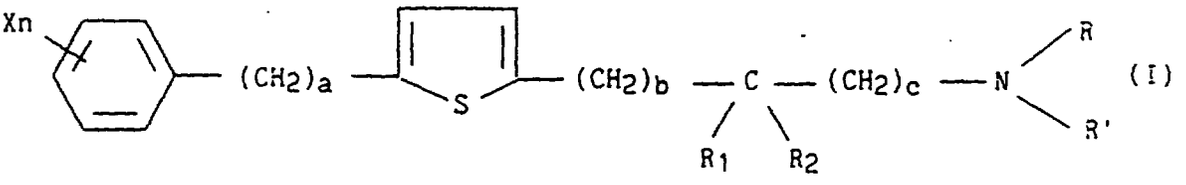
The present invention relates to new thiophene compounds, a process for the preparation thereof, and pharmaceutical compositions containing them.

It relates especially to thiophene compounds of the general formula I :



(I)

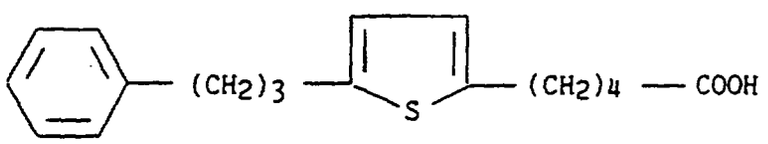
in which :

- X represents a hydrogen or halogen atom, a straight-chain or branched alkyl or alkoxy radical each having from 1 to 5 carbon atoms, or a dialkylamino radical in which each alkyl group contains from 1 to 5 carbon atoms;
- n represents 1 or 2;
- a represents an integer of from 2 to 6 inclusive;
- b represents 2 or 3;
- c represents 1 or 2, and is such that b+c = 4;
- R_1 and R_2, which may be the same or different, each represents a hydrogen atom or an alkyl radical having from 1 to 5 carbon atoms, or
- R_1 and R_2 together with the carbon atom to which they are bonded form a hydrocarbon ring containing from 3 to 6 carbon atoms; and
- R and R', which may be the same or different, each represents a hydrogen atom or an alkyl radical having from 1 to 5 carbon atoms, or
- R and R' together with the nitrogen atom to which they are bonded form a pentagonal or hexagonal heterocyclic radical optionally containing an oxygen atom or a second nitrogen atom which may itself be substituted by a straight-chain or branched alkyl radical containing from 1 to 5 carbon atoms or by an arylalkyl radical in which the alkyl group contains

from 1 to 5 carbon atoms and the aryl group is optionally mono- or poly-substituted by a halogen atom or an alkyl or alkoxy radical each having from 1 to 5 carbon atoms.

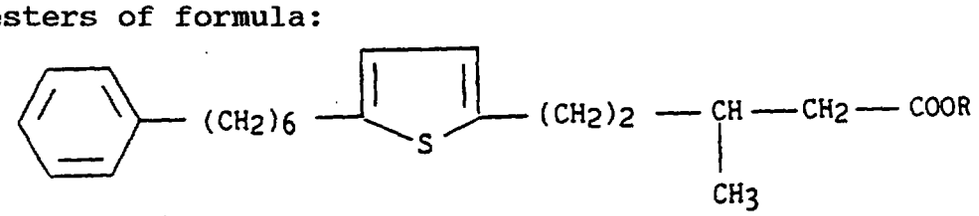
The prior art closest to the present invention is illustrated especially by:

Patent DE.3.407.510, which relates, inter alia, to the acid of the formula :

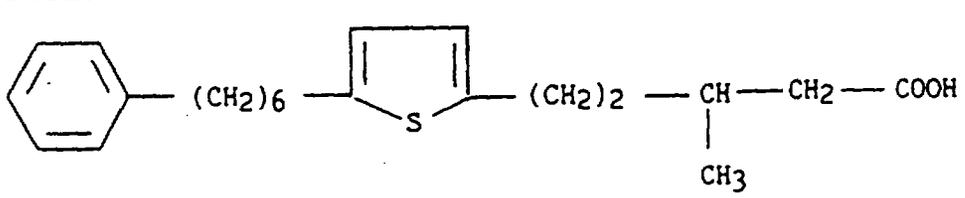


which has an anti-inflammatory activity;

