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(54) Imidazol-2-yl mercapto alkanoic acids, process for producing the same and pharmaceutical preparations containing the same.

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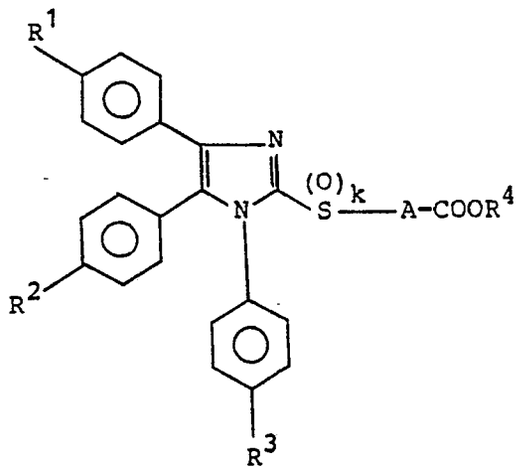
Description

The invention is related to imidazol-2-yl mercapto alkanoic acids, processes for their production, pharmaceutical preparations containing such compounds and their application for the treatment of inflammatory diseases and in particular diseases in relation with the lipid metabolism.

EP—A 51829 describes certain N-substituted omega(2-oxo-4-imidazolin-1-yl)-alkanoic acids and their derivatives having anti-thrombotic, anti-inflammatory, anti-sclerotic and lipid lowering properties. Chem. Abstract vol. 57, 2208c und d, describes 1.4.5-triphenylimidazolyl-thioacetic acid, 1-(p-tolyl)- and 1-(p-ethoxyphenyl)-4.5-diphenylimidazolyl-2-thioacetic acid and their preparation but gives no properties for these compounds.

EP—A—104 342 which falls under Article 54(3) describes certain triphenylimidazolyloxy-alkanoic acids and their derivatives having anti-thrombotic, anti-inflammatory, anti-sclerotic and lipid lowering properties.

The compounds according to the invention correspond to the formula I



I

wherein

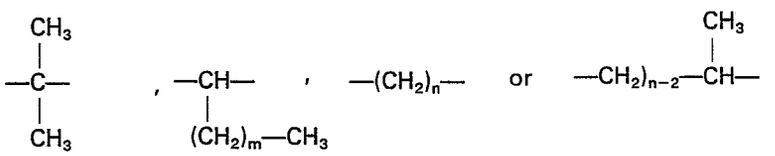
k is the numeral 0, 1 or 2,

R^1, R^2

and R^3 which are the same or different from each other, represent hydrogen, fluorine, chlorine, methyl, methoxy or trifluoromethyl,

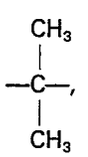
R^4 represents hydrogen, sodium, potassium, methyl, ethyl, propyl, isopropyl or butyl, and

A is the group



m being zero or a numeral from 1 to 8 and n being a numeral from 2 to 10.

Particularly preferred are those compounds of formula I, wherein A is the group $—(CH_2)_3—$ or



while k, R^1, R^2, R^3 and R^4 have the same meaning as above given in formula I.

Compounds according to invention are for instance:

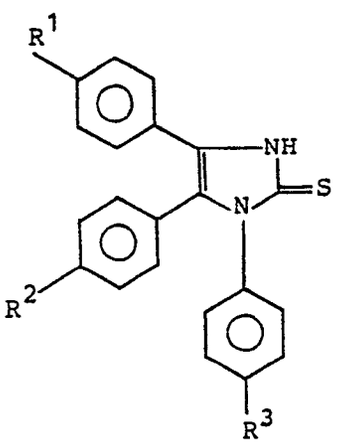
3-(1.4.5-triphenylimidazol-2-yl mercapto)propionic acid;
4-(1.4.5-triphenylimidazol-2-yl mercapto)butyric acid;
5-(1.4.5-triphenylimidazol-2-yl mercapto)valeric acid;
6-(1.4.5-triphenylimidazol-2-yl mercapto)caproic acid;
7-(1.4.5-triphenylimidazol-2-yl mercapto)enanthic acid;
8-(1.4.5-triphenylimidazol-2-yl mercapto)caprylic acid;
9-(1.4.5-triphenylimidazol-2-yl mercapto)perlagonic acid;
10-(1.4.5-triphenylimidazol-2-yl mercapto)capric acid;

