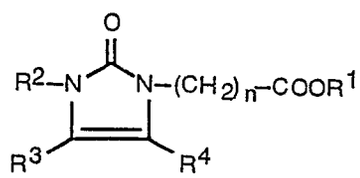
$$Y—(CH_2)_m—R \qquad V$$

wherein m and R have the same meaning as in formula I and Y is a usual group to be split off, and, if desired, converting the resulting ester of the general formula I ($R^1$ = alkyl or benzyl) in manners known per se into the acid of formula I ($R^1$ = H) and converting the same into an alkali salt of formula I ($R^1$ = alkali metal) or converting the resulting acid of the general formula ($R^1$ = H) or an alkali salt of formula I ($R^1$ = alkali metal) in manners known per se into an ester of formula I ($R^1 = C_{1-6}$-alkyl or benzyl).

20. Pharmaceutical preparations containing one or several of the active agents of claims 1 to 18 besides usual pharmaceutical carrier materials.

**Claim for the Contracting State: AT**

Process for producing N-substituted $\omega$-(2-oxo-4-imidazolin-1-yl) alcanoic acids and their derivatives having the general formula I



I

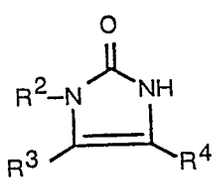
wherein

n is an integer from 1 to 10,

$R^1$ is hydrogen, an alkali metal ion or a straight or branched hydrocarbon group having from 1 to 6 carbon atoms or the benzyl group,

$R^2$ is $—(CH_2)_m—R$ wherein m is 0, 1 or 2,

R, $R^3$ and $R^4$ which may be identical or different from each other, represent hydrogen (with the exception of R if m is zero, the unsubstituted phenyl group or the phenyl group substituted by one or several equal or differing substituents selected from the group of halogen, $CH_3$—, $CH_3O$—, —$CF_3$, at least one of R, $R^3$ and $R^4$ representing the unsubstituted phenyl or the phenyl group substituted by one or several identical or differing substituents selected from the group of halogen, —$CH_3$, $CH_3O$—, —$CF_3$, characterizing in that a 4-imidazolin-2-one having the general formula II

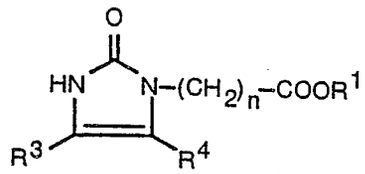


II

wherein $R^2$, $R^3$ and $R^4$ have the same meaning as in formula I, is subjected to reaction with an alkylating agent having the general formula III

$$X—(CH_2)_n—COOR^1 \qquad III$$

wherein n and $R^1$ have the same meaning as in formula I and X is halogen, in an organic solvent with the addition of an additional base, possibly in the presence of an alkali metal iodide as catalyst or an $\omega$-(2-oxo-4-imidazolin-1-yl) alcanoic acid, an ester thereof or an alkali metal salt of formula IV



IV

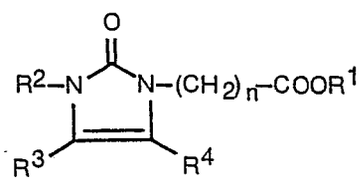
wherein $R^1$, $R^3$ and $R^4$ have the same meaning as in formula I, are subjected to reaction with an alkylating agent having the general formula V

$$Y—(CH_2)_m—R \qquad V$$

wherein m and R have the same meaning as in formula I and Y is a usual group to be split off, and, if desired, converting the resulting ester of the general formula I ($R^1$ = alkyl or benzyl) in manners known per se into the acid of formula I ($R^1$ = H) and converting the same into an alkali salt of formula I ($R^1$ = alkali metal) or converting the resulting acid of the general formula I ($R^1$ = H) or an alkali salt of formula I ($R^1$ = alkali metal) in manners known per se into an ester of formula I ($R^1$ = $C_{1-6}$-alkyl or benzyl).

