(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 051 829**
A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **81109294.9**

(22) Date of filing: **29.10.81**

(51) Int. Cl.³: **C 07 D 233/70**, A 61 K 31/415

(30) Priority: **11.11.80 DE 3042466**

(43) Date of publication of application: **19.05.82 Bulletin 82/20**

(84) Designated Contracting States: **AT BE CH FR GB IT LI LU NL SE**

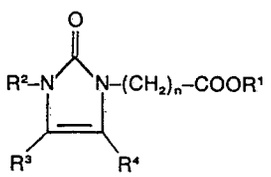
(71) Applicant: **A. Nattermann & Cie. GmbH, Nattermannallee 1, D-5000 Köln 30 (DE)**

(72) Inventor: **Lautenschläger, Hans-Heiner, Dr., Neusser Gasse 50, D-5024 Pulheim-Stommeln (DE)**
Inventor: **Betzing, Hans, Dr., Heidestock 7, D-5014 Kerpen-Horrem (DE)**
Inventor: **Stoll, Brigitte, Am Römerpfad 19, D-5024 Pulheim (DE)**
Inventor: **Probst, Manfred, Dr., Widderstrasse 32, D-5020 Frechen 4 (DE)**

(74) Representative: **Redies, Bernd, Dr. rer. nat. et al, Redies, Redies, Türk & Gille Brucknerstrasse 20, D-4000 Düsseldorf 13 (DE)**

(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.

(57) The present invention refers to new N-substituted ω-(2-oxo-4-imidazolin-1-yl) alcanoic acids as well as salts and esters thereof having the general formula I



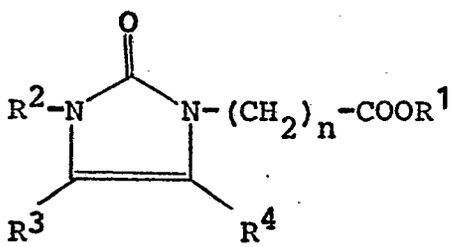
I

process for producing the same and these active agents containing pharmaceutical compounds.

EP 0 051 829 A1

As described in two own prior, non-published German patent applications (P 29 34 746.4 and P 29 5o 478.7), 5- and 4.5-substituted ω-(2-oxo-4-imidazolin-1-yl) alcanoic acids as well as their salts and esters have valuable pharmacological properties such as antithrombotic, antiarteriosklerotic, antiinflammatory and analgetic properties.

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



I

wherein

n is an integer ranging from 1 to 1o, 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 cero),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-, $-CF_3$, 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-, $-CF_3$.

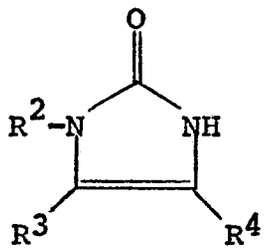
The present invention further refers to processes for producing the same.

The new compounds show interesting pharmacological properties such as antiallergic, antiasthmatic, antithrombotic, antiarteriosklerotic 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 deseases with at the same time favourable gastrointestinal properties. Furthermore, 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 ω-(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 ingredient 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 α-aminoketones or, respectively, from benzoketones with substituted ureas, is subjected to reaction with an alkylating agent of the general formula III

$$X-(CH_2)_n-COOR^1 \qquad \text{III}$$

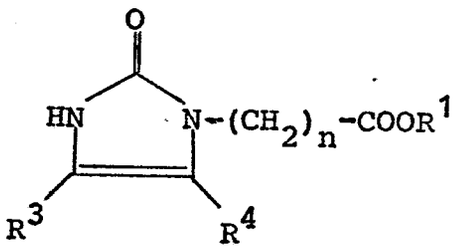
wherein n and R^1 have the same meaning as in formula I and X is a halogen atom, in an organic solvent such as acetone, methyl ethyl ketone, dimethylformamide with the addition of an auxiliary base such as sodium hydride, possibly in the presence of an alkali metal iodide as catalyst.

