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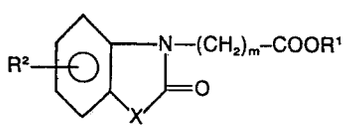
(54) Omega-(2-oxo-benzazolinyl)-alkanoic acid derivatives, process for producing the same and pharmaceutical compounds containing the same.

(57) The present invention refers to new ω-(2-oxo-benzazolinyl)-alkanoic acids as well as salts and esters thereof having the general formula I



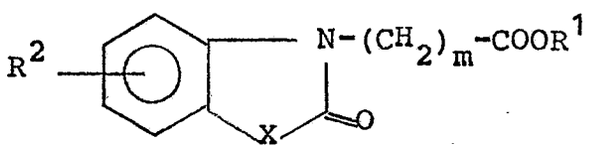
I,

process for producing the same and pharmaceutical preparations containing the same.

EP 0 051 827 A1

As described in three own prior, non-published German patent applications P 29 34 746.4, P 29 50 478.7 and P 29 35 902.2, ω-(2-oxo-4-imidazolin-1-yl)-alkanoic acids and ω-(2-oxo-4-oxazolin-3-yl)-alkanoic acids as well as salts and esters thereof have valuable pharmacological properties such as antithrombotic, antiarteriosklerotic, antiinflammatory and analgetic properties. They furthermore are useful in combination with antikoagulantia, in particular with heparine and heparinates.

It has now been found that the ω-(2-oxo-benzazolinyl)-alkanoic acids according to the present invention as well as their salts and esters having the general formula I represent valuable active agents for drugs. Thus, the present invention refers to the new compounds of the general formula I



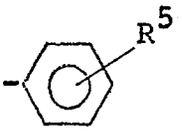
I

wherein

m is an integer from 6 to 10, preferably 6 to 8,

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

X is an oxygen atom, a sulphur atom or a NR^3-group, R^3 being H, $-(CH_2)_n-R^4$ with n being an integer from 0 to 7 and R^4 being a methyl group, the unsubstituted phenyl group or the substituted

phenyl group  and X being preferably the NR^3-group,

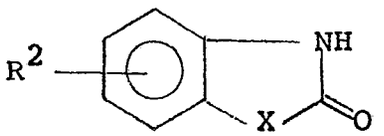
R^2 and R^5 which may be identical or different from each other represent hydrogen, halogen, the methyl, the trifluoromethy, the methoxy, the nitro or an amino group.

The present invention furthermore refers to process for producing the same and to pharmaceutical compounds comprising the same.

The new compounds show interesting pharmacological properties such as antiallergic, antiasthmatic, antiarteriosklerotic and antiinflammatory properties. They furthermore have an excellent compatibility by the stomach and, therefor, may be in particularly used for the treatment of allergic, asthmatic, thrombotic and arteriosklerotic diseases with at the same time favourable gastrointestinal properties. The compounds of the general formula I have a low toxicity. They therefor are important for the treatment both of human beings and such diseases in human beings.

The new ω-(2-oxo-benzazolinyl)-alkanoic acid derivatives may be used in the form of the free acids or as salts with pharmacologically compatible bases or in the form of their esters as active ingredients in drugs together with usual carrier materials or diluents. The compound are used in daily dosages ranging from 0.1 to 100 mg./kg.

The compounds according to the present invention are produced in manners known per se in that a benzazolin-2-one of the general formula II



II

wherein R^2 and X have the same meaning as in formula I, is reacted with an alkylating agent of the general formula III

$$Z-(CH_2)_m-COOR^1 \qquad III$$

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

Thereafter, the esters of formula I wherein R^1 is C_{1-6}-alkyl may be converted in manners known per se into an alkali metal salt of the general formula I wherein R^1 is an alkali metal, for instance by reaction with an alkali metal hydroxide in aqueous, alcoholic or alcoholic-ethereal solvents and into an acid of the general formula I with R^1 being hydrogen by subsequent addition of a mineral acid. Vice versa, an acid of the general formula I with R^1 being hydrogen and the alkali metal salts of the general formula I with R^1 being an alkali metal may be converted into an ester

of the general formula I with R^1 being C_{1-6} alkyl in manners know per se, for instance by subjecting an acid of the general formula I with R^1 being hydrogen to reaction with a solution of hydrochloric acid in the respective alcohol or by subjecting an acid or a salt thereof of the general formula I with R^1 being hydrogen or, respectively, an alkali metal ion, to reaction with thionylchloride and subjecting the resulting acid chloride to reaction with the respective alcohol.

The products of formula I wherein X is NR^3, R^3 being the $-(CH_2)_n-R^4$-group, R^4 having the same meaning as in formula I, may also be produced in that an ω-(2-oxo-benzazolinyl)-alkanoic acid or their derivative of formula I wherein X is NR^3 and R^3 is hydrogen, to reaction with an alkylating agent of formula IV

$$Y-(CH_2)_n-R^4 \qquad \text{IV}$$

wherein Y is halogen and n and R^4 have the same meaning as in formula I. Y may also be another usual and favourable group to be split off, for instance the azide group $-N_2$ or the radical of a sulphuric acid ester in particular of a sulphuric acid lower alkyl ester.

The compounds of formula I, wherein R^2 is NH_2, may be also be produced in usual manners from the corresponding compounds of formula I wherein R^2 is NO_2, by reduction, for instance with hydrogen, an alkali metal dithionite or other reducing agents.

