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

(11) Publication number: **0 130 526**
A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **84107292.9**

(22) Date of filing: **26.06.84**

(51) Int. Cl.⁴: **C 07 D 233/84**, A 61 K 31/415

(30) Priority: **02.07.83 DE 3323870**

(43) Date of publication of application: **09.01.85**
Bulletin 85/2

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

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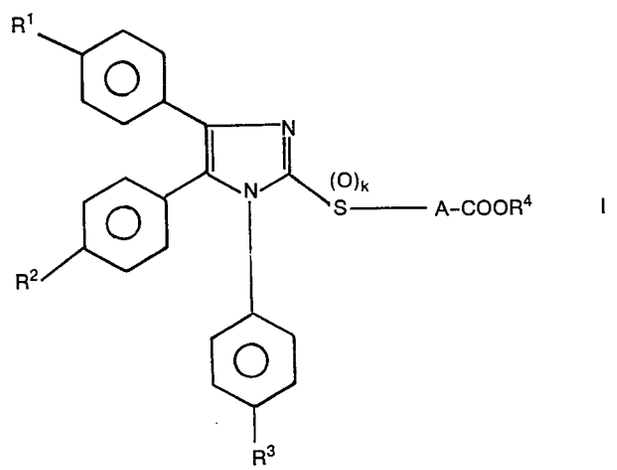
(54) Imidazol-2-yl mercapto alkanoic acids, process for producing the same and pharmaceutical preparations containing the same.

(57) The invention is related to imidazol-2-yl mercapto alkanoic acids having the formula I



I

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

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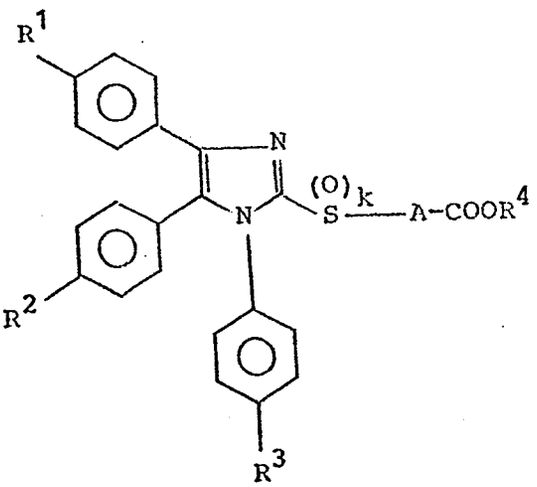
The invention is related to imidazol-2-yl mercapto alkanoic acids, processes for their production, pharmaceutical preparations containing such compounds and their application for the treatment of inflammatory diseases and in particular diseases in relation with the lipid metabolism.

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 $-\overset{CH_3}{\underset{CH_3}{C}}-$, $-\underset{(CH_2)_m-CH_3}{CH}-$, $-(CH_2)_n-$ or $-(CH_2)_{n-2}-\underset{CH_3}{CH}-$

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 $-\overset{CH_3}{\underset{CH_3}{C}}-$, 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) capronic 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) pelargonic acid;
1o-(1.4.5-triphenylimidazol-2-yl mercapto) caprinic 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-diphenyl-1-(2-fluorophenyl)-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-phenyl-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-diphenyl-1-(2-fluorophenyl)-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)-capronic 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)-caprinic acid;
2-(1.4.5-triphenylimidazol-2-yl mercapto)-undecanoic acid;
2-[1-(4-chlorophenyl)-4.5-diphenyl-imidazol-2-yl mercapto]-caprinic acid;
2-[4.5-diphenyl-1-(4-methoxyphenyl)-imidazol-2-yl mercapto]-caprinic acid;
2-[4.5-diphenyl-1-(4-methylphenyl)-imidazol-2-yl mercapto]-caprinic acid;

2-[4.5-diphenyl-1-(4-fluorophenyl)-imidazol-2-yl mercapto]-caprinic acid;

2-[4.5-bis-(4-chlorophenyl)-1-phenyl-imidazol-2-yl mercapto]-caprinic acid;

2-[4.5-bis-(4-fluorophenyl)-1-phenyl-imidazol-2-yl mercapto]-caprinic acid;

2-[4.5-bis-(4-methoxyphenyl)-1-phenyl-imidazol-2-yl mercapto]-caprinic acid;

2-[1.4.5-tris-(4-chlorophenyl)-imidazol-2-yl mercapto]-caprinic acid;