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 alcohol-ethereal 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 prdocued by subjecting an ω-(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 P 29 5o 478.7, to reaction with an alkylating agent of formula V

$$R^2\text{-}Y \qquad V$$

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 of 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 ω-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, 1o-chlorocaprinic acid, 1o-bromocaprinic acid, 1o-iodocaprinic acid, 11-chloroundecanoic acid, 11-bromoundecanoic acid, 11-iodoundecanoic acid.

Examples for the alkylating agents of formula V are:

Diazomethane, dimethylsulfate, chloromethane, bromomethane, 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 rektally 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 51o 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 (7o eV).

EXAMPLE 1

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

1.5 g of sodium hydride(8o % 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 1oo cc. of anhydrous dimethylformamide (DMF). The mixture is stirred at room temperature and heated to 6o°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 8o°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 17oo 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 NaJ (8o % suspension in mineral oil), 12.2 g of 1-(4-chloro-

phenyl)-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-bromo-caprylic 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 mineral 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-bromocaprylic 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 1o

8-/4-(4-Chlorophenyl)-2-oxo-3-phenyl-4-imidazolin-1-yl7 caprylic acid methyl ester

The product is produced as described in example 1 from 1.o5 g of NaH (8o % suspension in mineral oil), 9.5 g of 5-(4-chlorophenyl)-1-phenyl-4-imidazolin-2-one, 7o cc. of DMF, 8.3 g of 8-bromocaprylic acid methyl ester and 1.o5 g of NaJ.
Eluant in chromatographic purification: hexane/ethyl acetate.

Yield: 8.3 g, Fp. 83 to 84°C
IR (in KBr): 174o and 169o 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 (8o % suspension in mineral oil), 15 g of 1-benzyl-5-phenyl-4-imidazolin-2-one, 12o 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.

Yield: 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-bromoundecanoic 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}.

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 2o 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 3o 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 (1oo%), 187 (29%), 174 (65%),
159 (4.8%), 1o5 (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 8o 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 solution is shaken with ether, the aqueous phase is acidified with dilute hydrochloric acid and the precipitated acid is separated and dried.

Yield: 6.o g, Fp. 214 to 215°C
MS (m/e): 328 (1oo%), 284 (3o%), 269 (2.5%), 214 (14%).

EXAMPLE 19

7-/3-(4-Chlorophenyl-2-oxo-4-phenyl-4-imidazolin-1-yl7 enanthic acid

The prdocut is produced as described in example 18 from 13.5 g of 7-/3-(4-chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl7 enanthic acid ethel ester, 1.28 g of NaOH in 6o cc. of ethanol.

Yield: 1o.o g, Fp. 141°C
MS (m/e): 398 (1oo%), 284 (17%), 27o (27%), 214 (22%).

EXAMPLE 2o

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 6o 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. 11o to 1o1°C
MS (m/e): 392 (1oo%), 264 (11%), 25o (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 8o cc. of methanol. Further purification by chromatography on silicic acid gel using chloroform as eluant.

Yield: 3.6 g, Fp. 11o°C
MS (m/e): 396 (1oo%), 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-3-phenyl-4-imidazolin-1-yl] caprylic acid ethyl ester and o.56 g of NaOH in 3o 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 (1oo%), 284 (14%), 27o (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 2o.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 (1o%), 91 (1oo%).

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 o.64 g of NaOH in 3o 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 (1oo%), 325 (14%), 312 (23%), 18o (11%).

EXAMPLE 3o

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 o.53 g of NaOH in 25 cc. of methanol. Recrystallization from ether/hexane.

Yield: 3.9 g, Fp. 13o to 131°C
MS (m/e): 428 (1oo%), 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-dphenyl-3-methyl-2-oxo-4-imidazolin-1-yl) caprylic acid methyl ester and 2.1 g of NaOH in 1oo cc. of methanol. Further purification by chromatography on silicic acid gel using chloroform as eluant.