F.F.KNAPP et al., Journal of Nuclear Medicine, 27 (4), 521-531 (1986), which describes in particular the esters of formula:



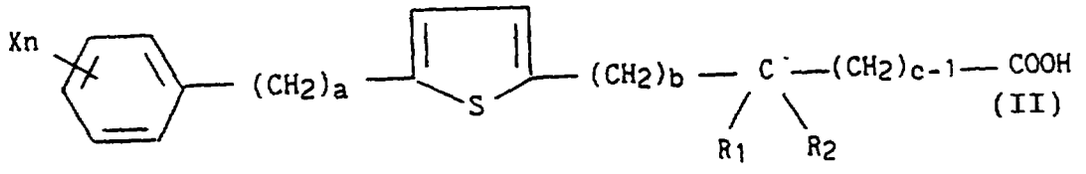
and M.M. GOODMANN et al., J. Med. Chem. 27, 390-397 (1984) which describes, inter alia, the compound of formula:



None of these references either describes or suggests the amines of the general formula I forming the subject of the present invention, which possess an anti-bone resorbent activity which is not mentioned at all for the structurally closest acids and esters of the prior art.

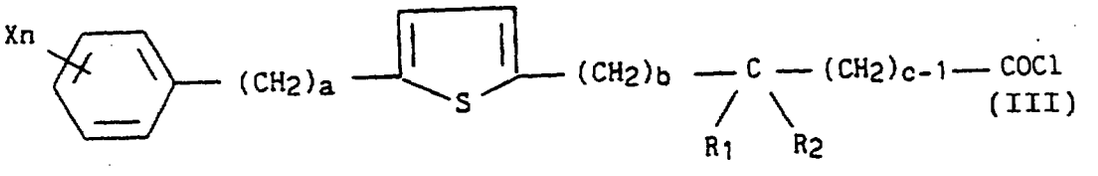
The present invention also relates to a process for the preparation of the compounds of the general formula I, which is characterised in that:

an acid of the general formula II:



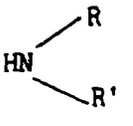
(II)

in which X, n, a, b, c, R_1 and R_2 are as defined hereinbefore is converted by means of, for example, thionyl chloride, into the corresponding acid chloride of the general formula III:



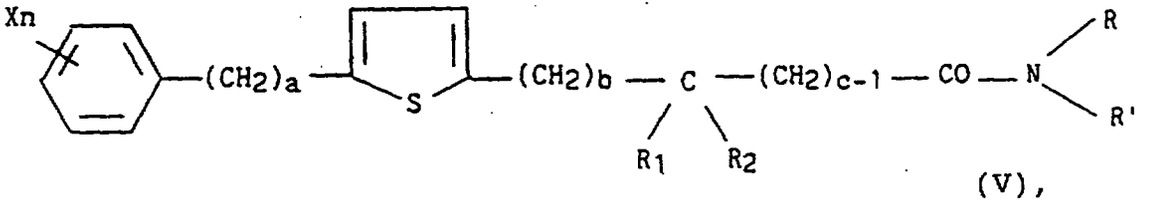
(III)

in which X, n, a, b, c, R_1 and R_2 are as defined hereinbefore,
which acid chloride is used to acylate an amine of the general formula IV:



(IV)

in which R and R' are as defined hereinbefore, and the amide so-obtained of the general formula V :



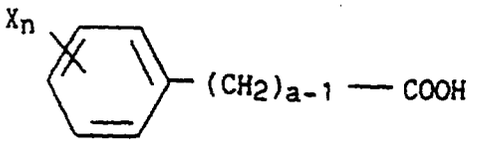
(V),

in which X, n, a, b, c, R_1, R_2, R and R' are as defined

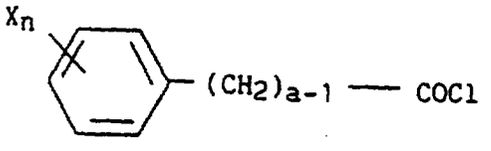
hereinbefore, is reduced.