**Revendications pour les Etats contractants: BE CH FR GB IT LI LU NL SE**

1. Acides $\omega$-(2-oxo-4-imidazolin-1-yl) alcanoiques N-substitués et leurs dérivés possédant la formule générale I



I

dans laquelle
n est un nombre entier de 1 à 10,
$R^1$ est un hydrogène, un ion métal alcalin ou un groupe d'hydrocarbure à chaîne droite ou ramifiée possédant de 1 à 6 atomes de carbone ou le groupe benzoyle,
$R^2$ est —$(CH_2)_m$—R dans lequel m vaut 0, 1 ou 2,
R, $R^3$ et $R^4$ qui peuvent être identiques ou différents l'un de l'autre, représentent un hydrogène (à l'exception de R si m vaut zéro), le groupe phényle non substitué ou le groupe phényle substitué par un ou plusieurs substituants égaux ou différents choisis parmi le groupe composé d'halogène, de $CH_3$—, de $CH_3O$—, de —$CF_3$, un au moins de R, $R^3$ et $R^4$ représentant le groupe phényle non substitué ou le groupe phényle substitué par un ou plusieurs substituants identiques ou différents choisis parmi le groupe composé d'halogène, de —$CH_3$, de $CH_3O$—, de —$CF_3$.

2. Acide [3-(4-chlorophényl)-2-oxo-4-phényl)-2-oxo-4-phényl-4-imidazolin-1-yl]acétique et les sels et esters compatibles d'un point de vue pharmaceutique avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

3. Acide 7-[3-(4-chlorophényl)-2-oxo-4-phényl-4-imidazolin-1-yl]énanthique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

4. Acide 7-(3-éthyl-4,5-diphényl-2-oxo-4-imidazolin-1-yl)énanthique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

5. Acide 8-(3,4-diphényl-2-oxo-4-imidazolin-1-yl)caprylique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

6. Acide 8-[3-(4-chlorophényl)-2-oxo-4-phényl-4-imidazolin-1-yl]caprylique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

7. Acide 8-[2-oxo-4-phényl-3-(3-trifluoro-méthylphényl)-4-imidazolin-1-yl]caprylique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

8. Acide 8-[3-(4-méthoxyphényl)-2-oxo-4-phényl-4-imidazolin-1-yl[caprylique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

9. Acide 8-[3-(4-méthylphényl)-2-oxo-4-phényl-4-imidazolin-1-yl]caprylique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

10. Acide 8-[3-(4-fluorophényl)-2-oxo-4-phényl-4-imidazolin-1-yl]caprylique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

11. Acide 8-[4-(4-chlorophényl)-2-oxo-3-phényl-4-imidazolin-1-yl]caprylique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

12. Acide 8-(3-benzyl-2-oxo-4-phényl-4-imidazolin-1-yl)-caprylique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

13. Acide 8-(2-oxo-3,4,5-triphényl-4-imidazolin-1-yl)-caprylique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

14. Acide 8-[4,5-bis-(2-fluorophényl)-3-méthyl-2-oxo-4-imidazolin-1-yl]caprylique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

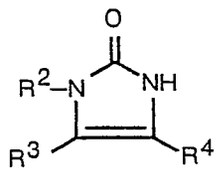
15. Acide 8-(4,5-diphényl-3-méthyl-2-oxo-4-imidazolin-1-yl)caprylique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

16. Acide 8-(3-méthyl-2-oxo-5-phényl-4-imidazolin-1-yl)-caprylique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

17. Acide 9-[3-(4-chlorophényl)-2-oxo-4-phényl-4-imidazolin-1-yl]pélargonique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

18. Acide 11-(3-éthyl-4,5-diphényl-2-oxo-4-imidazolin-1-yl)undécanoique et les sels et esters compatibles pharmaceutiquement avec des alcools hydrocarbyliques possédant 1 à 6 atomes de carbone dans le groupe hydrocarbylique ou avec un alcool benzylique.