Starting materials of formula II may for instance be: benzoxazolin-2-one, benzthioazolin-2-one, benzimidazolin-2-one and their derivatives substituted in 4-, 5-, 6- and 7-position by F, Cl, Br, CH_3, CF_3, CH_3O, NO_2 and NH_2 as well as the corresponding benzimidazolin-2-ones further substituted in the 1-position by R^3.

R^3 preferably represent straight hydrocarbon groups having from 1 to 8 carbon atoms (n = 0 to 7, R^4 = methyl), the unsubstituted phenyl group and the phenyl groups substituted in the 2-, 3- or 4-position by F, Cl, Br, CH_3, CF_3, CH_3O, NO_2 and NH_2 as well as the corresponding aralkyl groups for instance the unsubstituted benzyl- and phenylethyl group and such groups substituted as herein above given.

Alkylating agents of formula III may be the following ω-halogenoalkanoic acids:
the 7-chloro, the 7-bromo and the 7-iodoenanthic acid, the 8-chloro-, the 8-bromo- and the 8-iodocaprylic acid, the 9-chloro-, the 9-bromo- and the 9-iodopelargonic acid, the 10-chloro-, the 10-bromo- and the 10-iodocaprinic acid, the 11-chloro-, the 11-bromo- and the 11-iodoundecanoic acid.

Suitable alkylating agents according to formula IV are for instance:
diazomethane, dimethylsulfate, chloro-, bromo- and iodomethane,chloro-, bromo- and iodoethane, 3-chloro-, 3-bromo- and 3-iodopropane, 4-chloro-, 4-bromo- and 4-iodobutane, 5-chloro-, 5-bromo- and 5-iodopentane, 6-chloro-, 6-bromo- and 6-iodohexane, 7-chloro-, 7-bromo- and 7-iodoheptane, 8-chloro-, 8-bromo- and 8-iodooctane, benzylchloride, benzylbromide, benzyliodide

as well as the corresponding benzylhalides substituted by F, Cl, Br, CH_3, CF_3, CH_3O, NO_2 and/or NH_2, phenylethylchloride, phenylethylbromide, phenylethyliodide as well as the corresponding phenylethylhalides substituted by F, Cl, Br, CH_3, CF_3, CH_3O, NO_2 and/or NH_2. The unsubstituted and correspondingly in the phenyl group substituted 3-phenylpropyl-, 4-phenylbutyl-, 5-phenylpentyl-, 6-phenylhexyl-, 7-phenylheptyl- and 8-phenyloctylhalides.

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

The new compounds of formula I may be administered for instance orally, by injection or rectally as pharamceutical products which may be solid or liquid, in the form of suspensions or solutions. Such products are for instance tablets, powders, capsules, granules, ampoules, syrups and suppositories.

The production of the compounds according to the present invention is further illustrated by the follow examples.

The reported melting points have been measured on a Büchi 510 melting point apparatus, are given in ^oC and are not corrected. The reaction time is given in hours (h). The IR-Spektra have been registered with a Perkin-Elmer 257 and the mass spektra with a Varian MAT-311-A (70 eV).

EXAMPLE 1

7-(2-Oxo-benzoxazolin-3-yl)-enanthic acid ethyl ester

3.0 g. of sodium hydride (80 % suspension in mineral oil) are washed with n-pentane and added to a mixture of 13.5 g. of benzoxazolin-2-one and 200 cc. of anhydrous dimethylformamide (DMF). The mixture is stirred at room temperature and towards end of hydrogen formation at 60°C. Thereafter, 19.3 g. of 7-chloroenanthic acid ethyl ester and 3.0 g. of sodium iodide (NaJ) are added thereto and the mixture is heated to 80°C. for 8 hours. After cooling to room temperature, the mixture is diluted with water and extracted with chloroform ($CHCl_3$). The extract are consequetively washed with water, with 5 % $NaHCO_3$-solution and another time with water. The extract is dried over Na_2SO_4, the solvent is distilled off in a vacuum and the residue is further purified chromatographically on silicic acid using chloroform as eluant.

Yield: 23.4 g. (oil)

IR (film): 1780 and 1735 cm^{-1}.

EXAMPLE 2

8-(2-Oxo-benzoxazolin-3-yl)-caprylic acid methyl ester

The product is produced as described in example 1 from 3.0 g. of NaH (80 % suspension in mineral oil), 13.5 g. of benzoxazolin-2-one, 200 cc. of DMF, 23.7 g. of 8-bromo-caprylic acid ethyl ester and 3.0 g. of NaJ.

Eluant in chromatographic purification: hexane/ethyl acetate.

Yield: 20 g. Fp.: 47°C.

IR (in KBr): 1780 and 1740 cm^{-1}.

EXAMPLE 3

8-(5-Nitro-2-oxo-benzoxazolin-3-yl)-caprylic acid methyl ester

The product is produced as described in example 1 from 6 g. of NaH (80 % suspension in mineral oil), 36 g. of 5-nitrobenzoxazolin-2-one (produced in usual manner by reacting 2-amino-4-nitrophenol-hydrochloride with phosgene), 400 cc. of DMF, 47.4 g. of 8-bromo caprylic acid methyl ester and 6 g. of NaJ.

Yield: 25 g. Fp.: 50 to 51°C.
IR (film): 1780 and 1730 cm^{-1}.