It is especially advantageous to carry out this reduction by means of $LiAlH_4$ under reflux in a suitable solvent such as, for example, ether.

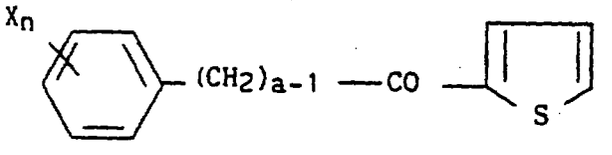
The acid of the general formula II used as starting material was prepared either from an acid of the general formula :



converted into the corresponding acid chloride of the general formula

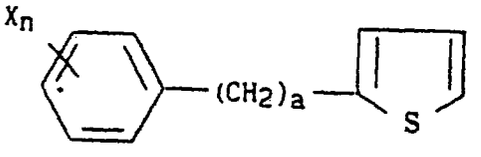


which, together with an equimolar amount of thiophene, is subjected to a Friedel-Crafts reaction in the presence of $AlCl_3$ or $SnCl_4$ to yield the compound of the general formula A :



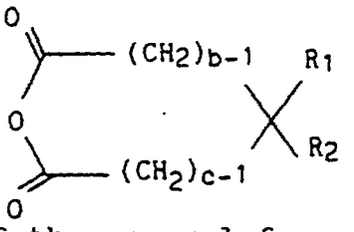
(A)

which, subjected to Wolff-Kishner reduction in the presence of potassium hydroxide and hydrazine, yields a compound of the general formula B :

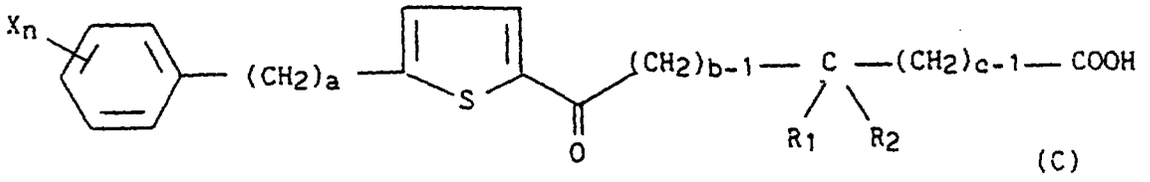


(B)

which, subjected to a Friedel-Crafts reaction with a substituted glutaric anhydride of the general formula :



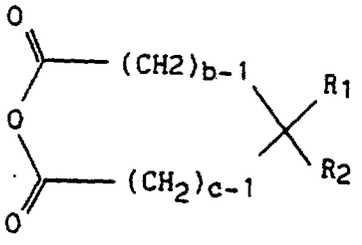
yields a compound of the general formula C :



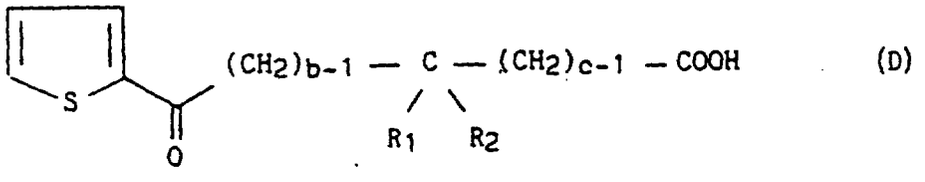
(C)

which, by means of Wolff-Kishner reduction, yields an acid of the general formula II;

or from thiophene and a substituted glutaric anhydride of the general formula :

