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(54) **-Omega-aryl-alkylthienyl compounds, process for their preparation and pharmaceutical products containing these compounds.**

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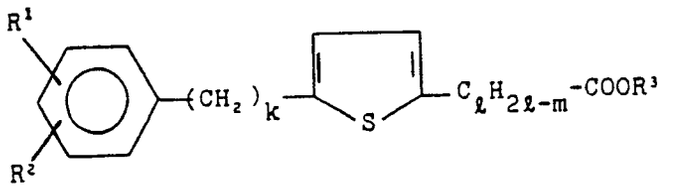
Description

The invention relates to ω-aryl-alkylthienyl compounds having the formula I



(I)

wherein k is an integer from 3 to 10, l is an integer from 4 to 10, m is zero or 2, R^1 and R^2 can be identical or different and independently of one another denote hydrogen, fluorine, chlorine, bromine or a C_{1-4}-alkyl, trifluoromethyl, hydroxyl, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-C_{1-4}-alkylamino, C_{1-4}-acylamino or nitro group and R^3 denotes hydrogen, an alkali metal ion, a straight-chain or branched alkyl group with 1 to 6 carbon atoms or a benzyl group.

Thus, the invention relates to omega-aryl-alkyl thienyl alkanoic acids of Formula I which in its $-C_lH_{2l-m}-$ part may contain a double bond. These acids are the corresponding omega-aryl-alkyl thienyl alkenoic acids of Formula I wherein m always is the integer 2 and the $-C_lH_{2l-m}-$ part of the molekule always is an alkenylene group having the Formula $-C_{4-10}H_{6-18}-$ and having an olefinically unsaturated double bond such as the $-CH_2-CH=CH-CH_2-$ group with l being 4 and m being 2. Compt. rend. No. 239 (1954) p. 1224 to 1226 discloses for instance the compounds 4-(5-Benzyl-thien-2-yl)butyric acid and 4-[5-(2-phenyl(ethyl)-thien-2-yl]-butyric acid.

The ω- aryl-alkylthienylalkanoic(alkenoic) acids according to the invention and their derivatives exhibit a powerful antiinflammatory activity which is particularly suitable for the treatment of chronically inflammatory processes (for example diseases of the rheumatic type) and they therefore are used in the treatment of such processes and diseases in humans. It was found surprisingly that, in contrast to the usual non-steroid antiinflammatories, the action is not to be attributed to inhibition of the cyclooxygenase activity but to immuno-modulatory properties, i.e. properties which have both a controlled stimulating effect and an inhibiting effect on the immune system. Thus, the substances exhibit, for example, inhibition of the complement system, on the one hand, and a stimulating action on lymphocites, on the other hand; in an animal model of adjuvant arthritis, for example, stimulating or inhibiting effects can be observed both on prophylactic and on therapeutic administration, depending upon the circumstances.

The peculiarity of the compounds according to the invention lies in the selective inhibition of the lipoxygenase metabolism product leukotriene B_4, whilst the enzyme cyclooxygenase remains uninfluenced.

The substances are furthermore used in the treatment of various ulcers in humans.

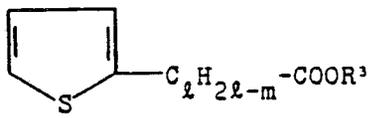
The compounds according to the invention include, for example ω-[5-(3-phenylpropyl)-thien-2-yl]-pentanoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-pent-4-enoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-hexanoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-hex-5-enoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-heptanoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-hept-6-enoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-octanoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-oct-7-enoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-nonanoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-non-8-enoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-decanoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-dec-9-enoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-undecanoic acid, ω-[5-(3-phenylpropyl)-thien-2-yl]-undec-10-enoic acid, ω-[5-(4-phenylbutyl)-thien-2-yl]-pentanoic acid, ω-[5-(4-phenylbutyl)-thien-2-yl]-pent-4-enoic acid, ω-[5-(4-phenylbutyl)-thien-2-yl]-hexanoic acid, ω-[5-(4-phenylbutyl)-thien-2-yl]-hex-5-enoic acid, ω-[5-(5-phenylpentyl)-thien-2-yl]-pentanoic acid, ω-[5-(5-phenylpentyl)-thien-2-yl]-pent-4-enoic acid, ω-[5-(5-phenylpentyl)-thien-2-yl]-hexanoic acid, ω-[5-(5-phenylpentyl)-thien-2-yl]-hex-5-enoic acid, ω-[5-(6-phenylhexyl)-thien-2-yl]-pentanoic acid, ω-[5-(6-phenylhexyl)-thien-2-yl]-pent-4-enoic acid, ω-(5-(6-phenylhexyl)-thien-2-yl]-hexanoic acid, ω-[5-(6-phenylhexyl)-thien-2-yl]-hex-5-enoic acid, ω-[5-(7-phenylheptyl)-thien-2-yl]-pentanoic acid, ω-[5-(7-phenylheptyl)-thien-2-yl]-pent-4-enoic acid, ω-[5-(7-phenylheptyl)-thien-2-yl]-hexanoic acid, ω-[5-(7-phenylheptyl)-thien-2-yl]-hex-5-enoic acid, ω-[5-(8-phenyloctyl)-thien-2-yl]-pentanoic acid, ω-[5-(8-phenyloctyl)-thien-2-yl]-pent-4-enoic acid, ω-[5-(8-phenyloctyl)-thien-2-yl]-hexanoic acid and ω-[5-(8-phenyloctyl)-thien-2-yl]-hex-5-enoic acid.

The hydrogen atoms of the phenyl radicals in the abovementioned compounds can be substituted by suitable substituents (radicals R^1 and R^2 in formula I), for example: 5-{5-[3-(4-fluorophenyl)-propyl]-thien-2-yl}-pentenoic acid, 5-{5-[3-(4-chloropheny)-propyl]-thien-2-yl}-pentanoic acid, 5-{5-[3-(3,4-dichlorophenyl)-propyl]-thien-2-yl}-pentanoic acid, 5-{5-[3-(4-methylphenyl)-propyl]-thien-2-yl}-pentanoic acid, 5-{5-[3-(4-methoxyphenyl)-propyl]-thien-2-yl}-pentanoic acid, 5-{5-[3-(3,4-dimethoxyphenyl)-propyl]-thien-2-yl}-pentanoic acid, 5-{5-[3-(4-hydroxyphenyl)-propyl]-thien-2-yl}-pentanoic acid, 5-{5-[3-(3,4-dihydroxyphenyl)-propyl]-thien-2-yl}-pentanoic acid and 5-{5-[3-(4-acetylaminophenyl)-propyl]-thien-2-yl}-pentanoic acid.