EXAMPLE 4

8-(5-Amino-2-oxo-benzoxazolin-3-yl)-caprylic acid methyl ester

6.7 g. of 8-(5-Nitro-2-oxo-benzoxazolin-3-yl)-caprylic acid methyl ester are dissolved in 100 cc. of methanol and the solution is heated to boiling. 20 cc. of water are added to the solution and within 1 hour 13.9 g. of sodium dithionite are added and the mixture is boiled so long until the starting yellow solution is decolourized. Thereafter, the solution is evaporated in a vacuum, the residue is stirred with dilute soda lye and the solid crude product as filtered off with suction. The crude product is washed with water, dried and further purified chromatographically on silicic acid using hexane/ethyl acetate as eluant.

Yield: 0.5 g. Fp.: 88 to 90°C.
IR (in KBr): 1755 (broad) with shoulders 1740 cm^{-1}.

EXAMPLE 5

8-(6-Methyl-2-oxo-benzoxazolin-3-yl)-caprylic acid methyl ester

The product is produced as described in example 1 from 3.6 g. of NaH (of 80 % suspension in mineral oil), 19.9 g. of 6-methylbenzoxazolin-2-one (produced in usual manners by subjecting 2-amino-5-methyl-phenol-hydrochloride to reaction with phosgene), 240 cc. of DMF, 28.4 g. of 8-bromo caprylic acid methyl ester and 3.6 g. NaJ.

Yield: 31.1 g. (oil)
IR (film): 1780 and 1740 cm^{-1}.

EXAMPLE 6

8-(5-Chloro-2-oxo-benzoxazolin-3-yl)-caprylic acid methyl ester

The product is produced as described in example 1 from 3 g. of NaH (80 % suspension in mineral oil), 17 g. of 5-chloro-benzoxazolin-2-one (produced in usual manners by subjecting 2-amino-4-chloro-phenol-hydrochloride to reaction with phosgene), 200 cc. of DMF, 23.7 g. of 8-bromo-caprylic acid methyl ester and 3 g. of NaJ.

Yield: 24 g. Fp.: 54 to 56°C.
IR (in KBr): 1780 and 1735 cm^{-1}.

EXAMPLE 7

8-(2-Oxo-benzthiazolin-3-yl)-caprylic acid methyl ester

The product is produced as described in example 1 from 3 g. of NaH (80 % suspension in mineral oil), 15.1 g. of benzthiazolin-2-one, 200 cc. of DMF, 23.7 g. of 8-bromo-caprylic acid methyl ester and 3 g. NaJ.

Yield: 26.6 g. (oil)
IR (film): 1740 and 1685 cm^{-1}.

EXAMPLE 8

8-(2-Oxo-benzimidazolin-1-yl)-caprylic acid methyl ester

The product is produced as described in example 1 from 2.8 g. of NaH (80 % suspension in mineral oil), 25 g. of benzimidazolin-2-one, 180 cc. of DMF, 22.1 g. of 8-bromocaprylic acid methyl ester and 2.8 g. of NaJ. Eluant in chromatographic purification: chloroform/methanol.

Yield: 12 g. Fp.: 88°C.
IR (in KBr): 1740 and 1700 cm^{-1}.

EXAMPLE 9

8-(3-Octyl-2-oxo-benzimidazolin-1-yl)-caprylic acid methyl ester

The product is produced as described in example 1 from 0.9 g. of NaH (80 % suspension in mineral oil), 7.5 g. of 1-octylbenzimidazolin-2-one (produced by alkylation from benzimidazolin-2-one with bromooctane according to example 8), 100 cc. of DMF, 7.1 g. of 8-bromocaprylic acid methyl ester and 0.9 g. of NaJ. Eluant in chromatographic purification: hexane/ethylacetate.

Yield: 6.4 g. (oil)
IR (film): 1740 and 1705 cm^{-1}.

EXAMPLE 10

7-(2-Oxo-3-phenyl-benzimidazolin-1-yl)-enanthic acid ethyl ester

The product is produced as described in example 1 from 1.9 g. of NaH (80 % suspension in mineral oil), 13.2 g. of 1-phenylbenzimidazolin-2-one (produced in usual

manner by subjecting N-phenyl-o-phenylendiamine to reaction with phosgene), 120 cc. of DMF, 12.1 g. of 7-chloroenanthic acid ethyl ester and 1.9 g. of NaJ. Eluant in chromatographic purification: hexane/ethylacetate.

Yield: 16.5 g. (oil)
IR (film): 1740 (shoulder) and 1720 cm^{-1}.

EXAMPLE 11

8-(2-Oxo-3-phenyl-benzimidazolin-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), 16.8 g. of 1-phenylbenzimidazolin-2-one, 160 cc. of DMF, 19.0 g. of 8-bromocaprylic acid methyl ester and 2.4 g. of NaJ. Eluant in chromatographic purification: hexane/ethylacetate.

Yield: 20 g. Fp.: 43 to 45°C.
IR (film): 1740 (shoulder) and 1715 cm^{-1}.

EXAMPLE 12

11-(2-Oxo-3-phenyl-benzimidazolin-1-yl)-undecanoic acid methyl ester

The product is produced as described in example 1 from 1.3 g. of NaH (80 % suspension in mineral oil), 10 g. of 1-phenylbenzimidazolin-2-one, 200 cc. of DMF, 13.3 g. of 11-bromoundecanoic acid methyl ester and 1.3 g. of NaJ. Eluant in chromatographic purification: hexane/ethylacetate.