Yield: 1o.2 g, Fp. 112 to 114°C
MS (m/e): 392 (1oo%), 263 (1o%), 25o (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 o.4 g of NaOH in 2o 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 (1oo%), 284 (11%), 27o (2o%), 214 (17%).

EXAMPLE 33

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

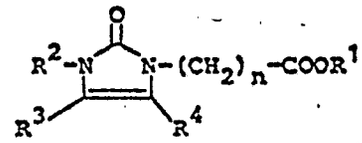
5 g of [3-(4-chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] acetic acid are dissolved in ethanol, the solution is neutralized with the equivalent amount of alcoholic soda lye and the resulting solution is evaporated to dryness in a vacuum. The solid residue is pulverized.

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-C$_6$H$_4$-	C$_6$H$_5$-	H	6	1690, 1570	7-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] enanthic acid
35	Na	C_2H_5	C$_6$H$_5$-	C$_6$H$_5$-	6	1690, 1575	7-(3-Ethyl-4.5-diphenyl-2-oxo-4-imidazolin-1-yl) enanthic acid
36	Na	C$_6$H$_5$-	C$_6$H$_5$-	H	7	1690, 1570	8-(3.4-Diphenyl-2-oxo-4-imidazolin-1-yl) caprylic acid
37	Na	Cl-C$_6$H$_4$-	C$_6$H$_5$-	H	7	1690, 1570	8-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid
38	Na	CF_3-C$_6$H$_4$-	C$_6$H$_5$-	H	7	1695, 1570	8-[2-Oxo-4-phenyl-3-(3-trifluoromethylphenyl)-4-imidazolin-1-yl] caprylic acid
39	Na	CH_3O-C$_6$H$_4$-	C$_6$H$_5$-	H	7	1690, 1570	8-[3-(4-Methoxyphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid
40	Na	CH_3-C$_6$H$_4$-	C$_6$H$_5$-	H	7	1690, 1570	8-[3-(4-Methylphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid
41	Na	F-C$_6$H$_4$-	C$_6$H$_5$-	H	7	1690, 1570	8-[3-(4-Fluorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid
42	Na	C$_6$H$_5$-	Cl-C$_6$H$_4$-	H	7	1685, 1565	8-[4-(4-Chlorophenyl)-2-oxo-3-phenyl-4-imidazolin-1-yl] caprylic acid
43	Na	C$_6$H$_5$-CH_2-	C$_6$H$_5$-	H	7	1690, 1570	8-(3-Benzyl-2-oxo-4-phenyl-4-imidazolin-1-yl) caprylic acid

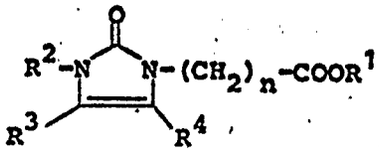


TABLE 1: Continuation

Example No.	R^1	R^2	R^3	R^4	n	IR maxima in KBr in cm^{-1}	corresponding acid
44	Na				7	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	Cl- 		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. o.7 g of thionylchloride are added thereto and the mixture is stirred at about 5o°C for 2 hours. The mixture is evaporated in a vacuum, the residue is mixed with a small amount of chloroform and o.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: o.5 g (oil)
IR (film): 175o and 171o cm^{-1}.

EXAMPLE 49

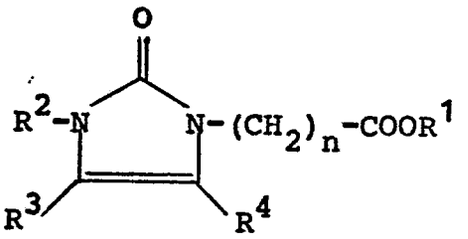
8-(4.5-Diphenyl-3-methyl-2-oxo-4-imidazolin-1-yl) caprylic acid benzyl ester

The product is prepared as described in Example 48 from 1.5 g of 8-(4.5-diphenyl-3-methyl-2-oxo-4-midazolin-1-yl) caprylic acid, o.55g of thionyl chloride and o.37 g of benzyl alcohol.