Besides the acids mentioned, the corresponding derivatives are compounds according to the invention, such as, for example, sodium salts, potassium salts, methyl esters, ethyl esters, isopropyl esters

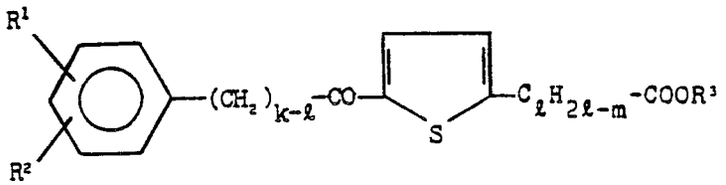
and benzyl esters, for example: sodium 5-[5-(3-phenylpropyl)-thien-2-yl]-pentanoate, potassium 5-[5-(3-phenylpropyl)-thien-2-yl]-pentanoate, methyl 5-[5-(3-phenylpropyl)-thien-2-yl]-pentanoate, ethyl 5-[5-(3-phenylpropyl)-thien-2-yl]-pentanoate, isopropyl 5-[5-(3-phenylpropyl)-thien-2-yl]-pentanoate and benzyl 5-[5-(3-phenylpropyl)-thien-2-yl]-pentanoate.

The ω-aryl-alkylthienylalkanoic(alkenoic) acids and their derivatives can be prepared by several processes. Thus, the saturated compounds can be synthesized by a process in which known ω-(2-thienyl)-alkanoic acid esters of the formula II



II

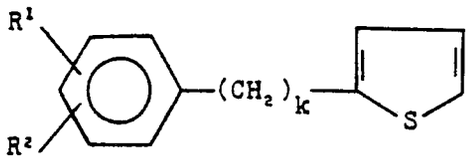
in which m is zero and l and R^3 have the meanings given in formula I, are reacted with ω-phenylalkanoic acid chlorides or anhydrides in the presence of Friedel-Crafts catalysts, such as, for example, aluminium chloride, tin tetrachloride, polyphosphoric acid, in inert solvents, such as, for example, carbon disulphide, dichloroethane, trichloroethane, nitrobenzene, to give 5-(ω-phenylalkanoyl)-thien-2-yl-alkanoic acid esters for the formula III



III

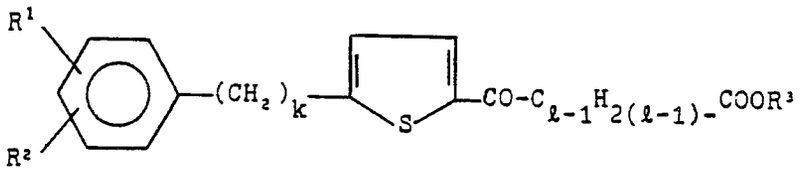
wherein m = 0 and k, l, R^1, R^2 and R^3 have the meanings given in formula I, and the compounds III are reduced and hydrolysed with hydrazine, preferably in the presence of an alkali metal hydroxide and high-boiling solvents, such as, for example, diglycol or triglycol, at temperatures of 150—220°C to give the compounds I according to the invention where R^3 = H. The compounds I wherein R^3 = H can in turn be esterified or converted into the alkali metal salts by the customary processes.

A further possibility of synthesizing the compounds I comprises a process in which ω-phenylalkyl-thiophenes of the formula IV



IV

wherein k, R^1 and R^2 have the meanings given in formula I, are reacted with dicarboxylic acid dichlorides, dicarboxylic acid monoester chlorides or dicarboxylic acid anhydrides in the presence of Friedel-Crafts catalysts, such as, for example, aluminium chloride, tin tetrachloride, polyphosphoric acid, in inert solvents, such as, for example, carbon disulphide, dichloroethane, trichloroethane, nitrobenzene, to give ω-oxo-ω-[5-(ω'-phenylalkyl)-thien-2-yl]-alkanoic acids or esters thereof, of the formula V



V

wherein k, l, R^1, R^2 and R^3 have the meanings given in formula I, and the compounds V are reduced and hydrolysed with hydrazine, preferably in the presence of an alkali metal hydroxide and high-boiling solvents, such as, for example, diglycol or triglycol, at temperatures of 150—220°C to give the compounds I according to the invention where R^3 = H.

The present invention also relates to pharmaceutical products containing compounds of the formula I. The pharmaceutical products according to the invention are those for enteral, such as oral or rectal, and parenteral administration, which contain the pharmaceutical active compounds by themselves or together

with a customary pharmaceutically usable excipient. The pharmaceutical formulation of the active compound is advantageously in the form of individual doses which are matched to the desired administration, such as, for example, tablets, coated tablets, capsules, suppositories, granules, solutions, emulsions or suspensions. The dosage of the compounds is usually between 0.1—500 mg per dose, preferably between 1—150 mg per dose, and can be administered once or several times, preferably two or three times, daily.

The preparation of the compounds according to the invention is illustrated in more detail by the following examples. The melting points given were measured with a Büchi 510 melting point determination apparatus and are uncorrected. The IR spectra were recorded with a Perkin Elmer 257 apparatus and the mass spectra with a MAT—311A apparatus.

Example 1

5-[5-(3-Phenylpropyl)-thien-2-yl]-valeric acid

a) Methyl 5-[5-(1-oxo-3-phenylpropyl)-thien-2-yl]-valerate

40 g of powdered aluminium chloride are added to 200 ml of 1,2-dichloroethane and 50 g of methyl 5-(2-thienyl)-valerate are added dropwise, while cooling with ice. 44.3 g of 3-phenylpropionyl chloride are then added such that the temperature does not rise above 20°C. The mixture is stirred at room temperature for 14 hours and poured onto ice and a little concentrated hydrochloric acid is added to dissolve precipitated aluminium chloride. The organic phase is separated off, the aqueous phase is extracted twice with dichloroethane, the organic extracts are combined, washed with 5% strength sodium bicarbonate solution and water and dried over sodium sulphate and the solvent is evaporated off in vacuo. The residue is purified by column chromatography (silica gel/chloroform).

Yield: 42 g of oil.