Yield: 15.8 g. Fp.: 74°C.
IR (in KBr): 1735 and 1705 cm^{-1}.

EXAMPLE 13

7-/3-(3-Chlorophenyl)-2-oxo-benzimidazolin-1-yl/-enanthic ethyl ester

The product is produced as described in example 1 from 1.2 g. of NaH (80 % suspension in mineral oil), 9.8 g. of 1-(3-chlorophenyl)-benzimidazolin-2-one (produced in usual manners by subjecting N-(3-chlorophenyl)-o-phenylene diamine to reaction of phosgene), 80 cc. of DMF, 7.7 g. of 7-chloroenanthic acid ethyl ester and 1.2 g. of NaJ.

Yield: 9.1 g. (oil)
IR (film): 1725 1725 cm^{-1} (broad).

EXAMPLE 14

8-/3-(3-Chlorophenyl)-2-oxo-benzimidazolin-1-yl/-caprylic acid methyl ester

The product is produces as described in example 1 from 1.2 g. of NaH (80 % suspension in mineral oil), 9.8 g. of 1-(3-chlorophenyl)-benzimidazolin-2-one, 80 cc. of DMF, 9.5 g. of 8-bromocaprylic acid methyl ester and 1.2 g. of NaJ.

Yield: 9.5 g. Fp.:40 to 42°C.
IR (film): 1725 cm^{-1} (broad).

EXAMPLE 15

8-(3-Benzyl-2-oxo-benzimidazolin-1-yl)-caprylic acid methyl ester

The product is produced as described in example 1 from 0.75 g. of NaH (80 % suspension in mineral oil), 5.6 g. of 1-benzylbenzimidazolin-2-one (produced in usual manners by alkylation of benzimidazolin-2-one with benzylchloride

according to example 8), 50 cc. of DMF, 5.9 g. of 8-bromocaprylic acid methyl ester and 0.75 g. of NaJ.

Yield: 4.1 g. (oil)
IR (film): 1740 and 1710 cm^{-1}.

EXAMPLE 16

8-[3-(2-Chlorobenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid methyl ester

The product is produced as described in example 1 from 0.72 g. of NaH (80 % suspension in mineral oil), 7 g. of 8-(2-oxobenzimidazolin-1-yl)-caprylic acid methyl ester, 100 cc. of DMF, 3.9 g. of 2-chlorobenzylchloride and 0.72 g. of NaJ. Eluant for chromatographic purification: hexane/ethylacetate.

Yirld: 6.4 g. (oil)
IR (film): 1735 and 1700 cm^{-1}

EXAMPLE 17

8-[3-(4-Chlorobenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid methyl ester

The product is produced as described in example 1 from 0.72 g. of NaH (80 % suspension in mineral oil), 7 g. of 8-(2-oxo-benzimidazolin-1-yl)-caprylic acid methyl ester, 100 cc. of DMF, 3.9 g. of 4-chlorobenzylchloride and 0.72 g. of NaJ. Eluant in chromatographic purification: hexane/ethylacetate.

Yield: 4.8 g. Fp.: 88°C.
IR (in KBr): 1735 and 1700 cm^{-1}.

EXAMPLE 18

8-[3-(4-Fluorobenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid methyl ester

The product is produced as described in example 1 from 0.72 g. of NaH (80 % suspension in mineral oil), 7 g. of 8-(2-oxo-benzimidazolin-1-yl)-caprylic acid methyl ester, 100 cc. of DMF, 3.5 g. of 4-fluorobenzylchloride and 0.72 g. of NaJ. Eluant for chromatographic purification: hexane/ethylacetate.

Yield: 7.5 g. Fp.: 48°C.
IR (film): 1735 and 1700 cm^{-1}.

EXAMPLE 19

8-[3-(4-Methylbenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid methyl ester

The product is produced as described in example 1 from 0.72 g of NaH (80 % suspension in mineral oil), 7 g. of 8-(2-oxo-benzimidazolin-1-yl)-caprylic acid methyl ester, 100 cc. of DMF, 3.4 g. of 4-methylbenzylchloride and 0.72 g. of NaJ. Eluant for chromatographic purification: hexane/ethylacetate.

Yield: 7.3 g. Fp.: 70°C.
IR (in KBr): 1740 and 1705 cm^{-1}.

EXAMPLE 20

8-[2-Oxo-3-(3-trifluoromethylbenzyl)-benzimidazolin-1-yl]-caprylic acid methyl ester

The product is produced as described in example 1 from 0.72 g. of NaH (80 % suspension in mineral oil), 7 g. of

8-(2-oxo-benzimidazolin-1-yl)-caprylic acid methyl ester, 100 cc. of DMF, 4.7 g. of 3-trifluoromethylbenzylchloride and 0.72 g. of NaJ. Eluant for chromatographic purification: hexane/ethylacetate.

Yield: 8.4 g. (oil)
IR (film): 1740 and 1710 cm^{-1}.

EXAMPLE 21

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

The product is produced as described in example 1 from 0.72 g. of NaH (80 % suspension in mineral oil), 7 g. of 8-(2-oxo-benzimidazolin-1-yl)-caprylic acid methyl ester, 100 cc. of DMF, 3.8 g. of 4-methoxybenzylchloride and 0.72 g. of NaJ. Eluant for chromatographic purification: hexane/ethylacetate.

Yield: 7.2 g. (oil)
IR (film): 1740 and 1710 cm^{-1}.