11-(1.4.5-triphenylimidazol-2-yl mercapto)undecanoic acid;
4-[4.5-diphenyl-1-(4-methoxyphenyl)-imidazol-2-yl mercapto]butyric acid;
4-[1-(4-chlorophenyl)-4.5-diphenylimidazol-2-yl mercapto]butyric acid;
4-[4.5-diphenyl-1-(4-methylphenyl)-imidazol-2-yl mercapto]butyric acid;
4-[4.5-bis-(4-chlorophenyl-1-phenyl-imidazol-2-yl mercapto]butyric acid;
4-[4.5-bis-(4-fluorophenyl-1-phenyl-imidazol-2-yl mercapto]butyric acid;
4-[4.5-bis-(4-methoxyphenyl)-1-imidazol-2-yl mercapto]butyric acid;
4-[1.4.5-tris-(4-chlorophenyl)imidazol-2-yl mercapto]butyric acid;
8-[4.5-diphenyl-1-(4-methoxyphenyl)-imidazol-2-yl mercapto]caprylic acid;
8-[1-(4-chlorophenyl)-4.5-diphenylimidazol-2-yl mercapto]caprylic acid;
8-[4.5-diphenyl-1-(4-methylphenyl)-imidazol-2-yl mercapto]caprylic acid;
8-[4.5-bis-(4-chlorophenyl)-1-phenyl-imidazol-2-yl mercapto]caprylic acid;
8-[4.5-bis-(4-fluorophenyl)-1-phenyl-imidazol-2-yl mercapto]caprylic acid;
8-[4.5-bis-(4-methoxyphenyl)-1-phenyl-imidazol-2-yl mercapto]caprylic acid;
8-[1.4.5-tris-(4-chlorophenyl)-imidazol-2-yl mercapto]caprylic acid;
8-[4.5-diphenyl-1-(4-trifluoromethylphenyl)-imidazol-2-yl mercapto]caprylic acid;
2-(1.4.5-triphenylimidazol-2-yl mercapto)-propionic acid;
2-(1.4.5-triphenylimidazol-2-yl mercapto)-butyric acid;
2-(1.4.5-triphenylimidazol-2-yl mercapto)-valeric acid;
2-(1.4.5-triphenylimidazol-2-yl mercapto)-caproic acid;
2-(1.4.5-triphenylimidazol-2-yl mercapto)-enanthic acid;
2-(1.4.5-triphenylimidazol-2-yl mercapto)-caprylic acid;
2-(1.4.5-triphenylimidazol-2-yl mercapto)-pelargonic acid;
2-(1.4.5-triphenylimidazol-2-yl mercapto)-capric acid;
2-(1.4.5-triphenylimidazol-2-yl mercapto)-undecanoic acid;
2-[1-(4-chlorophenyl)-4.5-diphenyl-imidazol-2-yl mercapto]capric acid;
2-[4.5-diphenyl-1-(4-methoxyphenyl)-imidazol-2-yl mercapto]capric acid;
2-[4.5-diphenyl-1-(4-methylphenyl)-imidazol-2-yl mercapto]capric acid;
2-[4.5-diphenyl-1-(4-fluorophenyl)--imidazol-2-yl mercapto]capric acid;
2-[4.5-bis-(4-chlorophenyl)-1-phenyl-imidazol-2-yl mercapto]capric acid;
2-[4.5-bis-(4-fluorophenyl)-1-phenyl-imidazol-2-yl mercapto]capric acid;
2-[4.5-bis-(4-methoxyphenyl)-1-phenyl-imidazol-2-yl mercapto]capric acid;
2-[1.4.5-tris-(4-chlorophenyl)-imidazol-2-yl mercapto]capric acid;
2-[4.5-diphenyl-1-(4-trifluoromethylphenyl)-imidazol-2-yl mercapto]capric acid;
2-methyl-2-(1.4.5-triphenylphenylimidazol-2-yl mercapto)propionic acid;
2-[4.5-bis-(4-chlorophenyl)-1-phenyl-1-imidazol-2-yl mercapto]-2-methylpropionic acid;
2-[4.5-bis-(4-methoxyphenyl)-1-phenyl-imidazol-2-yl mercapto)-2-methylpropionic acid;
as well as the corresponding sulfoxides, sulfones, esters and alkali metal salts.

The compounds according to invention show interesting pharmacological properties, in particular a lipid lowering as well as antiinflammatory activity with an excellent compatibility.

The present invention is further directed to processes for the preparation and to pharmaceutical preparations of these compounds and their use as drugs.

The compounds according to the present invention of formula I wherein k = 0 are produced in that a 4-imidazolin-2-thione of formula II



II

wherein R^1, R^2 and R^3 have the meaning given in formula I, is converted into the corresponding alkali metal salt by the addition of an auxiliary base such as sodium hydride or potassium hydride, in an inert organic solvent such as dimethylformamide, dimethylacetamide, tetramethylurea, tetrahydro thiophene-1.1-dioxide, and this alkali metal salt is subjected to reaction with an alkylating agent of the formula

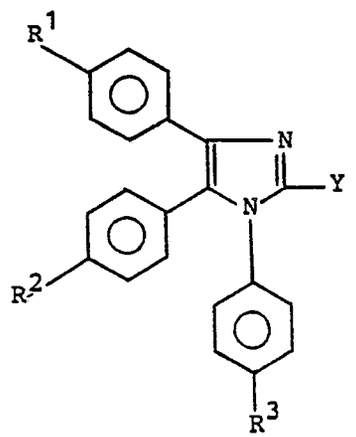
$$X—A—COOR^4 \qquad III$$

wherein A and R^4 have the meaning as given in formula I and X is a halogen, a tosyl group or a similar usual split-off group.

The starting materials of formula II are produced by known processes from the corresponding 4-imidazolin-2-ones by reaction with di-phosphoruspentasulfide in toluene or by reaction with Lawesson reagent or directly from the corresponding benzoines by reaction with phenylthiourea. Esters of formula I may be converted by usual processes, for instance by reaction with an alkali metal hydroxide in aqueous, aqueous-organic or organic solvents such as water, alcohols, ethers or mixtures thereof, into the corresponding alkali metal salts of formula I which may be converted into the corresponding acids of formula I by a subsequent addition of an inorganic acid (mineral acid).

On a contrary way, the esters of formula I may be produced from the acids of formula I and the alkali metal salts of formula I by usual processes, for instance by treating the acids with the corresponding alcohols with the addition of a mineral acid as catalyst or by reesterification with formic or acetic acid esters in the presence of a condensation agent such as dicyclohexyl carbodiimide or by alkylating the alkali metal salts of formula I with the corresponding alkyl halides, alkyl sulfates and like in inert solvents.

The compounds of formula I wherein k = 0 may also be prepared in that the starting material II is converted to the halo-derivative of formula IV



IV

wherein R^1, R^2 and R^3 have the meaning as given in formula I and X is a halogen atom, by means of a halogenating agent such as $POCl_3$ or PCl_5 and subsequently subjecting the intermediary products IV, with the addition of an auxiliary base such as alkali metal hydroxide, alkaline earth metal hydroxide, alkali metal hydride, to reaction with a compound of formula V

$$HS—A—COOR^4 \qquad V$$

wherein A and R^4 have the meaning as given in formula I, in inert organic solvents such as dimethylformamide, dimethylacetamide, tetramethylurea, alcohols and the like, possibly at elevated pressure. The sulfoxides and sulfones of formula I wherein k is 1 or, respectively, k is 2, are prepared from the mercapto esters wherein k is 0, by reaction with oxidizing agent such as with hydrogen peroxide in anhydrous acetic acid or acetone, with sodium metaperiodate/anhydrous acetic acid, potassium permanganate/mineral acid or organic peroxy acids such as m-chloroperbenzoic acid in $CHCl_3$, CH_2Cl_2 or similar inert solvents.