2-[4.5-diphenyl-1-(4-trifluoromethylphenyl)-imidazol-2-yl mercapto]-caprinic acid;

2-methyl-2-(1.4.5-triphenylimidazol-2-yl mercapto)-propionic acid;

2-[4.5-bis-(4-chlorophenyl)-1-phenyl-imidazol-2-yl mercapto]-2-methylpropionic acid;

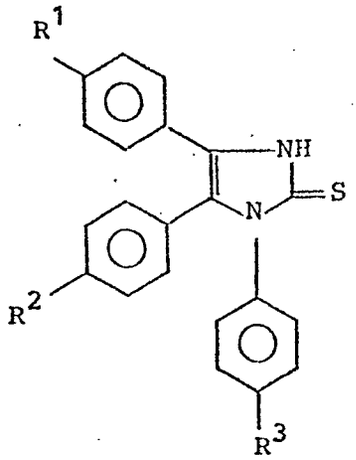
2-[4.5-bis-(4-methoxyphenyl)-1-phenyl-imidazol-2-yl mercapto]-2-methylpropionic acid;

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 as 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 III

$$X\text{-}A\text{-}COOR^4 \qquad III$$

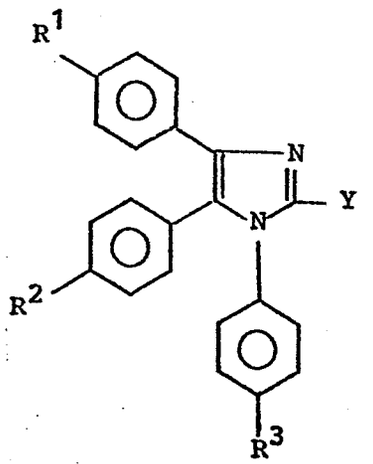
wherein A and R^4 have the meaning as given in formula I and X is a halogen, a tosyl group or a similar usual split-off group.

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 the 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

$HS\text{-}A\text{-}COOR^4$ 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 agents such as with hydrogen peroxide in anhydrous acetic acid or acetone, with sodium metaperiodate/anhydrous acetic acid, potassium permaganate/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 agents 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, emulsions or suspensions. The dosages usually are between 1 and 1000 mg per day, preferably between 10 and 500 mg per 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 point apparatus and are not corrected. The infrared spektra 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 8o % 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 6oo cc. of anhydrous dimethylformamide. The mixture is stirred at first at room temperature and then at 6o°C. until the end of hydrogen formation. After the addition of o.5 g of sodium iodide there are added dropwise 1o9 g of 8-bromooctanoic methyl ester. The resulting mixture is stirred for 4 hours at 6o°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.: 12o 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 8o % sodium hydride suspension in mineral oil,
5o g of 1.4.5-triphenyl-4-imidazolin-2-thione,
3oo 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 8o % sodium hydride suspension in mineral oil,
63.3 g of 1.4.5-triphenyl-4-imidazolin-2-thione,
2oo cc. of dimethylformamide,
39 g of 2-bromooctanoic acid ethyl ester.

The mixture is stirred for 4 hours at 15o°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 8o % sodium hydride suspension in mineral oil,
92.5 g of 1.4.5-triphenyl-4-imidazolin-2-thione,
3oo 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 8o°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 (1oo%), 269 (82%).

Example 5

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

17o 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 7oo cc. of methanol are added thereto. The mixture is stirred 24 hours at 4o to 5o°C., cooled, diluted with about 2 l of water and acidified with delute hydrochloric acid. The crude acid is filtered off, dried and recrystallized from toluene.

Yield: 151 g F.: 15o to 152°C.
IR (in KBr): 17o1 cm^{-1}
MS [m/e]: 47o(56%), 423(21%), 328(1oo%), 269(22%), 252 (1o%).

Example 6

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

8o g of 4-(1.4.5-triphenylimidazol-2-yl mercapto)-butyric acid ethyl ester are dissolved in 7oo cc. of ethanol at 8o°C. 22 g of sodium hydroxide dissolved in 2oo cc. of ethanol are added thereto and the mixture is stirred for 3 hours at 8o°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 (1oo%), 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 5oo cc. of ethanol,

11.5 g of sodium hydroxide in 1oo 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.: 1o8°C.