EXAMPLE 22

7-(2-Oxo-benzoxazolin-3-yl)-enanthic acid

18.4 g. of 7-(2-Oxobenzoxazolin-3-yl)-enanthic acid ethyl ester are dissolved in 60 cc. of methanol. 2.52 g. of sodium hydroxide are dissolved in methanol and added to the above solution. The mixture is stirred at room temperature for 24 hours, the solvent is distilled off and the residue is dissolved in water. The aqueous solution is shaken several times with chloroform, the chloroform solution is discarded. The aqueous phase is acidified with dilute hydrochloric acid and extracted with chloroform.

The chloroform solution is washed with water and dried over Na_2SO_4. The solvent is distilled off and the residue is purified chromatographically on silicic acid gel using hexane/ethylacetate as eluant.

Yield: 4.75 g. Fp.: 89°C.

MS /m/e/ : 263 (93 %), 148 (80 %), 135 (100 %).

EXAMPLE 23

8-(2-Oxo-benzoxazolin-3-yl)-caprylic acid

The product is produced as described in example 22 from 14.5 g. of 8-(2-oxo-benzoxazolin-3-yl)-caprylic acid methyl ester and 2.4 g. of NaOH. Eluant in chromatographic purification: chloroform.

Yield: 7.8 g. Fp.: 81 to 82°C.

MS /m/e/ : 277 (100 %), 148 (80 %), 135 (99 %).

EXAMPLE 24

8-(5-Nitro-2-oxo-benzoxazolin-3-yl)-caprylic acid

The product is produced as described in example 22 from 18.3 g. of 8-(5-nitro-2-oxo-benzoxazolin-3-yl)-caprylic acid methyl ester and 2.4 g. of NaOH. Eluant in chromatographic purification: chloroform.

Yield: 0.2 g. Fp.: 115°C.

MS /m/e/ : 322 (64 %), 263 (24 %), 193 (44 %), 180 (18 %), 98 (100 %).

EXAMPLE 25

8-(6-Methyl-2-oxo-benzoxazolin-3-yl)-caprylic acid

The product is produced as described in example 22 from

31 g. of 8-(6-methyl-2-oxo-benzoxazolin-3-yl)-caprylic acid methyl ester and 4.4 g. of NaOH. Eluant in chromatographic purification: chloroform.

Yield: 11.9 g. Fp.: 90 to 91°C.

MS /m/e/ : 291 (100 %), 162 (56 %), 149 (89 %).

EXAMPLE 26

8-(5-Chloro-2-oxo-benzoxazolin-3-yl)-caprylic acid

The product is produced as described in example 22 from 10.9 g. of 8-(5-chloro-2-oxo-benzoxazolin-3-yl)-caprylic acid methyl ester and 1.6 g. of NaOH. Eluant in chromatographic purification: chloroform.

Yield: 4.8 g. Fp.: 98 to 99°C.

MS /m/e/ : 311 (78 %), 182 (55 %), 169 (83 %).

EXAMPLE 27

8-(2-Oxo-benzthiazolin-3-yl)-caprylic acid

The product is produced as described in example 22 from 20 g. of 8-(2-oxo-benzthiazolin-3-yl)-caprylic acid methyl ester and 2.6 g. of NaOH.

Yield: 7.8 g. Fp.: 86°C.

MS /m/e/ : 293 (100 %), 165 (36 %), 151 (96 %).

EXAMPLE 28

8-(2-Oxo-benzimidazolin-1-yl)-caprylic acid

The product is produced as described in example 22 from 10 g. of 8-(2-oxo-benzimidazolin-1-yl)-caprylic acid methyl ester and 1.44 g. of NaOH.

Yield: 5.1 g. Fp.: 110°C.

MS /m/e/ : 276 (85 %), 147 (100 %), 134 (85 %).

EXAMPLE 29

8-(3-Octyl-2-oxo-benzimidazolin-1-yl)-caprylic acid

The product is produced as described in example 22 from 6.2 g. of 8-(3-octyl-2-oxo-benzimidazolin-1-yl)-caprylic acid methyl ester and 0.6 g. of NaOH.

Yield: 0.53 g. Fp.:85°C.

MS /m/e/ : 388 (100 %), 329 (14 %), 147 (17 %).

EXAMPLE 30

7-(2-Oxo-3-phenyl-benzimidazolin-1-yl)-enanthic acid

The product is produced as described in example 22 from 16 g. of 7-(2-oxo-3-phenyl-benzimidazolin-1-yl)-enanthic acid ethyl ester and 2.1 g. of NaOH.

Yield: 12.6 g. Fp.: 111 to 112°C.

MS /m/e/ : 338 (100 %), 223 (49 %), 210 (48 %).

EXAMPLE 31

8-(2-Oxo-3-phenyl-benzimidazolin-1-yl)-caprylic acid

The product is produced as described in example 22 from 15 g. of 8-(2-oxo-3-phenyl-benzimidazolin-1-yl)-caprylic acid methyl ester and 1.64 g. of NaOH.

Yield: 12.6 g. Fp.: 115 to 116°C.

MS /m/e/ : 353 (100 %), 223 (35 %), 210 (36 %).

EXAMPLE 32

11-(2-Oxo-3-phenyl-benzimidazolin-1-yl)-undecanoic acid

The product is produced as described in example 22 from

11 g. of 11-(2-oxo-3-phenyl-benzimidazolin-1-yl)-undecanoic acid methyl ester and 1.2 g. of NaOH.