The present invention also is related to pharmaceutical preparations which contain the new imidazol-2-yl mercapto alkanoic acids as free acid or as salts with pharmacologically compatible bases or as esters. The pharmaceutical preparations according to the present invention are used for enteral, i.e. oral or rectal or parenteral application. They contain the pharmaceutically active agent as such or together with usual pharmaceutically useful carrier materials. Preferably, the pharmaceutical preparations of the active agent represent single doses corresponding to the desired application such as tablets, dragees, capsules, suppositories, granulates, solutions, emulsion or suspensions. The dosages usually are between 1 and 100 mg per day, preferably between 10 and 500 mg er day which dose is administered once or several times, preferably twice or three times, per day.

The reported melting points have been measured by means of a Büchi-melting poing apparatus and are not corrected. The infrared spectra have been determined with a Nicolet® NIC—3600 and the mass spektra with a Varian® MAT—311A (70 eV).

Example 1

8-(1.4.5-Triphenylimidazol-2-yl mercapto)-octanoic acid methyl ester.

13.8 g of an 80% sodium hydride suspension in mineral oil are washed with pentane and are added to a mixture of 153 g of 1.4.5-triphenyl-4-imidazolin-2-thione in 600 cc. of anhydrous dimethylformamide. The mixture is stirred at first at room temperature and then at 60°C. until the end of hydrogen formation. After the addition of 0.5 g of sodium iodide there are added dropwise 109 g of 8-bromooctanoic methyl ester. The resulting mixture is stirred for 4 hours at 60°C., cooled, diluted with water and extracted with chloroform. The chloroform solution is washed with water, dried over sodium sulfate and evaporated. The residue is recrystallized from tetrahydro

Yield: 186.2 g F.: 120 to 121°C.

IR (in KBr): 1736 cm^{-1}.

Example 2

4-(1.4.5-Triphenylimidazol-2-yl mercapto)-butyric acid ethyl ester.

Similar to Example 1 from:

4.5 g of an 80 sodium hydride suspension in mineral oil,

50 g of 1.4.5-triphenyl-4-imidazolin-2-thione,

300 cc. of dimethylformamide,

4.5 g of sodium iodide,

23 g of 4-chlorobutyric acid ethyl ester.

Recrystallization of the crude product from ethanol.

Yield: 61 g F.: 118°C.

IR (in KBr): 1732 cm^{-1}.

Example 3

2-(1.4.5-Triphenylimidazol-2-yl mercapto)-octanoic acid ethyl ester. Similar to Example 1 from:

6.4 g of an 80% sodium hydride suspension in mineral oil,

63.3 g of 1.4.5-triphenyl-4-imidazolin-2-thione,

200 cc of dimethylformamide,

39 g of 2-bromooctanoic acid ethyl ester.

The mixture is stirred for 4 hours at 150°C. Purification of the crude product by column chromatography (silicic acid gel//hexane/acetic acid ethyl ester).

Yield: 61.5 g F.: 88°C.

IR (in KBr): 1734 cm^{-1}.

Example 4

2-Methyl-2-(1.4.5-triphenylimidazol-2-yl mercapto)-propionic acid ethyl ester. Similar to Example 1 from:

8.3 g of 80% sodium hydride suspension in mineral oil,

92.5 g of 1.4.5-triphenyl-4-imidazolin-2-thione,

300 cc. of dimethylformamide,

8.4 g of sodium iodide,

55 g of 2-bromoisobutyric acid ethyl ester.

The mixture is stirred for 2 hours at 80°C. Recrystallization of the crude product from acetic acid ethyl ester.

Yield 92 g F.: 167—169°C.

IR (in KBr): 1728 cm^{-1}

MS [m/e]: 442 (74%), 328 (100%), 269 (82%).

Example 5

8-(1.4.5-Triphenylimidazol-2-yl mercapto)-octanoic acid.

170 g of 8-(1.4.5-triphenylimidazol-2-yl mercapto)-octanoic acid methyl ester are dissolved in 1.2 l of tetrahydrofurane. 42 g of sodium hydride dissolved in 700 cc of methanol are added thereto. The mixture is stirred 24 hours at 40 to 50°C, cooled, diluted with about 2 l of water and acidified with dilute hydrochloric acid. The crude acid is filtered off, dried and recrystallized from toluene.

Yield: 151 g F.: 150 to 152°C.

IR (in KBr): 1701 cm^{-1}

MS [m/e]: 470 (56%), 423 (21%), 328 (100%), 269 (22%), 252 (10%).

Example 6

4-(1.4.5-Triphenylimidazol-2-yl mercapto)-butyric acid.

80g of 4-(1.4.5-triphenylimidazol-2-yl mercapto)-butyric acid ethyl ester are dissolved in 700 cc. of ethanol at 80°C. 22 g of sodium hydroxide dissolved in 200 cc. of ethanol are added thereto and the mixture is

stirred for 3 hours at 80°C. The solvent is distilled off, the residue is washed with ether and acidified with dilute hydrochloric acid. The resulting acid is triturated in chloroform, the chloroform solution is washed with water, dried over sodium sulfate and the solvent is distilled off.

Yield: 73 g F.: 165°C.

MS [m/e]: 414 (100%), 328 (69%), 269 (36%), 252 (12%).

Example 7

2-(1.4.5-Triphenylimidazol-2-yl mercapto)-octanoic acid.

Similar to Example 6 from:

48 g of 2-(1.4.5-triphenylimidazol-2-yl mercapto)-octanoic acid ethyl ester in 500 cc. of ethanol,

11.5 g of sodium hydroxide in 100 cc. of ethanol.

The mixture is stirred for 8 hours at room temperature. Recrystallization of the crude acid from hexane/acetic acid ethyl ester.

Yield: 34 g F.: 108°C.

MS [m/e]: 470 (33%), 426 (13%), 328 (100%), 269 (54%), 252 (48%).

Example 8

2-Methyl-2-(1.4.5-triphenylimidazol-2-yl mercapto)-propionic acid.