MS [m/e]: 47o(33%), 426(13%), 328(1oo%), 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 1ooo cc. of ethanol,

8.6 g of sodium hydroxide in 1oo cc. of ethanol.

The mixture is refluxed for 4 hours.

Yield: 31.5 g F.: 189 to 191°C.

IR (in KBr): 17o5 cm^{-1}

MS [m/e]: 414(8.5%), 328(94%), 294(16%), 261(1oo%).

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 25o cc. of 96 % ethanol. The equivalent amount of ethanolic sodalye (1 g of NaOH in 1o 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 1o

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

Similar to Example 9 from:

7o g of 4-(1.4.5-triphenylimidazol-2-yl mercapto)-butyric acid in 12oo 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 5oo cc. of 96 % ethanol,

2 g of NaOH in 2o cc. of ethanol.

Yield: 24.4 g

IR (in KBr): 16o4 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

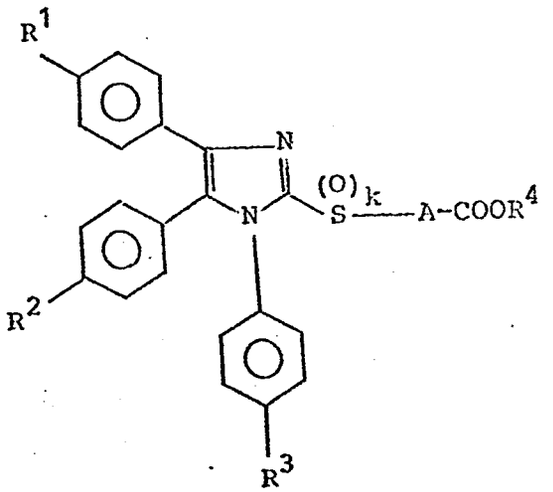
4-(1.4.5-Triphenylimidazol-2-yl sulfinyl)-butyric acid.

2o g of 4-(1.4.5-triphenylimidazol-2-yl mercapto)-butyric acid are dissolved in 5oo cc. of chloroform. A solution of 8.4 g of 3-chloroperbenzoic acid in 1oo cc. of chloroform is added slowly and dropwise at $0^{o}C$. After stirring for 3 hours at $0^{o}C$., 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.: $199^{o}C$.

Patent Claims:

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



I

wherein

k is the numeral 0, 1 or 2,

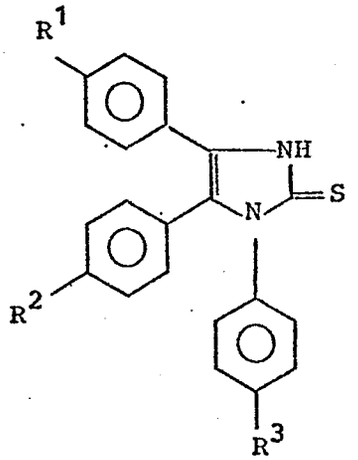
R^1, R^2 and R^3 which are the same or different from each other, represent hydrogen, fluorine, chlorine, methyl, methoxy or trifluoromethyl,

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

A is the group $-C(CH_3)_2-$, $-CH(CH_2)_m-CH_3-$, $-(CH_2)_n-$ or $-(CH_2)_{n-2}-CH(CH_3)-$

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



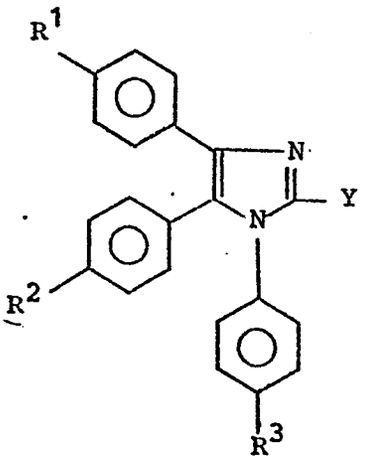
II

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

$$X\text{-}A\text{-}COOR^4 \qquad III$$

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

$$HS\text{-}A\text{-}COOR^4 \qquad V$$

wherein A and R^4 have the meaning as given in formula I, in an 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.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 84107292.9

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³ 4)
A	EP - A2 - 0 013 732 (SCHERING AKTIENGESELLSCHAFT) * Abstract; claim 44 * ----	1,2,4,5	C 07 D 233/84 A 61 K 31/415

TECHNICAL FIELDS SEARCHED (Int. Cl. ³ 4)

C 07 D 233/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	19-09-1984	BRUS

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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