Yield: 10.8 g. Fp.: 120°C.
MS /m/e/ : 394 (100 %), 223 (32 %), 210 (34 %).

EXAMPLE 33

7-/3-(3-Chlorophenyl)-2-oxo-benzimidazolin-1-yl/-enanthic acid

The product is produces as described in example 22 from 9 g. of 7-/3-(3-chlorophenyl)-2-oxo-benzimidazolin-1-yl/-enanthic acid ethyl ester and 1.76 g. of NaOH.

Yield: 5.4 g. Fp.: 101 to 103°C.
MS /m/e/ : 372 (100 %), 313 (41 %), 257 (65 %), 244 (61 %)

EXAMPLE 34

8-/3-(3-Chlorophenyl)-2-oxo-benzimidazolin-1-yl/-caprylic acid

The product is produced as described in example 22 from 9.3 g. of 8-/3-(3-chlorophenyl)-2-oxo-benzimidazolin-1-yl/-caprylic acid methyl ester and 2.56 g. of NaOH.

Yield: 4.2 g. Fp.: 98 - 99°C.
MS /m/e/ : 386 (100 %), 327 (13 %), 257 (40 %), 244 (38 %).

EXAMPLE 35

8-(3-Benzyl-2-oxo-benzimidazolin-1-yl)-caprylic acid

The product is produced as described in example 22 from 4.3 g. of 8-(3-benzyl-2-oxo-benzimidazolin-1-yl)-caprylic

acid methyl ester and 0.5 g. of sodium hydroxide.

Yield: 2.7 g. Fp.: 100 to 101°C.

MS /m/e/ : 366 (72 %), 237 (17 %), 224 (28 %), 91 (100 %).

EXAMPLE 36

8-/3-(2-Chlorobenzyl)-2-oxo-benzimidazolin-1-yl/-caprylic acid

The product is produced as described in example 22 from 6.4 g. of 8-/3-(2-chlorobenzyl)-2-oxo-benzimidazolin-1-yl/-caprylic acid methyl ester and 1.2 g. of sodium hydroxide.

Yield: 5.8 g. Fp.: 118°C.

MS /m/e/ : 400 (64 %), 365 (100 %), 271 (10 %), 258 (9 %), 125 (68 %).

EXAMPLE 37

8-/3-(4-Chlorobenzyl)-2-oxo-benzimidazolin-1-yl/-caprylic acid

The product is produced as described in example 22 from 4 g. 8-/3-(4-chlorobenzyl)-2-oxo-benzimidazolin-1-yl/-caprylic acid methyl ester and 0.8 g. of NaOH.

Yield: 3.5 g. Fp.: 123°C.

MS /m/e/ : 400 (100 %), 271 (8 %), 258 (13 %), 125 (91 %).

EXAMPLE 38

8-/3-(4-Fluorobenzyl)-2-oxo-benzimidazolin-1-yl/-caprylic acid

The product is produced as described in example 22 from 7.5 g. of 8-/3-(4-fluorobenzyl)-2-oxo-benzimidazolin-1-yl/-caprylic acid methyl ester and 1.5 g. of NaOH.

Yield: 6 g. Fp.: 112 to 114°C.
MS [m/e] : 384 (82 %), 255 (8 %), 242 (14 %), 109 (100 %).

EXAMPLE 39

8-[3-(4-Methylbenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid

The product is produced as described in example 22 from 7.3 g. of 8-[3-(4-methylbenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid methyl ester and 1.5 g. of NaOH.

Yield: 6.5 g Fp.: 109 to 113°C.
MS [m/e] : 380 (76 %), 252 (3 %), 238 (6%), 105 (100 %).

EXAMPLE 40

8-[2-Oxo-3-(3-trifluoromethylbenzyl)-benzimidazolin-1-yl]-caprylic acid

The product is produced as described in example 22 from 5.7 g. of 8-[2-oxo-3-(3-trifluoromethylbenzyl)-benzimidazolin-1-yl]-caprylic acid methyl ester and 1.5 g. of NaOH.

Yield: 5.7 g. Fp.: 109 to 111°C.
MS [m/e] : 434 (100 %), 305 (22 %), 292 (25 %), 159 (61 %).

EXAMPLE 41

8-[3-(4-Methoxybenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid

The product is produced as described in example 22 from 7 g. of 8-[3-(4-methoxybenzyl)-2-oxo-benzimidazolin-1-yl]-

caprylic acid methyl ester and 1.4 g. of NaOH. Recrystallization from ether.

Yield: 4.7 g. Fp.: 106 to 108°C.

MS /m/e/ : 396 (24 %), 254 (0,7 %), 121 (100 %).

EXAMPLE 42

7-(2-Oxo-benzoxazolin-3-yl)-enanthic acid sodium salt

7-(2-Oxo-benzoxazolin-3-yl)-enanthic acid is dissolved in ethanol and neutralized with alcoholic soda lye. The mixture is evaporated to dryness in a vacuum and the solid residue is pulverized.

IR (in KBr): 1760 and 1565 cm^{-1}.

As described in Example 42, the following sodium salts are produced (Examples 43 to 61).

EXAMPLE 43

8-(2-Oxo-benzoxazolin-3-yl)-caprylic acid sodium salt.
IR (in KBr): 1770 and 1565 cm^{-1}.

EXAMPLE 44

8-(5-Nitro-2-oxo-benzoxazolin-3-yl)-caprylic acid sodium salt.
IR (in KBr): 1770 and 1565 cm^{-1}.