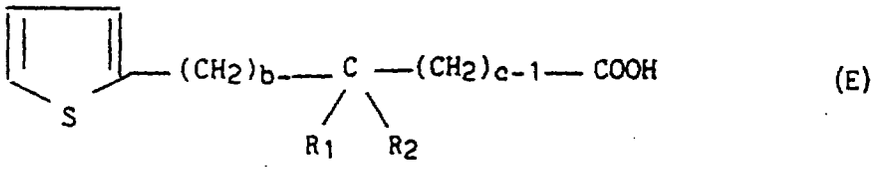


which is subjected to a Friedel-Crafts reaction in the presence of $AlCl_3$ in nitrobenzene to yield a compound of the general formula D :



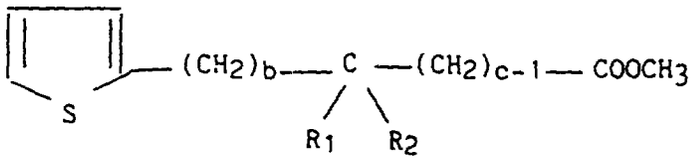
(D)

which is reduced according to the Wolff-Kishner method by means of hydrazine and potassium hydroxide to yield an acid of the general formula E :



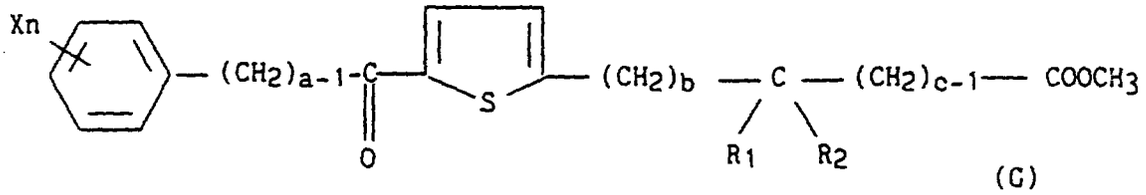
(E)

which is esterified by CH_3OH/PTSA to yield an ester of the general formula F :



(F)

which is subjected to Friedel-Crafts acylation with $SnCl_4$ and CH_2Cl_2 to yield an ester of the general formula G :



(G)

which, by means of Wolff-Kishner reduction using hydrazine and potassium hydroxide, yields an acid of the general formula II;

the variables X, n, a, b, c, R_1, R_2, R and R′ in each of the above formulae having the meanings given hereinbefore.

The compounds of the general formula I yield salts with physiologically tolerable acids, which salts, as such, are included in the present invention.