IR (film): 1740, 1655 cm^{-1}.

b) 5-[5-(3-Phenylpropyl)-thien-2-yl]-valeric acid

14 g of methyl 5-[5-(1-oxo-3-phenylpropyl)-thien-2-yl]-valerate, 100 ml of triethylene glycol, 7.8 g of potassium hydroxide and 4.8 g of hydrazine hydrate are mixed, the mixture is heated under reflux for 2 hours and a mixture of hydrazine and water is then slowly distilled off, until the temperature in the reaction mixture is 195°C. When the evolution of nitrogen has ended, the solution is cooled, diluted with 100 ml of water, acidified and extracted with ether. The ether extract is washed with water and dried over sodium sulphate and the solvent is stripped off. The residue is purified by column chromatography (silica gel/chloroform).

Yield: 2.8 g of oil.

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

MS [m/e]: 302 (M^+, 100%), 215 (56%), 198 (72%) and 111 (41%).

Example 2

Sodium 5-[5-(3-phenylpropyl)-thien-2-yl]-valerate

3 g of 5-[5-(3-phenylpropyl)-thien-2-yl]-valerate are mixed with 50% strength ethanol and the equivalent amount of sodium hydroxide, the mixture is stirred for 1 hour and the solvent is stripped off in vacuo. The residue is powdered.

Yield: quantitative.

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

Example 3

5-[5-(5-Phenylpentyl)-thien-2-yl]-valeric acid

a) Methyl 5-[5-(1-oxo-5-phenylpentyl)-thien-2-yl]-valerate

This compound is prepared analogously to Example 1a from: 100 ml of 1,2-dichloroethane, 21 g of aluminium chloride, 26 g of methyl 5-(2-thienyl)-valerate and 27 g of 5-phenylvaleryl chloride.

Yield: 31 g of oil.

IR (film): 1740, 1660 cm^{-1}.

b) 5-[5-(5-Phenylpentyl)-thien-2-yl]-valeric acid

This compound is prepared analogously to Example 1b from: 15 g of methyl 5-[5-(1-oxo-5-phenylpentyl)-thien-2-yl]-valerate, 7.6 g of potassium hydroxide, 100 ml of triethylene glycol and 5 g of hydrazine hydrate.

Yield: 7.4 g of melting point 33°C.

IR (in KBr): 1712 cm^{-1}.

MS [m/e]: 330 (M^+, 100%), 243 (86%), 197 (93%) and 91 (40%).

Example 4

Sodium 5-[5-(5-phenylpentyl)-thien-2-yl]-valerate

This compound is prepared analogously to Example 2.

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

Example 5

5-[5-(6-Phenylhexyl)-thien-2-yl]-valeric acid

a) Methyl 5-[5-(1-oxo-6-phenylhexyl)-thien-2-yl]-valerate

This compound is prepared analogously to Example 1a from: 100 ml of 1,2-dichloroethane, 24.2 g of aluminium chloride, 30.6 g of methyl 5-(2-thienyl)-valerate and 34.0 g of 5-phenylvaleryl chloride.

Yield: 40.1 g.

b) 5-[5-(6-Phenoxyhexyl)-thien-2-yl]-valeric acid

This compound is prepared analogously to Example 1b from: 22.8 g of methyl 5-[5-(1-oxo-6-phenylhexyl)-thien-2-yl]-valerate, 11.1 g of potassium hydroxide, 250 ml of triethylene glycol and 7.0 g of hydrazine hydrate.

Yield: 14.5 g of melting point 54°C.

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

MS [m/e]: 344 (M^+, 83%), 257 (68%), 197 (100%) and 91 (72%).

Example 6

Sodium 5-[5-(6-phenylhexyl)-thien-2-yl]-valerate

This compound is prepared analogously to Example 2.

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

Example 7

Ethyl 5-[5-(3-phenylpropyl)-thien-2-yl]-valerate

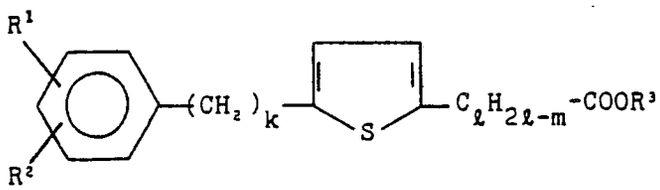
3 g of 5-[5-(3-phenylpropyl)-thien-2-yl]-valeric acid are dissolved in 10 ml of ethanol and the solution is saturated with HCl gas. The solution is stirred at room temperature for 24 hours and concentrated in vacuo. Purification by column chromatography (silica gel/hexane/ethyl acetate).

Yield: 2.95 g of oil.

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

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

1. ω-Aryl-alkylthienyl compounds having the Formula I

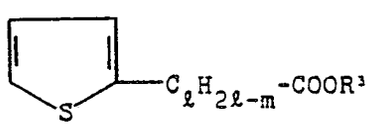


(I)

wherein k is an integer from 3 to 10, l is an integer from 4 to 10, m is zero or 2, R^1 and R^2 can be identical or different and independently of one another are hydrogen, fluorine, chlorine, bromine, C_{1-4}-alkyl, trifluoromethyl, hydroxyl, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino, di-C_{1-4}-alkylamino, C_{1-4}-acylamino and nitro and R^3 is hydrogen, an alkali metal ion, a straight-chain or branched alkyl group with 1 to 6 carbon atoms or a benzyl group.

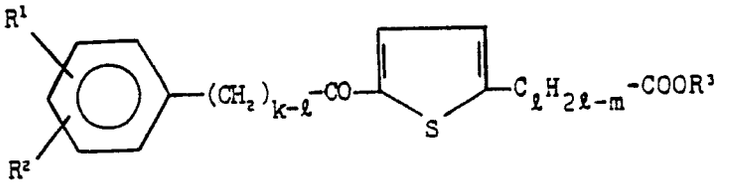
2. ω-Aryl-alkylthienyl compounds according to claim 1 wherein k is an integer from 3 to 10, l is an integer from 4 to 10, m is zero or 2, R^1 and R^2 can be identical or different and independently of one another are hydrogen, fluorine, chlorine, methyl, trifluoromethyl, hydroxyl, methoxy, amino or acetylamino and R^3 is hydrogen, an alkali metal ion or methyl, ethyl or isopropyl.