EXAMPLE 45

8-(6-Methyl-2-oxo-benzoxazolin-3-yl)-caprylic acid sodium salt.
IR (in KBr): 1770 and 1565 cm^{-1}.

EXAMPLE 46

8-(5-Chloro-2-oxo-benzoxazolin-3-yl)-caprylic acid sodium salt.
IR (in KBr): 1780 and 1565 cm^{-1}.

EXAMPLE 47

8-(2-Oxo-benzthiazolin-3-yl)-caprylic acid sodium salt.
IR (in KBr): 1680 and 1565 cm^{-1}.

EXAMPLE 48

8-(2-Oxo-benzimidazolin-1-yl)-caprylic acid sodium salt.
IR (in KBr): 1720 and 1575 cm^{-1}.

EXAMPLE 49

8-(3-Octyl-2-oxo-benzimidazolin-1-yl)-caprylic acid sodium salt.
IR (in KBr): 1710 and 1565 cm^{-1}.

EXAMPLE 50

7-(2-Oxo-3-phenyl-benzimidazolin-1-yl)-enanthic acid sodium salt.
IR (in KBr): 1710 and 1565 cm^{-1}.

EXAMPLE 51

8-(2-Oxo-3-phenyl-benzimidazolin-1-yl)-caprylic acid sodium salt.
IR (in KBr): 1710 and 1570 cm^{-1}.

EXAMPLE 52

11-(2-Oxo-3-phenyl-benzimidazolin-1-yl)-undecanoic sodium salt.
IR (in KBr): 1715 and 1565 cm^{-1}.

EXAMPLE 53

7-[3-(3-Chlorophenyl)-2-oxo-benzimidazolin-1-yl]-enanthic acid sodium salt.
IR (in KBr): 1715 and 1565 cm^{-1}.

EXAMPLE 54

8-[3-(3-Chlorophenyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid sodium salt.
IR (in KBr): 1715 and 1565 cm^{-1}.

EXAMPLE 55

8-(3-Benzyl-2-oxo-benzimidazolin-1-yl)-caprylic acid sodium salt.
IR (in KBr): 1705 and 1565 cm^{-1}.

EXAMPLE 56

8-[3-(2-Chlorobenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid sodium salt.
IR (in KBr): 1710 and 1570 cm^{-1}.

EXAMPLE 57

8-[3-(4-Chlorobenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid sodium salt.
IR (in KBr): 1710 and 1580 cm^{-1}.

EXAMPLE 58

8-[3-(4-Fluorobenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid sodium salt.
IR (in KBr): 1710 and 1565 cm^{-1}.

EXAMPLE 59

8-[3-(4-Methylbenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid sodium salt.
IR (in KBr): 1710 and 1565 cm^{-1}.

EXAMPLE 60

8-[2-Oxo-3-(3-trifluoromethylbenzyl)-benzimidazolin-1-yl]-caprylic acid sodium salt.
IR (in KBr): 1710 and 1565 cm^{-1}.

EXAMPLE 61

8-[3-(4-Methoxybenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid sodium salt.
IR (in KBr): 1710 and 1565 cm^{-1}.

EXAMPLE 62

8-(2-Oxo-3-phenyl-benzimidazolin-1-yl)-caprylic acid hexylester

5 cc. of thionylchloride are added to 1 g. of 8-(2-oxo-3-phenyl-benzimidazolin-1-yl)-caprylic acid and the mixture is stirred at room temperature for 2 hours. Unreacted thionylchloride is evaporated in a vacuum, the residue is dissolved in a small amount of anhydrous chloroform and 238 mg. of hexanol are added to the

solution. The mixture is stirred at room temperature for 4 hours, consequetively washed with 5 % $NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated in a vacuum. The residue is further purified chromatographically on silicic acid gel using hexane/ethyl acetate as eluant.

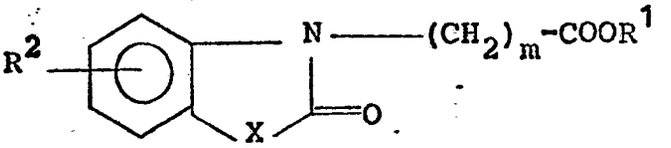
Yield: 500 mg. (oil)

MS [m/e] : 436 (100 %), 335 (20 %), 223 (38 %), 210 (37 %).

As described in example 62 or by reaction of the ω-(2-oxobenzazolinyl)-alkannoic acids with solutions of hydrochloric acid in alcohols (as described in the examples of German patent applications P 29 34 746.4, P 29 35 902.2 and P 29 50 478.7) all esters claimed in claim 1 may be produced.

CLAIMS:

1. ω-(2-Oxo-benzazolinyl)-alkanoic acids and their derivatives having the general formula I



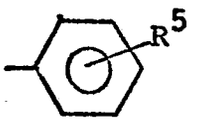
I

wherein

m is an integer ranging from 6 to 10

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

X is oxygen, sulphur or a NR^3-group, R^3 representing -H, $-(CH_2)_n-R^4$ with n being an integer from 0 to 7 and R^4 being a methyl group, the unsubstituted phenyl group or the substituted phenyl group



,

R^2 and R^5 which may be identical or different from each other, represent hydrogen, halogen, a methyl, a trifluoromethyl, a methoxy, a nitro or an amino group.