19. Procédé de fabrication des composés de formule I selon les revendications 1 à 18, caractérisé en ce qu'une 4-imidazolin-2-one possédant la formule générale II

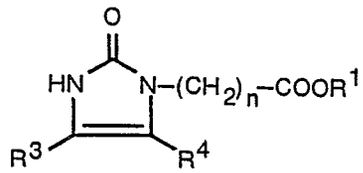



II

dans laquelle $R^2$, $R^3$ et $R^4$ ont la même signification que dans la formule I, est soumise à une réaction avec un agent d'alkylation possédant la formule générale III

$$X—(CH_2)_n—COOR^1 \qquad III$$

dans laquelle n et $R^1$ ont la même signification que dans la formule I et X est un atome d'halogène, dans un solvant organique avec l'addition d'une base supplémentaire, avec la présence possible d'un iodure de métal alcalin comme catalyseur ou un acide $\omega$-(2-oxo-4-imidazolin-1-yl)alcanoique, un ester de celui-ci ou un sel de métal alcalin de formule IV



IV

dans laquelle $R^1$, $R^3$ et $R^4$ ont la même signification que dans la formule I, est sousmis à une réaction avec un agent d'alkylation possédant la formule générale V

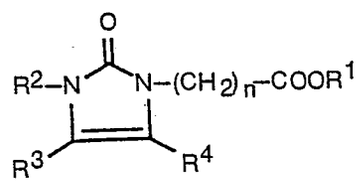
$$Y—(CH_2)_m—R \qquad V$$

dans laquelle m et R ont la même signification que dans la formule I et Y est un groupe usuel à éliminer, et, si on le désire, on convertit l'ester résultant de formule générale I ($R^1$ = alkyle ou benzyle) par des manières connues en soi en l'acide de formule I ($R^1$ = H) et on convertit la même en un sel alcalin de formule I ($R^1$ = métal alcalin) ou on convertit l'acide résultant de formule générale I ($R^1$ = H) ou un sel alcalin de formule I ($R^1$ = métal alcalin) par des manières connues en soi en un ester de formule I ($R^1$ = alkyle en $C_{1-6}$ ou benzyle).

20. Préparations pharmaceutiques contenant une ou plusieurs des substances actives des revendications 1 à 18 en plus des matériaux véhicules pharmaceutiques habituels.

**Revendication pour l'Etat contractant: AT**

1. Procédé de préparation des acides $\omega$-(2-oxo-4-imidazolin-1-yl) alcanoïques N-subtitués, et leurs dérivés, possédant la formule générale I:



I

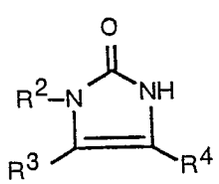
dans laquelle

n est un nombre entier de 1 à 10,

$R^1$ est un hydrogène, un ion métal alcalin ou un groupe d'hydrocarbure à chaîne droite ou ramifiée possédant de 1 à 6 atomes de carbone ou le groupe benzoyle,

$R^2$ est $(CH_2)_m$—R dans lequel m vaut 0, 1 ou 2,

R, $R^3$ et $R^4$ qui peuvent être identiques ou différents l'un de l'autre, représentent un hydrogène (à l'exception de R si m vaut zéro), le groupe phényle non substitué ou le groupe phényle substitué par un ou plusieurs substituants égaux ou différents choisis parmi le groupe composé d'halogène, de $CH_3$—, de $CH_3O$—, de —$CF_3$, un au moins de R, $R^3$ et $R^4$ représentant le groupe phényle non substitué ou le groupe phényle substitué par un ou plusieurs substituants identiques ou différents choisis parmi le groupe composé d'halogène, de —$CH_3$, de $CH_3O$—, de —$CF_3$, caractérisé en ce qu'une 4-imidazolin-2-one possédant la formule générale II:

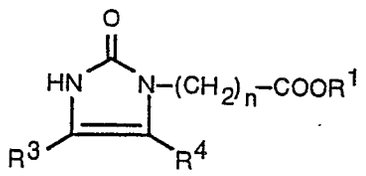


II

dans laquelle $R^2$, $R^3$ et $R^4$ ont la même signification que dans la formule I, est soumise à une réaction avec un agent d'alkylation possédant la formule générale III

$$X—(CH_2)_n—COOR^1 \qquad III$$

dans laquelle n et $R^1$ ont la même signification que dans la formule I et X est un atome d'halogène, dans un solvant organique avec l'addition d'une base supplémentaire, avec la présence possible d'un iodure de métal alcalin comme catalyseur ou un acide $\omega$-(2-oxo-4-imidazolin-1-yl)-alcanoïque, un ester de celui-ci ou un sel de métal alcalin de formule IV



IV

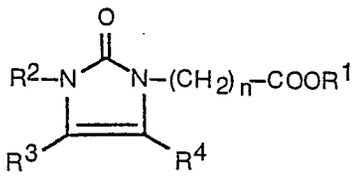
dans laquelle $R^1$, $R^3$ et $R^4$ ont la même signification que dans la formule I, est soumis à une réaction avec un agent d'alkylation possédant la formule générale V

$$Y—(CH_2)_m—R \qquad V$$

dans laquelle m et R ont la même signification que dans la formule I et Y est un groupe usuel à éliminer, et, si on le désire, on convertit l'ester obtenu de formule générale I ($R^1$ = alkyle ou benzyle) par des manières connues en soi en l'acide de formule I ($R^1$ = H) et on convertit le même en un sel alcalin de formule I ($R^1$ = métal alcalin) ou on convertit l'acide résultant de formule générale I ($R^1$ = H) ou un sel alcalin de formule I ($R^1$ = métal alcalin) par des manières connues en soi en un ester de formule I ($R^1$ = alkyle en $C_{1-6}$ ou benzyle).

**Patentansprüche für die Vertragsstaaten: BE CH FR GB IT LI LU NL SE**

1. N-substituierte $\omega$-(2-Oxo-4-imidazolin-1-yl)alkansäuren und ihre Derivate mit der allgemeinein Formel I



I

worin bedeuten:

n eine ganze Zahl von 1 bis 10,

$R^1$ Wasserstoff, ein Alkalimetallion oder eine unverzweigte oder verzweigte Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatom oder die Benzylgruppe,

$R^2$ —$(CH_2)_m$—R, worin m die Zahl 0, 1 oder 2 darstellt,

R, $R^3$ und $R^4$, die identisch oder voneinander verschieden sein können, Wasserstoff (mit Ausnahme von R, wenn m = Null), die unsubstituierte Phenylgruppe oder die Phenylgruppe, die substituiert ist durch einen oder mehrere gleiche oder verschiedene Substituenten, ausgewählt aus der Gruppe Halogen, $CH_3$—, $CH_3O$—, —$CF_3$, wobei mindestens einer der Reste R, $R^3$ und $R^4$ die un substituierte Phenylgruppe oder die durch einen oder mehere identische oder verschiedene Substituenten, ausgewählt aus der Gruppe Halogen, —$CH_3$, $CH_3O$—, —$CF_3$, substituierte Phenylgruppe darstellt.