3. Process for the preparation of compounds of the formula I according to Claims 1 and 2, characterised in that ω-(2-thienyl)-alkanoic acid esters of the formula II



II

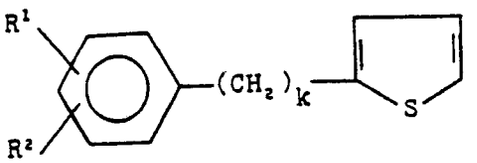
in which m is zero and l and R^3 have the meanings given in formula I, are treated with ω-phenylalkanoic acid chlorides or anhydrides under the customary conditions of the Friedel-Crafts reaction to give 5-(ω-phenylalkanoyl)-thien-2-ylalkanoic acid esters of the formula III



III

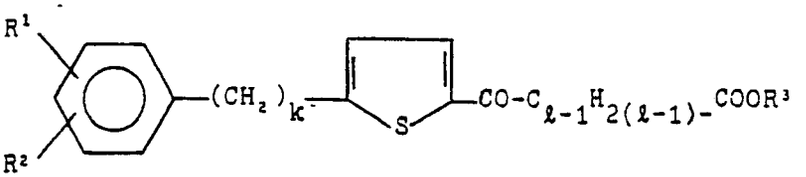
wherein m is zero and k, l, R^1, R^2 and R^3 have the meanings given in formula I, and the compounds III are reduced and hydrolysed with hydrazine in the presence of an alkali metal hydroxide under the customary conditions of the Wolff-Kishner or Huang-Minlon reduction to give the compounds I according to the invention where R^3 = H, and these are in turn esterified or converted into the alkali metal salts by the customary processes.

4. Process for the preparation of compounds of the formula I according to Claims 1 and 2, characterised in that ω-phenylalkylthiophenes of the formula IV



IV

wherein k, R^1 and R^2 have the meanings given in formula I, are reacted with dicarboxylic acid dichlorides, dicarboxylic acid monoester chlorides or dicarboxylic acid anhydrides under the customary conditions of the Friedel-Crafts reaction to give ω-oxo-ω-[5-(ω'-phenylalkyl)-thien-2-yl]-alkanoic acid or esters thereof of the formula V



V

wherein k, l, R^1, R^2 and R^3 have the meanings given in formula I, and the compounds V are reduced in the presence of an alkali metal hydroxide under the customary conditions of the Wolff-Kishner reduction to give the compounds I according to the invention where R^3 = H and m = 0.

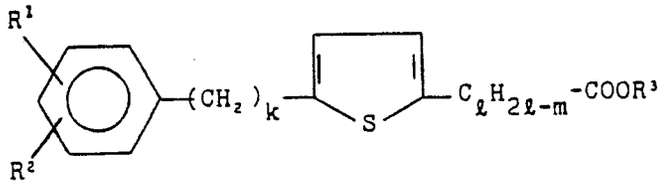
5. Process for the preparation of compounds of the formula I according to Claims 1 and 2, where l = 4—10 and m = 2, characterised in that aldehydes of the formula VI are reacted with ω-hydroxycarbonylalkyl- or ω-alkoxycarbonylalkyl-phosphonium salts or -phosphonic acid esters under the conditions of the Wittig or Wittig-Horner synthesis, the acids or esters of the compounds I being formed.

6. Pharmaceutical products, characterised in that they contain a compound of the formula I according to Claims 1 and 2 as the active compound, mixed with customary pharmaceutical auxiliaries and excipients.

7. The use of a compound of formula I according to Claims 1 and 2 for the preparation of pharmaceutical products for the treatment of chronically inflammatory processes or for the treatment of various ulcers or for the treatment of cancer.

Claims for the Contracting State: AT

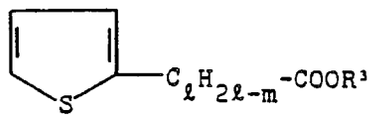
1. Process for the preparation of ω-aryl-alkylthienyl compounds having the formula I



(I)

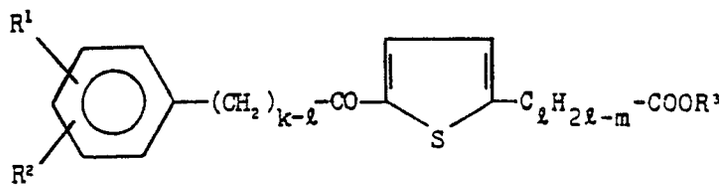
wherein k is an integer from 3 to 10, l is an integer from 4 to 10, m is zero or 2, R^1 and R^2 can be identical or different and independently of one another are hydrogen, fluorine, chlorine, bromin, C_{1-4}-alkyl, trifluoro-

methyl, hydroxyl, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino, di-C_{1-4}-alkylamino, C_{1-4}-acylamino and nitro and R^3 is hydrogen, an alkali metal ion, a straight-chain or branched alkyl group with 1 to 6 carbon atoms or a benzyl group, characterised in that ω-(2-thienyl)-alkanoic acid esters of the formula II



II

in which m is zero and l and R^3 have the meanings given in formula I, are reacted with ω-phenylalkanoic acid chlorides or anhydrides under the customary conditions of the Friedel-Crafts reaction to give 5-(ω-phenylalkanoyl)-thien-2-ylalkanoic acid esters of the formula III

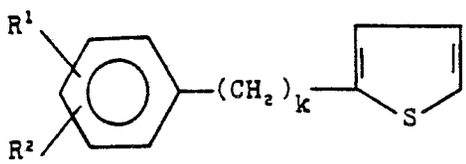


III

wherein m is zero and k, l, R^1, R^2 and R^3 have the meanings given in formula I, and the compounds III are reduced and hydrolysed with hydrazine in the presence of an alkali metal hydroxide under the customary conditions of the Wolff-Kishner or Huang-Minlon reduction to give the compounds I according to the invention where R^3 = H, and these are in turn esterified or converted into the alkali metal salts by the customary processes.

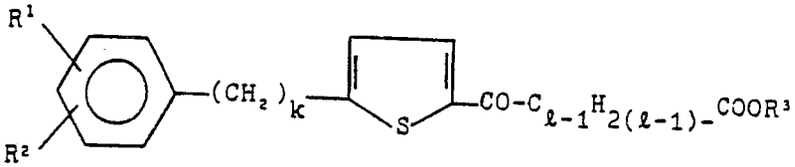
2. Process according to claim 1, wherein k is an integer from 3 to 10, l is an integer from 4 to 10, m is zero or 2, R^1 and R^2 can be identical or different and independently of one another are hydrogen, fluorine, chlorine, methyl, trifluoromethyl, hydroxyl, methoxy, amino or acetylamino and R^3 is hydrogen, an alkali metal ion or methyl, ethyl or isopropyl.