2. 7-(2-Oxo-benzoxazolin-3-yl)-enanthic acid and their pharmacologically compatible salts and esters.

3. 8-(2-Oxo-benzoxazolin-3-yl)-caprylic acid and their pharmacologically compatible salts and esters.

4. 8-(5-Nitro-2-oxo-benzoxazolin-3-yl)-caprylic acid and their pharmacologically compatible salts and esters.

5. 8-(5-Amino-2-oxo-benzoxazolin-3-yl)-caprylic acid and their pharmacologically compatible salts and esters.

6. 8-(6-Methyl-2-oxo-benzoxazolin-3-yl)-caprylic acid and their pharmacologically compatible salts and esters.

7. 8-(5-Chloro-2-oxo-benzoxazolin-3-yl)-caprylic acid and their pharmacologically compatible salts and esters.

8. 8-(2-Oxo-benzthiazolin-3-yl)-caprylic acid and their pharmacologically compatible salts and esters.

9. 8-(2-Oxo-benzimidazolin-1-yl)-caprylic acid and their pharmacologically compatible salts and esters.

10. 8-(3-Octyl-2-oxo-benzimidazolin-1-yl)-caprylic acid and their pharmacologically compatible salts and esters.

11. 7-(2-Oxo-3-phenyl-benzimidazolin-1-yl)-enanthic acid and their pharmacologically compatible salts and esters.

12. 8-(2-Oxo-3-phenyl-benzimidazolin-1-yl)-caprylic acid and their pharmacologically compatible salts and esters.

13. 11-(2-Oxo-3-phenyl-benzimidazolin-1-yl)-undecanoic acid and their pharmacologically compatible salts and esters.

14. 7-[3-(3-Chlorophenyl)-2-oxo-benzimidazolin-1-yl]-enanthic acid and their pharmacologically compatible salts and esters.

15. 8-[3-(3-Chlorophenyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid and their pharmacologically compatible salts and ester.

16. 8-(3-Benzyl-2-oxo-benzimidazolin-1-yl)-caprylic acid and their pharmacologically compatible salts and esters.

17. 8-[3-(2-Chlorobenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid and their pharmacologically compatible salts and esters.

18. 8-[3-(4-Chlorobenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid and their pharmacologically compatible salts and esters.

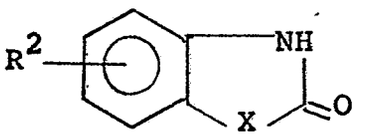
19. 8-[3-(4-Fluorobenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid and their pharmacologically compatible salts and esters.

20. 8-[3-(4-Methylbenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid and their pharmacologically compatible salts and esters.

21. 8-[2-Oxo-3-(3-trifluoromethylbenzyl)-benzimidazolin-1-yl]-caprylic acid and their pharmacologically compatible salts and esters.

22. 8-[3-(4-Methoxybenzyl)-2-oxo-benzimidazolin-1-yl]-caprylic acid and their pharmacologically compatible salts and esters.

23. Process for producing the compounds of formula I according to claims 1 to 22 characterized in that a benzazolin-2-one of the general formula II



II

wherein R^2 and X have the same meaning as in formula I, are subjected to reaction with an alkylating agent of formula III

$$Z-(CH_2)_m-COOR^1 \qquad III$$

wherein m and R^1 have the same meaning as in formula I and Z is a halogen, in an organic solvent with the addition of an auxiliary base, possibly in the presence of an alkali metal iodide as catalyst and, if desired, the resulting ester of formula I (R^1= C_{1-6}-alkyl) is converted in usual manners into an acid of formula I (R^1 = H) and this acid is converted into an alkali metal salt of formula I (R^1 = alkali metal) or into an acid of formula I (R^1 = H) and an alkali metal salt of formula I (R^1 = alkali metal) is converted in usual manners into an ester of formula I (R^1 = C_{1-6}-alkyl).

24. Process for producing the compounds of formula I according to claims 1 to 22, wherein X is $=NR^3$ and R^3 is $-(CH_2)_n-R^4$, n and R^4 having the same meaning as in formula I, characterized in that a compound of formula I wherein X is $=NR^3$ and R^3 is hydrogen, is subjected to reaction with an alkylating agent of formula IV

$$Y-(CH_2)_n-R^4 \qquad IV$$

wherein Y is a usual group to be split off and n and R^4 have the same meaning as in formula I, in usual manners.

25. Pharmaceutical compounds comprising one of the active agents as claimed in claims 1 to 22 besides usual pharmacologically compatible carrier materials and/or diluents.

European Patent Office

EUROPEAN SEARCH REPORT

0051827
Application number
EP 81109292.3

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
	DE - A1 - 2 429 562 (INST. NAT..) * Claim 1 * & GB-A-1 425 429 --	1
	DE - A1 - 2 705 844 (HERCK) * Claim 1 * & GB-A-1 520 699 --	1
	US - A - 3 812 138 (HEISE) * Abstract * --	1
	EP - A1 - 0 001 349 (MONSANTO) * Abstract * --	1
	EP - A1 - 0 007 161 (MONSANTO) * Abstract * ----	1

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 263/58
C 07 D 277/68
C 07 D 235/26
A 61 K 31/42
A 61 K 31/425
A 61 K 31/415

TECHNICAL FIELDS SEARCHED (Int. Cl.³)

C 07 D 235/00
C 07 D 263/00
C 07 D 277/00

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	01-02-1982	HAMMER

EPO Form 1503.1 06.78