2. [3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imdazolin-1-yl]-essigsäure und die pharmazeutische verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

3. 7-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl]önanthsäure und die pharmazeutische verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

4. 7-(3-Ethyl-4,5-diphenyl-2-oxo-4-imidazolin-1-yl)önanthsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

5. 8-(3,4-Diphenyl-2-oxo-4-imidazolin-1-yl)caprylsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

6. 8-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl]caprylsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

7. 8-[2-Oxo-4-phenyl-3-(3-trifluoromethylphenyl)-4-imidazolin-1-yl]caprylsäure und die pharmazeutisch verträglischen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

8. 8-[3-(4-Methoxyphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl]-carpylsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

9. 8-[3-(4-Methylphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl]caprylsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

10. 8-[3-(4-Fluorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl]caprylsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

11. 8-[4-(4-Chlorophenyl)-2-oxo-3-phenyl-4-imidazolin-1-yl]caprylsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

12. 8-(3-Benzyl-2-oxo-4-phenyl-4-imidazolin-1-yl)caprylsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

13. 8-(2-Oxo-3,4,5-triphenyl-4-imidazolin-1-yl)caprylsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

14. 8-[4,5-Bis-(2-fluorophenyl)-3-methyl-2-oxo-4-imidazolin-1-yl]caprylsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

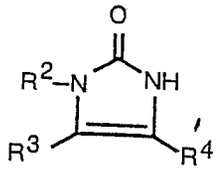
15. 8-(4,5-Diphenyl-3-methyl-2-oxo-4-imidazolin-1-yl)caprylsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

16. 8-(3-Methyl-2-oxo-5-phenyl-4-imidazolin-1-yl)caprylsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzyalkohol.

17. 9-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl]-pelargonsäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

18. 11-(3-Ethyl-4,5-diphenyl-2-oxo-4-imidazolin-1-yl)undecansäure und die pharmazeutisch verträglichen Salze und Ester mit Hydrocarbylalkoholen mit 1 bis 6 Kohlenstoffatomen in der Hydrocarbylgruppe oder mit Benzylalkohol.

19. Verfahren zur Herstellung der Verbindungen der Formel I nach den Ansprüchen 1 bis 18, dadurch gekennzeichnet, daß ein 4-Imidazolin-2-on mit der allgemeinen Formel II

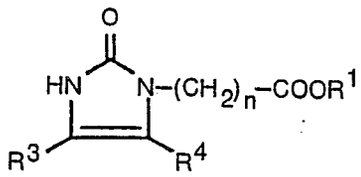



II

worin $R^2$, $R^3$ und $R^4$ die gleiche Bedeutung wie in der Formel I haben, mit einem Alkylierungsmittel mit der allgemeinen Formel III

$$X—(CH_2)_n—COOR^1 \qquad III$$

worin n und $R^1$ die gleiche Bedeutung wei in der Formel I haben und X Halogen bedeutet, in einem organischen Lösungsmittel unter Zugabe einer zusätzlichen Base, möglicherweise in Gegenwart eines Alkalimetalljodids als Katalysator, umgesetzt wird oder eine $\omega$-(2-Oxo-4-imidazolin-1-yl)alkansäure, ein Ester derselben oder ein Alkalimetallsalz der Formel IV



IV

worin $R^1$, $R^3$ und $R^4$ die gleiche Bedeutung wie in der Formel I haben, mit einem Alkylierungsmittel der allgemeinen Formel V

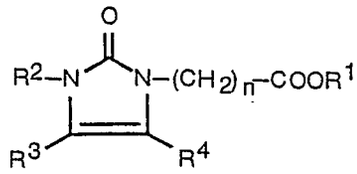
$$Y—(CH_2)_m—R \qquad V$$

worin m und R die gleiche Bedeutung wie in der Formel I haben und Y eine übliche abspaltbare Gruppe bedeutet, umgesetzt wird und gewünschtenfalls der resultierende Ester der allgemeinen Formel I ($R^1$ = Alkyl oder Benzyl) auf an sich bekannte Weise in die Säure der Formel I ($R^1$ = H) umgewandelt wird un dieselbe in ein Alkalisalz der Formel I ($R^1$ = Alkalimetall) umgewandelt wird oder die resultierende Säure der allgemeinen Formel I ($R^1$ = H) oder ein Alkalisalz der Formel I ($R^1$ = Alkalimetall) auf an sich bekannte Weise in einen Ester der Formel I ($R^1 = C_{1-6}$—Alkyl oder Benzyl) überführt wird.