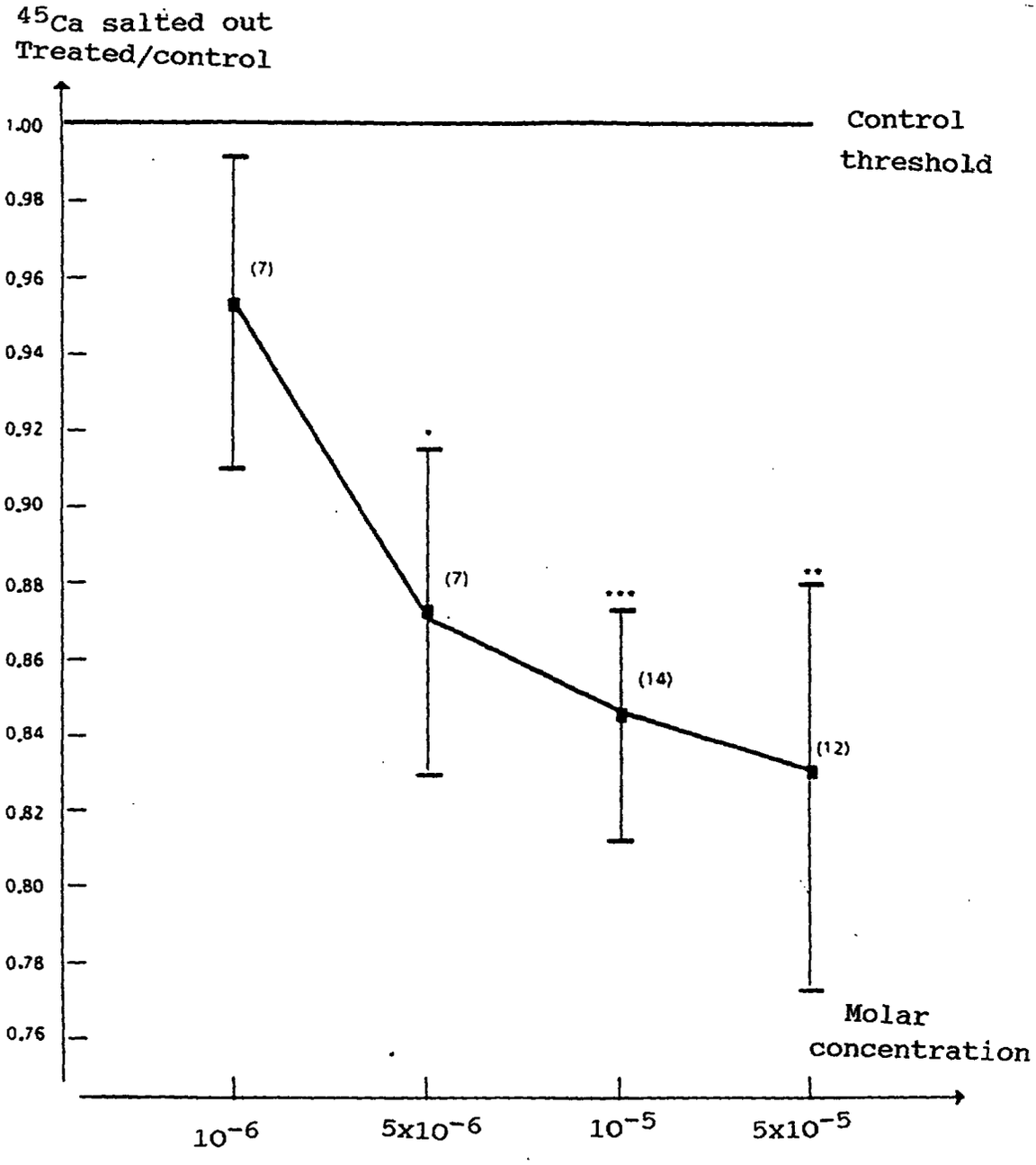
The amides of the general formula V, intermediates produced in the synthesis of compounds of the general formula I, are new products which, as such, are included in the present invention.

The compounds of the present invention have valuable pharmacological and therapeutic properties especially on bone metabolism.

In a bone hyperresorption test, with retinoic acid, carried out on cultured mice calvaria in accordance with a method inspired by J.J. REYNOLDS et al. - Calc. Tiss.

Res. 4, 339-349, (1970) - the compounds of the present invention exhibited an antiresorbent activity of from 5 to 20 % at molar concentrations of from 10^{-6} to $5x10^{-5}$.

For example, in this test the compound forming the subject of Example 8 exhibited the activity expressed by the following graph :



Each value on the ordinate is the mean value ± SEM (the

number of calvaria treated being indicated in brackets). Comparison with the control mean value *p<0.05, **p<0.01, ***p<0.001.

Moreover, certain compounds of the present invention, and especially the compound forming the subject of Example 9, exerted a stimulating activity on bone formation in vitro (incorporation of ^{3}H-proline in the bone tissue of mice calvaria, cultured according to the method described by M.C. MEIKLE et al. - Calcif. Tissue Int. 34, 359-364, (1982) - at concentrations of 10^{-6} to 10^{-5}M).

These compounds exhibited those valuable properties on bone metabolism yet still retained an inhibitory activity on the release of lipoxygenase-dependent metabolites of arachidonic acid with IC_{50} values of from 10^{-6} to 10^{-5}M (method of studying the biosynthesis of metabolites of arachidonic acid by rat polynucleates stimulated by ionophore A 23187; measured by HPLC with radioactive detection).