Similar to Example 6 from:

32 g of 2-methyl-2-(1.4.5-triphenylimidazol-2-yl mercapto)-propionic acid ethyl ester in 1000 cc. of ethanol,

8.6 g of sodium hydroxide in 100 cc. of ethanol.

The mixture is refluxed for 4 hours.

Yield: 31.5 g F.: 189 to 191°C.

IR (in KBr): 1705 cm^{-1}

MS [m/e]: 414 (8.5%), 328 (94%), 294 (16%), 261 (100%).

Example 9

8-(1.4.5-Triphenylimidazol-2-yl mercapto)-octanoic acid sodium salt.

12 g of 8-(1.4.5-triphenylimidazol-2-yl mercapto)-octanoic acid are dissolved in 250 cc. of 96% ethanol. The equivalent amount of ethanolic sodalye (1 g of NaOH in 10 cc. of ethanol) is added and the mixture is stirred for a short time and evaporated to dryness in a vacuo. The residue is pulverized.

Yield: 12.1 g.

IR (in KBr): 1558 cm^{-1}.

Example 10

4-(1.4.5-Triphenylimidazol-2-yl mercapto)-butyric acid sodium salt.

Similar to Example 9 from:

70 g of 4-(1.4.5-triphenylimidazol-2-yl mercpato)-butyric acid in 1200 cc. of 96% ethanol,

6.7 g of NaOH in 67 cc. of ethanol.

Yield: 71.5 g.

IR (in KBr): 1561 cm^{-1}.

Example 11

The sodium salt of 2-(1.4.5-triphenylimidazol-2-yl mercapto)-octanoic acid.

Similar to Example 9 from:

24 g of 2-(1.4.5-triphenylimidazol-2-yl mercapto)-octanoic acid in 500 cc. of 96% ethanol,

2 g of NaOH in 20 cc. of ethanol.

Yield: 24.4 g.

IR (in KBr): 1604 cm^{-1}.

Example 12

The sodium salt of 2-(1.4.5-triphenylimidazol-2-yl mercapto)-propionic acid.

Similar to Example 9 from:

32 g of 2-methyl-2-(1.4.5-triphenylimidazol-2-yl mercapto)-propionic acid in 1000 cc. of 96% ethanol,

2.9 g of NaOH in 30 cc. of ethanol.

Yield: 32.5 g.

IR (in KBr): 1617 cm^{-1}.

Similar to Examples 9 to 12 the sodium salts of all other acids according to the present invention have been produced.

Example 13

4-(1.4.5-Triphenylimidazol-2-yl sulfonyl)-butyric acid.

15 g of 4-(1.4.5-triphenylimidazol-2-yl mercapto)-butyric acid are dissolved in 100 cc. of anhydrous acetic acid at 80°C. and 3.5 cc. of a 30% solution of hydrogen peroxide is added dropwise. The solution is

stirred, until the acid starting product has been reacted completely. Upon cooling, the sulfone crystallized, is filtered off with suction, washed with little acetic acid and water and is dried in a vacuo.

Yield: 11.1 g F.: 202 to 204°C.

IR (in KBr): 1720 cm^{-1}.

MS [m/e]: 446 (27%), 295 (100%), 268 (20%).

Example 14

The sodium salt of 4-(1.4.5-triphenylimidazol-2-yl sulfonyl)-butyric acid.

Similar to Example 9 from:

4-(1.4.5-Triphenylimidazol-2-yl sulfonyl)-butyric acid and NaOH in 96% ethanol.

IR (in KBr): 1575 cm^{-1}.

Example 15

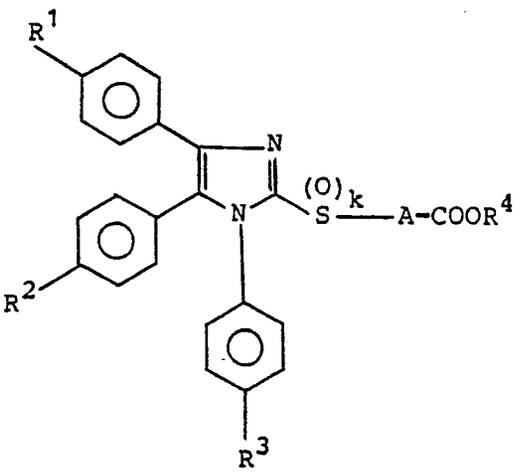
4-(1.4.5-Triphenylimidazol-2-yl sulfinyl)-butyric acid.

20 g of 4-(1.4.5-triphenylimidazol-2-yl mercapto)-butyric acid are dissolved in 500 cc. of chloroform. A solution of 8.4 g of 3-chloroperbenzoic acid in 100 cc. of chloroform is added slowly and dropwise at 0°C. After stirring for 3 hours at 0°C., the chloroform solution is washed with water, dried over sodium sulfate and the solvent is evaporated in a vacuo. The residue is washed several times with ether and recrystallized from ethanol.

Yield: 13.1 g F.: 199°C.

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

1. Imidazol-2-yl mercapto alkanoic acids having the formula I



I

wherein

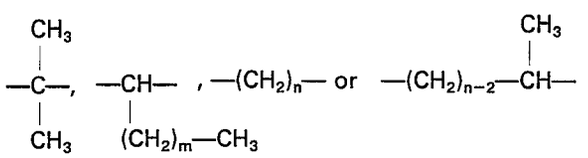
k is the numeral 0, 1 or 2,

R^1, R^2

and R^3 which are the same or different from each other, represent hydrogen, fluorine, chlorine, methyl, methoxy or trifluoromethyl,

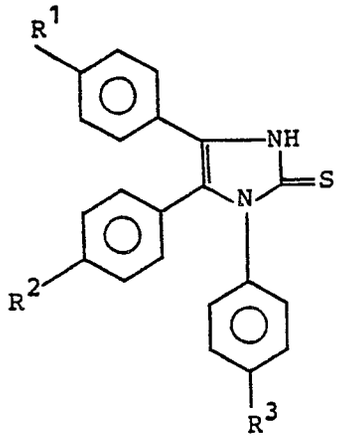
R^4 represents hydrogen, sodium, potassium, methyl, ethyl, propyl, isopropyl or butyl, and

A is the group



m being zero or a numeral from 1 to 8 and n being a numeral from 2 to 10.