20. Pharmazeutische Präparate, die einen oder mehrere der aktiven Agentien der Ansprüche 1 bis 18 neben üblichen pharmazeutischen Trägermaterialien enthalten.

**Patentanspruch für den Vertragsstaat: AT**

Verfahren zur Herstellung von N-substituierten $\omega$-(2-Oxo-4-imidazolin-1-yl)alkansäure und ihren Derivaten mit der allgemeinen Formel I



I

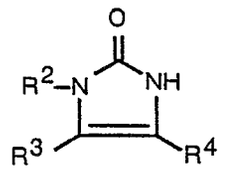
worin bedeuten:

n eine ganze Zahl von 1 bis 10,

$R^1$ Wasserstoff, ein Alkalimetallion oder eine unverzweigte oder verzweigte Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatom oder die Benzylgruppe,

$R^2$ —$(CH_2)_m$—R, worin m die Zahl 0, 1 oder 2 darstellt,

R, $R^3$ und $R^4$, die gleich oder voneinander verschieden sein können, jeweils Wasserstoff (mit Ausnahme von R, wenn m = 0), die unsubstituierte Phenylgruppe oder die Phenylgruppe, die substituiert ist durch einen oder mehr gleiche oder verschiedene Substituenten, ausgewählt aus der Gruppe Halogen, $CH_3$—, $CH_3O$—, —$CF_3$, wobei mindestens einer der Reste R, $R^3$ und $R^4$ die unsubstituierte Phenylgruppe oder die Phenylgruppe, die durch einen oder mehr gleiche oder verschiedene Substituenten, ausgewählt aus der Gruppe Halogen, —$CH_3$, $CH_3O$—, —$CF_3$, substituiert ist, darstellt, dadurch gekennzeichnet, daß ein 4-Imidazolin-2-on der allgemeinen Formel II

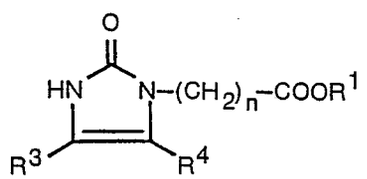


II

worin $R^2$, $R^3$ und $R^4$ die gleichen Bedeutungen wie in der Formel I haben, einem Alkylierungsmittel der allgemeinen Formel III

$$X—(CH_2)_n—COOR^1 \qquad III$$

worin n und $R^1$ die gleichen Bedeutungen wie in der Formel I haben und X Halogen bedeutet, in einem organischen Lösungsmittel unter Zugabe einer zusätzlichen Base, möglicherweise in Gegenwart eines Alkalimetalljodids als Katalysator umgesetzt wird, oder daß eine $\omega$-(2-Oxo-4-imidazolin-1-yl)alkansäure, ein Ester davon oder ein Alkalimetallsalz der Formel IV



IV

worin $R^1$, $R^3$ und $R^4$ die gleichen Bedeutungen wie in der Formel I haben, mit einem Alkylierungsmittel der allgemeinen Formel V

$$Y—(CH_2)_m—R \qquad V$$

worin m und R die gleichen Bedeutungen wie in der Formel I haben und Y eine übliche abspaltbare Gruppe bedeutet, umgesetzt wird und gewünschtenfalls der resultierende Ester der allgemeinen Formel I ($R^1$ = Alkyl oder Benzyl) auf an sich bekannte Weise in die Säure der Formel I ($R^1$ = H) überführt wird und dieselbe in ein Alkalisalz der Formel I ($R^1$ = Alkalimetall) überführt wird oder die resultierende Säure der allgemeinen Formel I ($R^1$ = H) oder ein Alkalisalz der Formel I ($R^1$ = Alkalimetall) auf an sich bekannte Weise in einen Ester der Formel I ($R^1 = C_{1-6}$Alkyl oder Benzyl) überführt wird.