3. Process for the preparation of compounds of the formula I according to Claims 1 and 2, characterised in that ω-phenylalkylthiophenes of the formula IV



IV

wherein k, R^1 and R^2 have the meanings given in formula I, are reacted with dicarboxylic acid dichlorides, dicarboxylic acid monoester chlorides or dicarboxylic acid anhydrides under the customary conditions of the Friedel-Crafts reaction to give ω-oxo-ω-[5-(ω'-phenylalkyl)-thien-2-yl]-alkanoic acid or esters thereof of the formula V



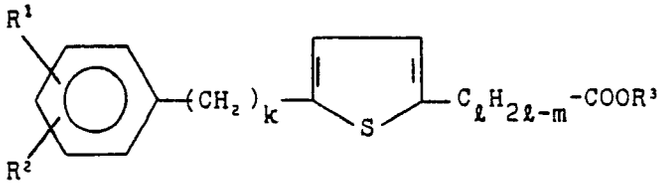
V

wherein k, l, R^1, R^2 and R^3 have the meanings given in formula I, and the compounds V are reduced in the presence of an alkali metal hydroxide under the customary conditions of the Wolff-Kishner reduction to give the compounds I according to the invention where R^3 = H and m = 0.

4. Process for the preparation of compounds of the formula I according to claims 1 and 2, where l = 4—10 and m = 2, characterised in that aldehydes of the formula VI are reacted with ω-hydroxycarbonylalkyl- or ω-alkoxycarbonylalkyl-phosphonium salts or -phosphonic acid esters under the conditions of the Wittig or Wittig-Horner synthesis, the acids or esters of the compounds I being formed.

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

1. ω-Aryl-alkylthienverbindungen der allgemeinen Formel I

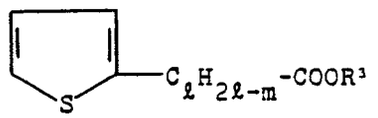


(I)

worin k eine ganze Zahl von 3—10, l eine ganze Zahl von 4—10, m Null oder 2, R^1 und R^2 gleich oder verschieden sein können und gleich unabhängig voneinander Wasserstoff, Fluor, Chlor, Brom oder eine C_{1-4}-Alkyl-, Trifluoromethyl-, Hydroxy- C_{1-4}-Alkoxy-, Amino-, C_{1-4}-Alkylamino oder Di-C_{1-4}-alkylamino-, C_{1-4}-Acylamino- oder Nitro-Gruppe, R^3 Wasserstoff, ein Alkaliion oder eine geradkettige oder verzweigte Alkylgruppe mit 1—6 Kohlenstoffatomen oder einen Benzylrest bedeuten.

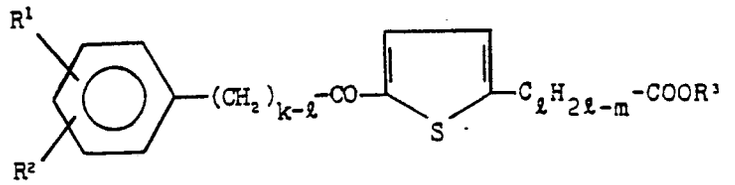
2. ω-Aryl-alkylthienylverbindungen der allgemeinen Formel I, worin k eine ganze Zahl von 3—10, l eine ganze Zahl von 4—10, m Null oder 2, R^1 und R^2 gleich oder verschieden sein können und unabhängig voneinander Wasserstoff, Fluor, Chlor, eine Methyl-, Trifluoromethyl-, Hydroxy-, Methoxy-, Amino- oder Acetylamino-Gruppe, R^3 Wasserstoff, ein Alkaliion oder Methyl, Ethyl, Isopropyl bedeuten.

3. Verfahren zur Herstellung von Verbindungen der Formel I gemäß den Ansprüchen 1 und 2, dadurch gekennzeichnet, daß man ω-(2-Thienyl)-alkansäureester der Formel II



II

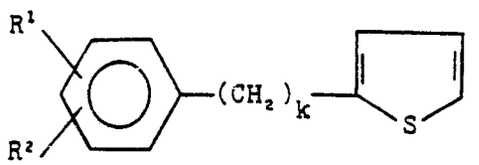
in der m Null ist und l und R^3 die in Formel I angegebenen Bedeutungen haben, unter den üblichen Bedingungen der Friedel-Crafts-Reaktion mit ω-Phenylalkansäurechloriden oder -anhydriden zu 5-(ω-Phenylalkanoyl)-thien-2-ylalkansäureestern der Formel III umsetzt,



III

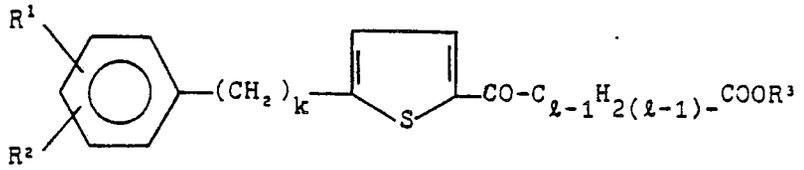
worin m Null ist und k, l, R^1, R^2, R^3 die in Formel I angegebenen Bedeutungen haben, und die Verbindungen III mit Hydrazin in Gegenwart von Alkalihydroxid unter den üblichen Bedingungen der Wolff-Kishner- bzw. Huang-Minlon-Reduktion zu den erfindungsgemäß'en Verbindungen I mit R^3 = H reduziert und verseift, die ihrerseits nach den gebräuchlichen Verfahren verestert oder in die Alkalisalze überführt werden.

4. Verfahren zur Herstellung von Verbindungen der Formel I gemäß den Ansprüchen 1 und 2, dadurch gekennzeichnet, daß man ω-Phenylalkylthiophene der Formel IV



IV

worin k, R^1, R^2 die in Formel I angegebenen Bedeutungen haben, unter den üblichen Bedingungen der Friedel-Crafts-Reaktion mit Dicarbonsäuredichloriden, Dicarbonsäuremonoesterchloriden oder Dicarbonsäureanhydriden zu ω-Oxo-ω-[5-(ω'-phenylalkyl)-thien-2-yl]-alkansäuren bzw. deren Estern der Formel V umsetzt



V

worin k, l, R^1, R^2, R^3 die in Formel I angegebenen Bedeutungen haben, und die Verbindungen V in Gegenwart von Alkalihydroxid unter den üblichen Bedingungen der Wolff-Kishner-Reduktion zu den erfindungsgemäßen Verbindungen I mit R^3 = H und m = 0 reduziert.