Yield: 1.4 g (oil)
IR (film): 174o and 17oo cm^{-1}.

PATENT CLAIMS:

1. N-substituted ω-(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 cero, 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 thereof.

3. 7-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] enanthic acid and the pharmaceutically compatible salts and esters thereof.

4. 7-(3-ethyl-4.5-diphenyl-2-oxo-4-imidazolin-1-yl) enanthic acid and the pharmaceutically compatible salts and esters thereof.

5. 8-(3.4-Diphenyl-2-oxo-4-imidazolin-1-yl) caprylic acid and the pharmaceutically compatible salts and esters thereof.

6. 8-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid and the pharmaceutically compatible salts and esters thereof.

7. 8-[2-Oxo-4-phenyl-3-(3-trifluoromethyl-phenyl)-4-imidazolin-1-yl] caprylic acid and the pharmaceutically compatible salts and esters thereof.

8. 8-[3-(4-Methoxyphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid and the pharmaceutically compatible salts and esters thereof.

9. 8-[3-(4-Methylphenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid and the pharmaceutically compatible salts and esters thereof.

10. 8-[3-(4-Fluorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] caprylic acid und the pharmaceutically compatible salts and esters thereof.

11. 8-[4-(4-Chlorophenyl)-2-oxo-3-phenyl-4-imidazolin-1-yl] caprylic acid and the pharmaceutically compatible salts and esters thereof.

12. 8-(3-Benzyl-2-oxo-4-phenyl-4-imidazolin-1-yl) caprylic acid and the pharmaceutically compatible salts and esters thereof.

13. 8-(2-Oxo-3.4.5-triphenyl-4-imidazolin-1-yl)caprylic acid and the pharmaceutically compatible salts and esters thereof.

14. 8-[4.5-Bis-(2-fluorophenyl)-3-methyl-2-oxo-4-imidazolin-1-yl] caprylic acid and the pharmaceutically compatible salts and esters thereof.

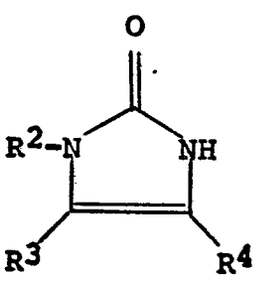
15. 8-(4.5-Diphenyl-3-methyl-2-oxo-4-imidazolin-1-yl) caprylic acid and the pharmaceutically compatible salts and esters thereof.

16. 8-(3-Methyl-2-oxo-5-phenyl-4-imidazolin-1-yl) caprylic acid und the pharmaceutically compatible salts and esters thereof.

17. 9-[3-(4-Chlorophenyl)-2-oxo-4-phenyl-4-imidazolin-1-yl] pelargonic acid and the pharmaceutically compatible salts and esters thereof.

18. 11-(3-Ethyl-4.5-diphenyl-2-oxo-4-imidazolin-1-yl) undecanoic acid and the pharmaceutically compatible salts and esters thereof.

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

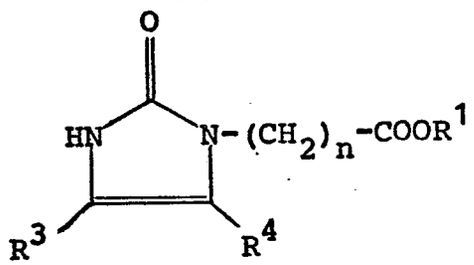


II

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 ω-(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).

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

European Patent Office

EUROPEAN SEARCH REPORT

Application number
0051829
EP 81109294.9

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
P	US - A - 4 238 618 (SCHOLZ) (09-12-1980) * Claim 1 * & DE-A1-2 713 431 (28-09-1978) ----	1,19

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 233/70
A 61 K 31/415

TECHNICAL FIELDS SEARCHED (Int. Cl.³)

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application,
L: citation for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	13-02-1982	BRUS

EPO Form 1503.1 06.78