2. Process for the production of compounds of formula I according to claim 1 wherein k is 0, characterized in that a 4-imidazolin-2-thione of the formula II



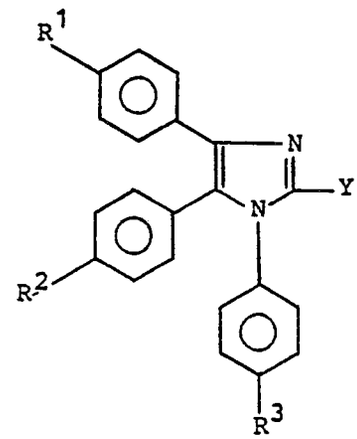
II

wherein R^1, R^2 and R^3 have the meaning as given in formula I, is converted into an alkali metal salt thereof by the addition of an auxiliary base in an inert organic solvent and subjecting this alkali metal salt to reaction with an alkylating agent of the formula III

$$X—A—COOR^4 \qquad III$$

wherein A and R^4 have the meaning as given in formula I and X is a halogen, a tosyl group or another usual split-off group.

3. Process for the production of compounds of Formula I according to claim 1 wherein k is 0, characterized in that a 2-halogeno-imidazole of the formula IV



IV

wherein R^1, R^2 and R^3 have the meaning as given in Formula I and Y is a halogen, is subjected to reaction with a compound of formula V

$$HS—A—COOR^4 \qquad V$$

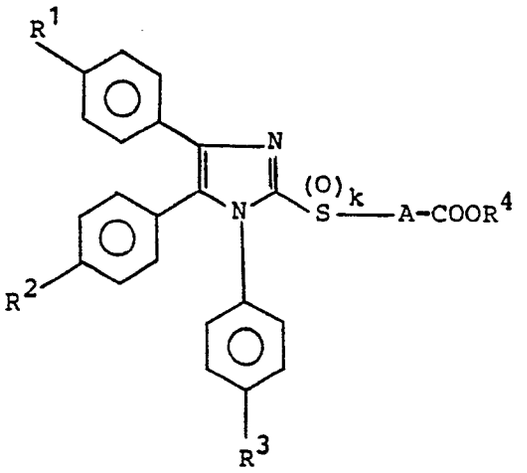
wherein A and R^4 have the meaning as given in formula I, in inert organic solvent with the addition of an auxiliary base.

4. Process for the production of compounds of formula I according to claim 1 wherein k is the numeral 1 or 2, characterized in that a compound of formula i wherein k is zero, is subjected to reaction with an oxidizing agent, possibly in an inert solvent, to yield a compound of formula I wherein k is 1 or 2.

5. Pharmaceutical preparations characterized in that they contain a compound of formula I according to claim 1 as active agent mixed with usual pharmaceutical auxiliary and carrier materials.

Claims for the Contracting State: AT

1. Process for producing imidazol-2-yl-mercapto alkanoic acids having the formula I



I

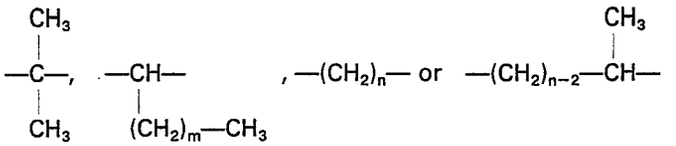
wherein

k is the numeral 0, 1 or 2,

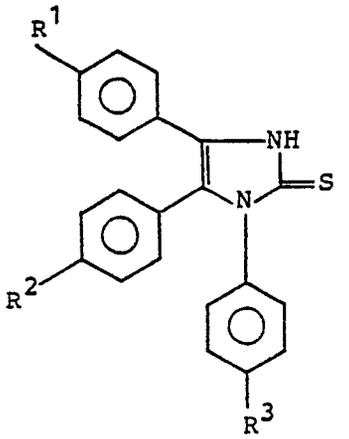
R^1, R^2 and R^3 which are the same or different from each other, represent hydrogen, fluorine, chlorine, methyl, methoxy or trifluoromethyl,

R^4 represents hydrogen, sodium, potassium, methyl, ethyl, propyl, isopropyl or butyl, and

A is the group



m being zero or a numeral from 1 to 8 and n being a numeral from 2 to 10, characterized in that a 4-amidazolin-2-thione of the formula II



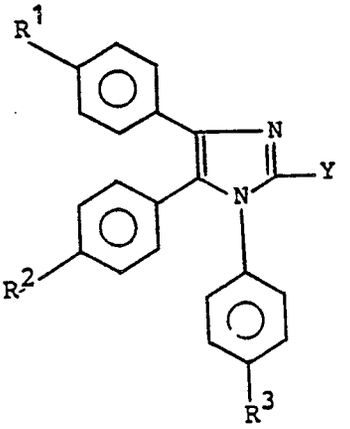
II

wherein R^1, R^2 and R^3 have the meaning as given in formula I, is converted into an alkali metal salt thereof by the addition of an auxiliary base in an inert organic solvent and subjecting this alkali metal salt to reaction with an alkylating agent of the formula III

$$X—A—COOR^4 \qquad III$$

wherein A and R^4 have the meaning as given in formula I and X is a halogen, a tosyl group or another usual split-off group and, if desired, said compound of formula I with k = zero, is subjected to reaction with an oxidizing agent, possibly in an inert solvent.