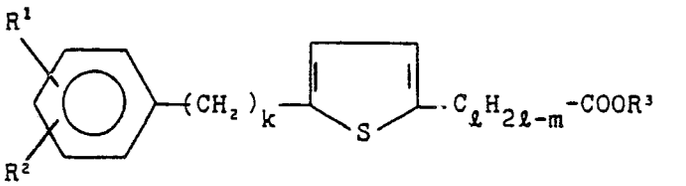
5. Verfahren zur Herstellung von Verbindungen der Formel I, gemäß den Ansprüchen 1 und 2, mit l = 4—10 und m = 2, dadurch gekennzeichnet, daß man Aldehyde der Formel VI mit ω-Hydroxycarbonalalkyl- oder ω-Alkoxycarbonylalkylphosphoniumsalzen bwz. -phosphonsäureestern unter den Bedingungen der Wittig- bzw. Wittig-Horner-Synthese umsetzt, wobei die Säuren oder Ester der Verbindungen I entstehen.

6. Pharmazeutische Präparate, dadurch gekennzeichnet, daß sie eine Verbindung der Formel I gemäß den Ansprüchen 1 und 2 als Wirkstoff im Gemisch mit üblichen pharmazeutischen Hilfs- und Trägerstoffen enthalten.

7. Verwendung einer Verbindung der Formel I gemäß Anspruch 1 und 2 zur Herstellung von pharmazeutischen Produkten zur Behandlung chronisch entzündlicher Prozesse oder zur Behandlung verschiedener Geschwülste oder zur Behandlung von Krebs.

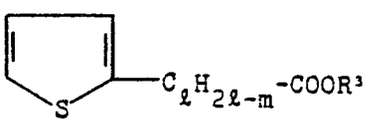
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung von ω-Aryl-alkylthienverbindungen der allgemeinen Formel I



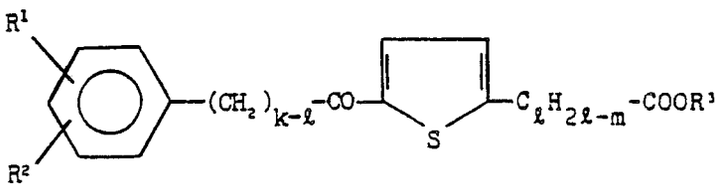
(I)

worin k eine ganze Zahl von 3—10, l eine ganze Zahl von 4—10, m Null oder 2, R^1 und R^2 gleich oder verschieden sein können und unabhängig voneinander Wasserstoff, Fluor, Chlor, Brom oder eine C_{1-4}-Alkyl-, Trifluoromethyl-, Hydroxy-, C_{1-4}-Alkoxy-, Amino-, C_{1-4}-Alkylamino oder Di-C_{1-4}-alkylamino-, C_{1-4}-Acylamino- oder Nitro-Gruppe, R^3 Wasserstoff, ein Alkaliion oder eine geradkettige oder verzweigte Alkylgruppe mit 1—6 Kohlenstoffatomen oder einen Benzylrest bedeuten, dadurch gekennzeichnet, daß man ω-(2-Thienyl)-alkansäureester der Formel II



II

in der m Null ist und l und R^3 die die Formel I angegebenen Bedeutungen haben, unter den üblichen Bedingungen der Friedel-Crafts-Reaktion mit ω-Phenylalkansäurechloriden oder -anhydriden zu 5-(ω-Phenylalkanoyl)-thien-2-ylalkansäureestern der Formel III umsetzt,

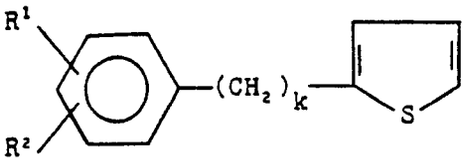


III

worin m Null ist und k, l, R^1, R^2, R^3 die in Formel I angegebenen Bedeutungen haben, und die Verbindungen III mit Hydrazin in Gegenwart von Alkalihydroxid unter den üblichen Bedingungen der Wolff-Kishner- bzw. Huang-Minlon-Reduktion zu den erfindungsgemäßen Verbindungen I mit R^3 = H reduziert und verseift, die ihrerseits nach den gebräuchlichen Verfahren verestert oder in die Alkalisalze überführt werden.

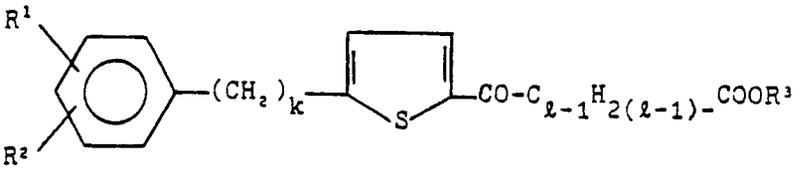
2. Verfahren gemäß Anspruch 1, worin k eine ganze Zahll von 3—10, l eine ganze Zahl von 4—10, m Null oder 2, R^1 und R^2 gleich oder verschieden sein können und unabhängig voneinander Wasserstoff, Fluor, Chlor, eine Methyl-, Trifluormethyl-, Hydroxy-, Methoxy-, Amino- oder Acetylamino-Gruppe, R^3 Wasserstoff, ein Alkaliion oder Methyl, Ethyl, Isopropyl bedeuten.

3. Verfahren zur Herstellung der Verbindungen der Formel I gemäß den Ansprüchen 1 und 2, dadurch gekennzeichnet, daß man ω-Phenylalkylthiophene der Formel IV



IV

worin k, R^1, R^2 die in Formel I angegebenen Bedeutungen haben, unter den üblichen Bedingungen der Friedel-Crafts-Reaktion mit Dicarbonsäuredichloriden, Dicarbonsäuremonoesterchloriden oder Dicarbonsäureanhydriden zu ω-Oxo-ω-[5-(ω'-phenylalkyl)-thien-2-yl]-alkansäuren bzw. deren Erstern der Formel V umsetzt



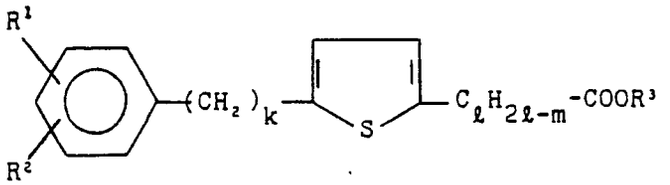
V

worin k, l, R^1, R^2, R^3 die in Formel I angegebenen Bedeutungen haben, und die Verbindungen V in Gegenwart von Alkalihydroxid unter den üblichen Bedingungen der Wolff-Kishner- Reduktion zu den erfindungsgemäßen Verbindungen I mit R^3 = H und m = 0 reduziert.