On the other hand, these compounds are not toxic on acute oral administration to mice ($LD_{50} \geq 1000$ mg/kg).

As a result, the pharmacological properties and the absence of toxicity of the compounds of the present invention permit their use in pathologies characterised by a loss of bone tissue, such as osteoporosis, Paget's disease, periodontitis and rheumatoid polyarthritis.

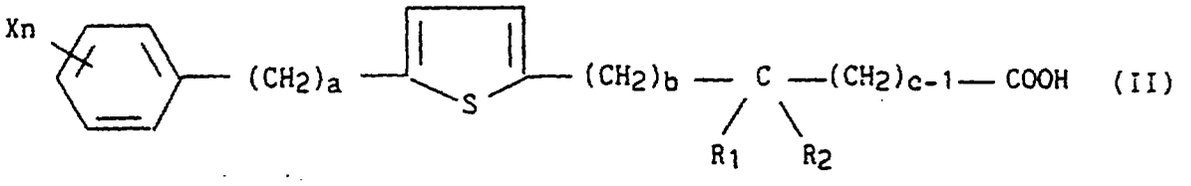
The present invention also relates to pharmaceutical compositions containing as active ingredient a compound of the general formula I or a physiologically tolerable salt thereof, in admixture or association with an appropriate pharmaceutical excipient, such as, for

example, glucose, lactose, starch, talc, ethyl cellulose, magnesium stearate or cocoa butter.

The pharmaceutical compositions so-obtained are generally in dosage form and may be, for example, in the form of tablets, dragées, gelatin capsules, suppositories, injectable or drinkable solutions and, depending on the cases in question, may be administered orally, rectally or parenterally.

The following Examples illustrate the present invention.

I) <u>Synthesis of the starting materials of the general formula II :</u>



(II)

A) First method :

a) Preparation of compounds of the general formula A :

150.18 g (1 mol) of hydrocinnamic acid are added in portions to 95 ml (1.3 mol) of thionyl chloride in the cold while stirring. The reaction mixture is stirred for one hour and then heated to 40°C until the evolution of gas has ceased. Excess thionyl chloride is distilled off under reduced pressure.

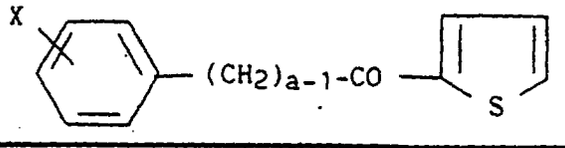
The acid chloride so-obtained and 82.55 g (1.1 mol) of thiophene are dissolved in 1.2 l of anhydrous dichloromethane. The temperature is adjusted to 0°C with

brine. 312.6 g (1.2 mol) of tin chloride are added dropwise, while stirring vigorously and maintaining the temperature at 0°C. After one hour at 0°C, the reaction mixture is stirred for 12 hours at room temperature, hydrolysed with 600 ml of 6N HCl solution and decanted, and the aqueous phase is extracted 4 times with 100 ml of dichloromethane each time. The organic phases are filtered through Celite, washed with an N HCl solution, an N NaOH solution and with water, then dried over magnesium sulphate and decolourised with animal black. After the solvent has been distilled off 216 g of crude oil remain.

This crude product can be distilled to yield 2-(3-phenylpropanoyl)-thiophene, b.p./$_{10}^{-2}$ torr = 135°C.

The products listed in the following Table 1 were prepared in this manner.

Table 1 : Compounds of formula :



a	X
2	H
2	p.CH_3
3	H
3	m.F
3	p. Cl
3	m. CH_3
3	p.CH_3
3	p. OCH_3
4	H
4	p. CH_3
6	H

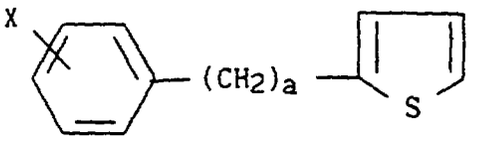
b) Preparation of compounds of the general formula B :

90 g (0.416 mol) of 2-(3-phenylpropanoyl)-thiophene are introduced into 500 ml of triethylene glycol. Dissolution is effected by heating to 70°C with stirring. 62 g (1.56 mol) of hydrazine hydrate (80 %) are added in one batch and the temperature is increased to 100°C. 75 g (1.335 mol) of potassium hydroxide are then rapidly added and refluxing is maintained for 45 minutes.