2. Process for producing of compounds of formula I according to claim 1, characterized in that a 2-halogenoimidazole of the formula IV



IV

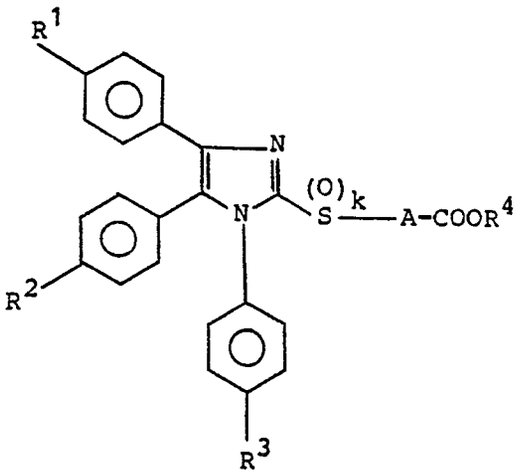
wherein R^1, R^2 and R^3 have the meaning as given in Formula I and Y is a halogen, is subjected to reaction with a compound of formula V

$$HS—A—COOR^4 \qquad V$$

wherein A and R^4 have the meaning as given in formula I, in inert organic solvent with the addition of an auxiliary base, and if desired, said compound of formula I with k = zero, is subjected to reaction with an oxidizing agent, possibly in an inert solvent.

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

1. Imidazol-2-ylthiolalkansäuren der allgemeinen Formel I,



I

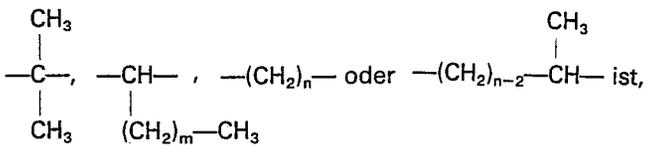
worin

k die Zahl 0, 1 oder 2 ist,

R^1, R^2 und R^3, die gleich oder voneinander verschieden sind, Wasserstoff, Fluor, Chlor, Methyl, Methoxy, Trifluormethyl bedeuten

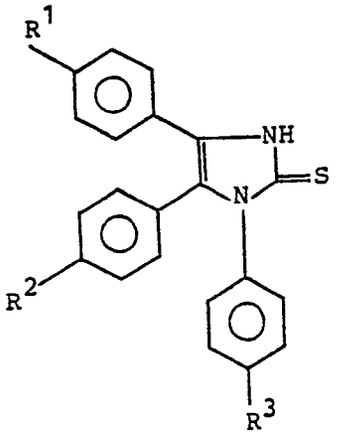
R^4 Wasserstoff, Natrium, Kalium, Methyl, Ethyl, Propyl, Isopropyl oder Butyl ist,

A die Gruppe



worin m eine ganze Zahl von 1 bis 8 und n eine ganze Zahl von 2 bis 10 darstellt.

2. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Anspruch 1, worin k = 0 ist, dadurch gekennzeichnet, daß man eine 4-Imidazolin-2-thion der allgemeinen Formel II,



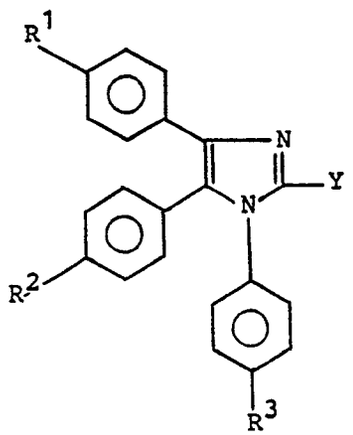
II

worin R^1, R^2 und R^3 die in Formel I angegebenen Bedeutungen besitzen, in einem indifferenten organischen Lösungsmittel durch Zugabe einer Hilfsbase in das Alkalisalz überführt und dieses miteinem Alkylierungsmittel der allgemeinen Formel III,

$$X—A—COOR^4 \qquad III$$

worin A und R^4 die in Formel I angegebebenen Bedeutungen besitzen und X ein Halogenatom, der Tosyloxyrest odereine andere übliche Abgangsgruppe darstellt, umsetzt.

3. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Anspruch 1, worin k = 0 ist, dadurch gekennzeichnet, daß man ein 2-Halogenimidazol der Formel IV,



IV

worin R^1, R^2 und R^3 die in Formel I angegebenen Bedeutungen haben und Y ein Halogenatom ist, unter Zusatz einer Hilfsbase mit einer Verbvindung der Formel V,

$$HS—A—COOR^4 \qquad V$$

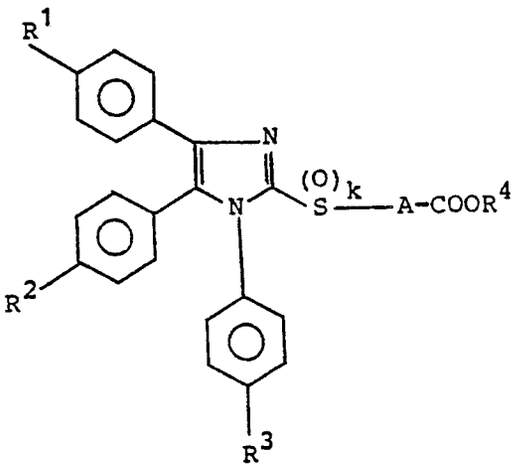
worin A und R^4 die in Formel I angegebenen Bedeutungen haben, in einem indifferenten Lösungsmittel umsetzt.

4. Verfahren zur Herstellung von Verbindungen der Formel I gemäß dem Anspruch 1, worin k die Zahl 1 oder 2 ist, dadurch gekennzeichnet, daß man eine Verbindung der Formel I, worin k = 0 ist, gegebenenfalls in einem inerten Lösungsmittel, miteinem sauerstoffabgebenden Reagenz zu dern Verbindungen der Formel I mit k = 1 bzw. k = 2 umsetzt.

5. Pharmazeutische Präparate, dadurch gekennzeichnet, daß sie eine Verbindung der Formel I gemäß dem Anspruch 1 als Wirkstoff im Gemisch mit üplichen pharmazeutischen Hilfs- und Trägerstoffen enthalten.