4. Verfahren zur Herstellung von Verbindungen der Formel I gemäß den Ansprüchen 1 und 2, worin l = 4—10 und m = 2 ist, dadurch gekennzeichnet, daß man Aldehyde der Formel VI mit ω-Hydroxycarbonalalkyl- oder ω-Alkoxycarbonylalkylphosphoniumsalzen bzw. -phosphonsäureestern unter den Bedingungen der Wittig- bzw. Wittig-Horner-Synthese umsetzt, wobei die Säuren oder Ester der Verbindungen I entstehen.

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

1. Composés ω-aryl-alkylthiényliques de formule I:

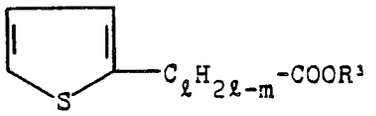


(I)

dans laquelle k représente un nombre entier de 3 à 10, l représenté un nombre entier de 4 à 10, m est égal à zéro ou 2, les groupes R^1 et R^2 peuvent être identiques ou différents et ils représentent indépendamment l'un de l'autre, un atome d'hydrogène, de fluor, de chlore, de brome, un groupe alkyle en C_1—C_4, trifluorométhyle, hydroxyle, alkoxy en C_1—C_4, amino, alkylamino en C_1—C_4, di(alkyle en C_1—C_4)amino, acylamino en C_1—C_4 et nitro, et R^3 représente un atome d'hydrogène, un ion de métal alcalin, un groupe alkyle à chaîne droite ou ramifiée comportant de 1 à 6 atomes de carbone, ou un groupe benzyle.

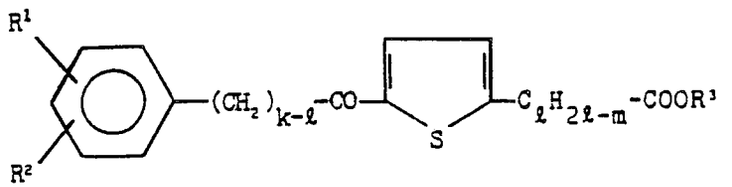
2. Composés ω-aryl-alkylthiényliques selon la revendication 1, dans lesquels k représente un nombre entire de 3 à 10, l représente un nombre entier de 4 à 10, m est égal à zéro ou 2, les groupes R^1 et R^2 peuvent être identiques ou différents et ils représentent indépendamment l'un de l'autre, un atome d'hydrogène, de fluor, de chlore, un groupe méthyle, trifluorométhyle, hydroxyle, méthoxy, amino ou acétylamino, et R^3 représente un atome d'hydrogène, un ion de métal alcalin, ou un groupe méthyle, éthyle ou isopropyle.

3. Procédé de préparation de composés de formule I selon les revendications 1 et 2, caractérisé en ce que l'on fait réagir des esters d'acide ω-(2-thiényl)-alkanoïque de formule II:



II

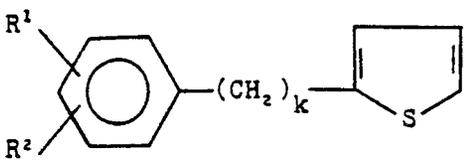
dans lequelle m est égal à zéro, et l et R^3 ont les mêmes définitions que dans la formule I, avec des chlorures ou des anhydrides d'acide ω-phénylalkanoïque dans les conditions habituelles de la réaction de Friedel et Crafts pour obtenir des esters d'acide 5-(ω-phénylalkanoyl)-thién-2-yl-alkanoïque de formule III:



III

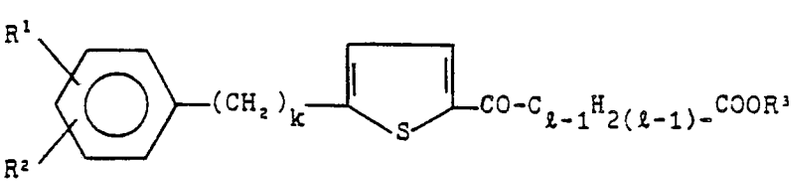
dans laquelle m est égal à 0 et k, l, R^1, R^2 et R^3 ont les mêmes définitions que dans la formule I, et les composés III sont réduits et hydrolysés avec de l'hydrazine en présence d'un hydroxyde de métal alcalin dans les conditions habituelles de la réduction de Wolff-Kishner ou de Huang-Minlon pour obtenir les composés I de la présente invention dans lesquels R^3 = H, et ces derniers sont ensuite estérifiés ou convertis en les sels de métal alcalin correspondants selon les procédés habituels.

4. Procédé de préparation de composés de formule I selon les revendications 1 et 2, caractérisé en ce que l'on fait réagir des ω-phénylalkylthiophènes de formule IV:



IV

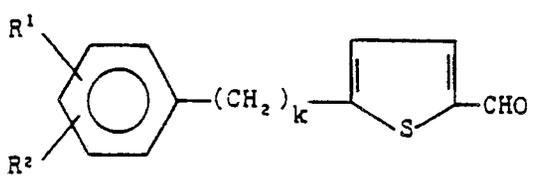
dans laquelle k, R^1 et R^2 ont les mêmes définitions que dans la formule I, avec des dichlorures d'acide dicarboxylique, des chlorures de monoester d'acide dicarboxylique ou des anhydrides d'acide dicarboxylique dans les conditions habituelles de la réaction de Friedel et Crafts pour obtenir un acide ω-oxo-ω-[5-(ω'-phénylalkyl)-thién-2-yl]-alkanoïque ou les esters de celui-ci de formule V:



V

dans laquelle k, l, R^1, R^2 et R^3 ont les mêmes définitions que dans la formule I, et les composés V sont réduits en présence d'un hydroxyde de métal alcalin dans les conditions habituelles de la réduction de Wolff-Kishner pour obtenir les composés I de la présente invention dans lesquels R^3 = H et m = 0.

5. Procédé de préparation de composés de formule I selon les revendications 1 et 2, dans lequel l = 4 à 10 et m = 2, caractérisé en ce que l'on fait réagir des aldéhydes de formule VI:



VI

dans laquelle k, R^1 et R^2 ont les mêmes définitions que dans la formule I, avec des sels de ω-hydroxy-carbonyl-alkyl ou de ω-alkoxycarbonylalkyl-phosphonium, ou des esters d'acide ω-hydroxycarbonylalkyl ou ω-alkoxycarbonylalkyl-phosphonique dans les conditions de synthèse de Wittig ou de Wittig-Horner, pour former les acides ou les esterts des composés I.