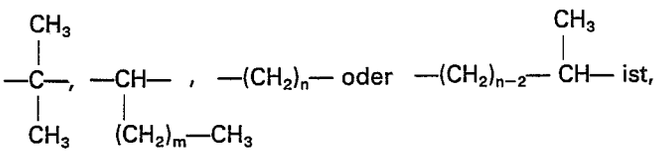
Patentansprüche für den Vertragsstatt: AT

1. Verfahren zur Herstellung Imidazol-2-ylthioalkansäuren der allgemeinen Formel I,

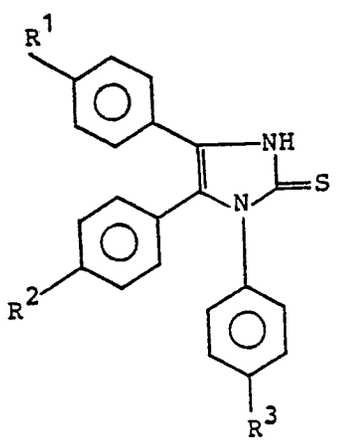


I

worin
k die Zahl 0, 1 oder 2 ist,
R^1, R^2 und R^3, die gleich oder voneinander verschieden sind, Wasserstoff, Fluor, Chlor, Methyl, Methoxy, Trifluormethyl bedeuten
R^4 Wasserstoff, Natrium, Kalium, Methyl, Ethyl, Propyl, Isopropyl oder Butyl ist,
A die Gruppe



worin m eine ganze Zahl von 1 bis 8 und n eine ganze Zahl von 2 bis 10 darstellt, dadurch gekennzeichnet, daß man ein 4-Imidazolin-2-thion der allgemeinen Formel II,



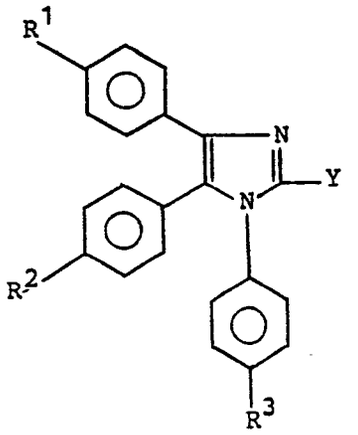
II

worin R^1, R^2 und R^3 die in Formel I angegebenen Bedeutungen besitzen, in einem indifferenten organischen Lösungsmittel durch Zugabe einer Hilfsbase in das Alkalisalz überführt und dieses miteinem Alkylierungsmittel der allgemeinen Formel III,

$$X—A—COOR^4 \qquad III$$

worin A und R^4 die in Formel I angegebebenen Bedeutungen besitzen und X ein Halogenatom, der Tosyloxyrest odereine andere übliche Abgangsgruppe darstellt, umsetzt, und falls erwünscht, die erhaltene Verbindung der Formel I, worin k = 0 ist, mit einem Oxydationsmittel, gegebenenfalls in einem inerten Lösungsmittel, umsetzt.

2. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Anspruch 1, dadurch gekennzeichnet, daß man ein 2-Halogenimdazol der Formel IV,



IV

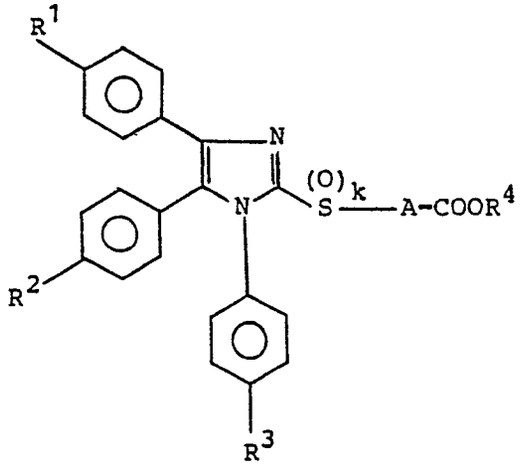
worin R^1, R^2 und R^3 die in Formel I angegebenen Bedeutungen haben und Y ein Halogenatom ist, unter Zusatz einer Hilfsbase mit einer Verbindung der Formel V,

$$HS—A—COOR^4 \qquad V$$

worin A und R^4 die in Formel I angegebenen Bedeutungen haben, in einem indifferenten Lösungsmittel umsetzt, und, falls erwünscht, die erhaltene Verbindung der Formel I, worin k = 0 ist, mit einem Oxydationsmittel, gegebenenfalls in einem inerten Lösungsmittel, umsetzt.

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

1. Acides imidazol-2-yl mercapto alcanoïques de formule I:



I

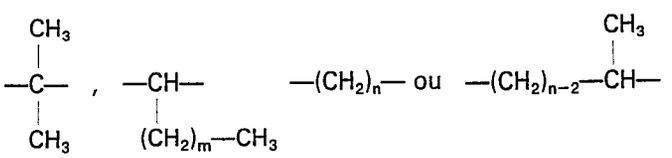
dans laquelle

k représente le nombre 0, 1 ou 2;

R^1, R^2 et R^3 qui sont identiques ou différents les uns des autres, représentent un atome d'hydrogène, de fluor, de chlore, un groupe méthyle, méthoxy ou trifluorométhyle;

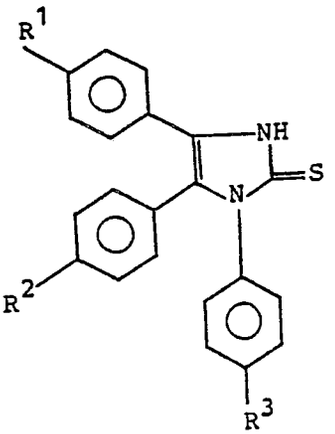
R^4 représente un atome d'hydrogène, de sodium, de potassium, un groupe méthyle, éthyle, propyle, isopropyle ou butyle; et

A represésente le group



m étant égal à zéro ou représentant un nombre de 1 à 8, et n représentant un nombre de 2 à 10.