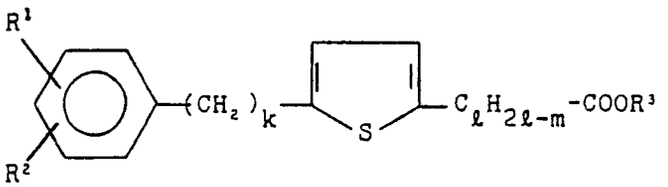
6. Produits pharmaceutiques caractérisés en ce qu'ils contiennent un composé de formule I selon les

revendications 1 et 2 comme composé actif, en mélange avec des adjuvants et des excipients pharmaceutiques habituels.

7. Utilisation d'un composé de formule I selon les revendications 1 et 2 pour la préparation de produits pharmaceutiques pour le traitement de réactions inflammatoires chroniques, pour le traitement de divers ulcères ou pour le traitement d'un cancer.

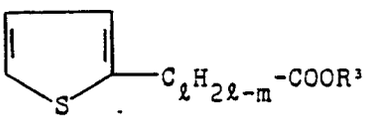
Revendications our l'Etat contractant: AT

1. Procédé de préparation de composés ω-aryl-alkylthiényliques de formule I:



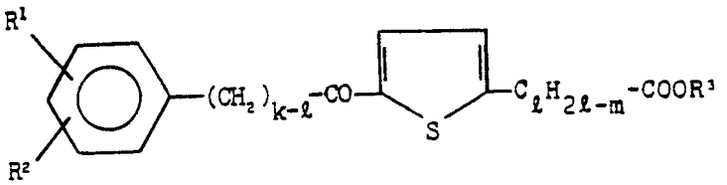
(I)

dans laquelle k représente un nombre entier de 3 à 10, l représente un nombre entier de 4 à 10, m est égal à zéro ou 2, les groupes R^1 et R^2 peuvent être identiques ou différents et ils représentent indépendamment l'un de l'autre, un atome d'hydrogène, de fluor, de chlore, de brome, un groupe alkyle en C_1—C_4, trifluorométhyle, hydroxyle, alcoxy en C_1—C_4, amino, alkylamino en C_1—C_4, di-(alkyle en C_1—C_4)-amino, acylamino en C_1—C_4 et nitro, et R^3 représente un atome d'hydrogène, un ion de métal alcalin, un groupe alkyle à chaîne droite ou ramifiée comportant de 1 à 6 atomes de carbone, ou un groupe benzyle, caractérisé en ce que l'on fait réagir des esters d'acide ω-(2-thiényl)-alcanoïque de formule II:



II

dans laquelle m est égal à zéro, et l et R^3 ont les mêmes définitions que dans la formule I, avec des chlorures ou des anhydrides d'acides ω-phénylalcanoïque dans les conditions habituelles de la réaction de Friedel et Crafts pour obtenir des esters d'acide 5-(ω-phénylalcanoyl)-thién-2-yl-alcanoïque de formule III:

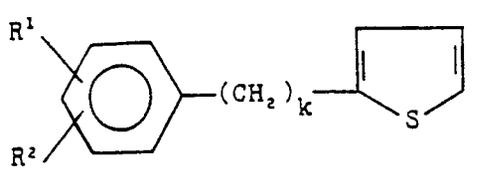


III

dans laquelle m est égal à 0 et k, l, R^1, R^2 et R^3 ont les mêmes définitions que dans la formule I, et les composés III sont réduits et hydrolysés avec de l'hydrazine en présence d'un hydroxyde de métal alcalin dans les conditions habituelles de la réduction de Wolff-Kishner ou de Huang-Minlon pour obtenir les composés I de la présente invention dans lesquels R^3 = H, et ces derniers sont ensuite estérifiés ou convertis en les sels de métal alcalin correspondants selon les procédés habituels.

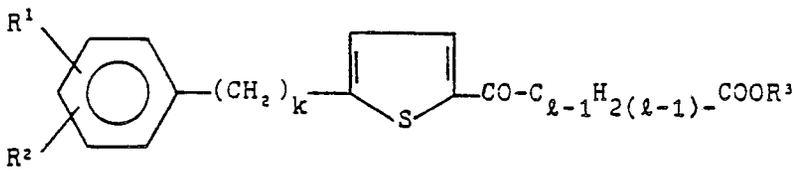
2. Procédé selon la revendication 1, dans lequel k représente un nombre entier de 3 à 10, l représente un nombre entier de 4 à 10, m est égal à zéro ou 2, les groupes R^1 et R^2 peuvent être identiques ou différents et ils représentent indépendamment l'un de l'autre, un atome d'hydrogène, de fluor, de chlore, un groupe méthyle, trifluorométhyle, hydroxyle, méthoxy, amino ou acétylamino, et R^3 représente un atome d'hydrogène, un ion de métal alcalin, ou un groupe méthyle, éthyle ou isopropyle.

3. Procédé de préparation de composé de formule I selon les revendications 1 et 2, caractérisé en ce que l'on fait réagir des ω-phénylalkylthiophènes de formule IV:



IV

dans laquelle k, R^1 et R^2 ont les mêmes définitions que dans la formule I, avec des dichlorures d'acide dicarboxylique, des chlorures de monoester d'acide dicarboxylique ou des anhydrides d'acide dicarboxylique dans des conditions habituelles de la réaction de Friedel et Crafts pour obtenir un acice ω-oxo-ω-[5-(ω'-phénylalkyl)-thién-2-yl]-alcanoïque ou les esters de celui-ci de formule V:



V

dans laquelle k, l, R^1, R^2 et R^3 ont les mêmes définitions que dans la formule I, et les composés V sont réduits en présence d'un hydroxyde de métal alcalin dans les conditions habituelles de la réduction de Wolff-Kishner pour obtenir les composés I de la présente invention dans lesquels R^3 = H et m = 0.

4. Procédé de préparation de composés de formule I selon les revendications 1 et 2, dans lequel l = 4 à 10 et m = 2, caractérisé en ce que l'on fait réagir des aldéhydes de formule VI avec des sels de ω-hydroxycarbonylalkyl ou de ω-alcoxycarbonylalkylphosphonium, ou des esters d'acide ω-hydroxycarbonylalkyl ou ω-alcoxycarbonylalkylphosphonique dans les conditions de synthèse de Wittig ou de Wittig-Horner, pour former les acides ou les esters des composés I.