2. Procédé de préparation des composés de formule I suivant la revendication 1, dans lesquels k représente 0, caractérisé en ce qu'on convertit une 4-imidazolin-2-thione de formule II:



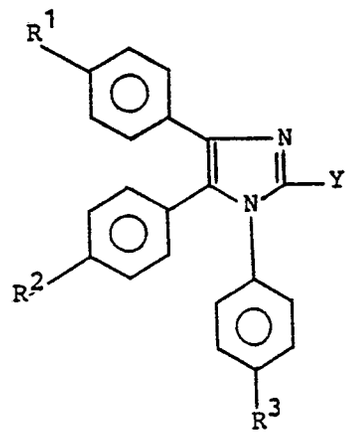
II

dans laquelle R^1, R^2 et R^3 ont les mêmes définitions que celles données dans la formule I, en un sel de métal alcalin de celui-ci par addition d'une base auxiliaire dans un solvant organique inerte, et en ce qu'on soumet ce sel de métal alcalin à une réaction avec un agent d'alkylation de formule III:

$$X—A—COOR^4 \qquad III$$

dans laquelle A et R^4 ont les mêmes définitions que celles données dans la formule I, et X représente un atome d'halogène, un groupe tosyle ou un autre groupe partant classique.

3. Procédé de préparation des composés de formule I suivant la revendication 1, dans lesquels k représente 0, caractérisé en ce qu'on fait réagir un 2-halogéno-imidazole de formule IV:



IV

dans laquelle R^1, R^2 et R^3 ont les mêmes définitions que celles données dans la formule I et Y représente un atome d'halogène, avec un composé de formule V:

$$HS—A—COOR^4 \qquad V$$

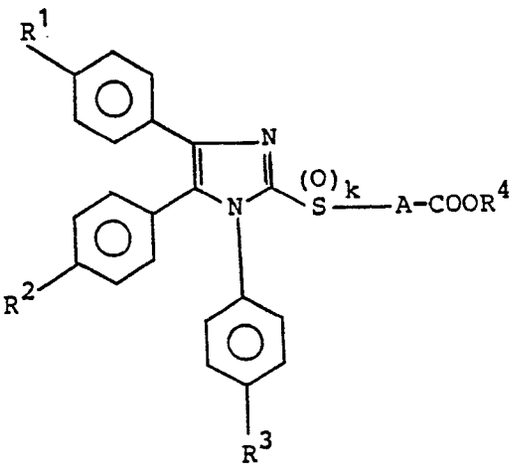
dans laquelle A et R^4 ont les mêmes définitions que celles données dans la formule I dans un solvant organique inerte en ajoutant une base auxiliaire.

4. Procédé de préparation des composés de formule I suivant la revendication 1, dans lesquels k représente le nombre 1 ou 2, caractérisé en ce qu'on fait réagir un composé de formule I dans laquelle k représente 0 avec un agent oxydant, éventuellement dans un solvant inerte pour obtenir un composé de formule I dans laquelle k représente 1 ou 2.

5. Préparations pharmaceutiques caractérisées en ce qu'elles contiennent un composé de formule I suivant la revendication 1 comme agent actif mélangé avec un agent auxiliaire et des véhicules pharmaceutiques classiques.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'acides imidazol-2-yl-mercapto alconoïques de formule I:



I

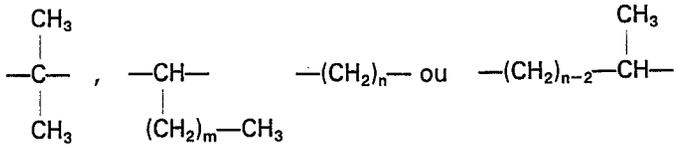
dans laquelle

k représente le nombre 0, 1 ou 2;

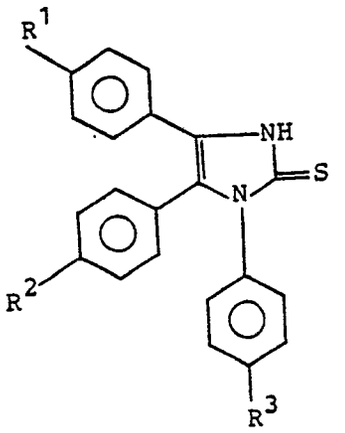
R^1, R^2 et R^3 qui sont identiques ou différents les uns des autres, représentent un atome d'hydrogène, de fluor, de chlore, un groupe méthyle, méthoxy ou trifluorométhyle;

R^4 représente un atome d'hydrogène, de sodium, de potassium, un groupe méthyle, éthyle, propyle, isopropyle ou butyle; et

A represésente le group



m étant égal à zéro ou représentant un nombre de 1 à 8, et n représentant un nombre de 2 à 10; caractérisé en ce qu'on convertit une 4-imidazolin-2-thione de formule II:



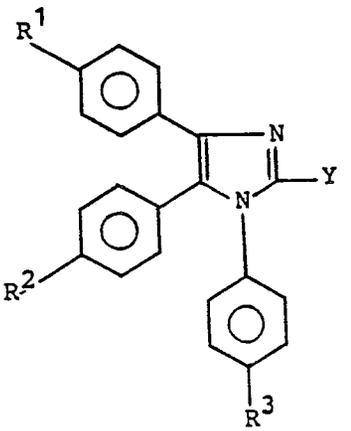
II

dans laquelle R^1, R^2 et R^3 ont les mêmes définitions que celles données dans la formule I, en un sel de métal alcalin de celui-ci en ajoutant une base auxiliaire dans un solvant organique inerte, et on fait reagir ce sel de métal alcalin avec un agent d'alkylation de formule III:

$$X—A—COOR^4 \qquad III$$

dans laquelle A et R^4 ont les mêmes définitions que celles données dans la formule I, et X représente un atome d'halogène, un groupe tosyle ou un autre groupe partant classique et si on le souhaite, on fait réagir ledit composé de formule I dans laquelle k représente 0 avec un agent oxydant éventuellement dans un solvant inerte.

2. Procédé de préparation de composés de formule I suivant la revendication 1, caractérisé en ce qu'on fait réagir un 2-halogéno-imidazole de formule IV:



IV

dans laquelle R^1, R^2 et R^3 ont les mêmes définitions que celles données dans la formule I et Y représente un atome d'halogène, avec un composé de formule V:

$$HS—A—COOR^4 \qquad V$$

dans laquelle A et R^4 ont les mêmes définitions que celles données dans la formule I dans un solvant organique inerte en ajoutant une base auxiliaire, et si on le souhaite, on fait réagir ledit composé de formule I dans laquelle k représente 0 avec un agent oxydant éventuellement dans un solvant inerte.