The water that has formed is distilled off until the temperature reaches 210-220°C. Refluxing is thus maintained for 2 hours then the temperature of the reaction mixture is adjusted to 40°C. The mixture is hydrolysed with 400 ml of water and 100 ml of concentrated HCl, then extracted in succession with 250 ml of ether then three times with 80 ml of ether each time. The organic phase is washed in succession with a normal solution of HCl, water, a saturated aqueous solution of sodium bicarbonate, then water and is finally dried over $MgSO_4$ and decolourised with animal black. The solvent is distilled off leaving 70 g of 2-(3-phenylpropyl)-thiophene in the form of a crude oil.

The products listed in the following Table 2 were also prepared in this manner.

Table 2 : Compounds of the formula :



a	X
2	H
2	p.CH_3
3	H
3	m.F
3	p. Cl
3	m. CH_3
3	p.CH_3
3	p. OCH_3
3	p.OH
4	H
4	p.CH3
6	H

c) Preparation of compounds of the general formula C :

35 g (0.173 mol) of 2-(3-phenylpropyl)-thiophene and 27.05 g (0.190 mol) of 3,3-dimethylglutaric anhydride are dissolved in 500 ml of nitrobenzene. The temperature of the reaction mixture is adjusted to 0°C and 57.67 g (0.433 mol) of aluminium chloride are added in portions while stirring vigorously and maintaining the temperature at 5°C.

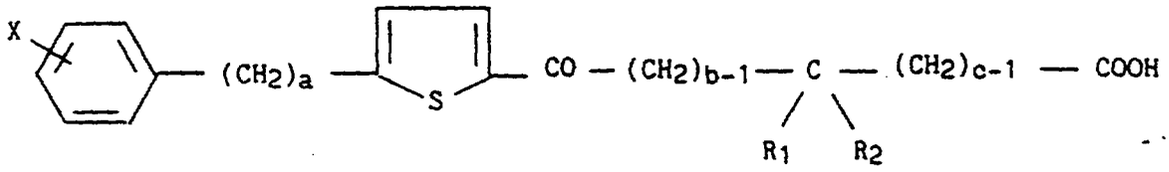
After 1 hour at 5°C, stirring is continued for 12 hours at room temperature.

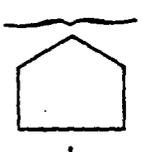
The mixture is poured onto 500 g of ice to which 50 ml of concentrated HCl have been added. The

hydrolysis is continued for 2 hours with stirring, then the organic phase is largely decanted off and the nitrobenzene distilled off with steam.

The acid is extracted 3 times with 100 ml of ether each time, the organic phase is dried over $MgSO_4$ and the solvent is distilled off. The residue is dissolved in 200 ml of saturated sodium bicarbonate solution, extracted with 50 ml of ether and decolourised with animal black. The aqueous solution is acidified with aqueous 4N HCl and extracted 3 times with 100 ml of ether each time. The organic phase is washed with aqueous 1N HCl, then with water, and dried for 3 hours over $MgSO_4$. The solvent is distilled off leaving 55 g of a pale-yellow oil which slowly crystallises to give 5-(3-phenylpropyl)-2-(3,3-dimethylglutaryl)-thiophene. The products listed in the following Table 3 were prepared in this manner.

Table 3 : Compounds of the formula :



X	a	b	c	R_1	R_2
H	2	2	2	CH_3	CH_3
p.CH_3	2	2	2	CH_3	CH_3
H	3	2	2	H	H
p.CH_3	3	2	2	H	H
H	3	2	2	CH_3	H
p.CH_3	3	2	2	CH_3	H
H	3	2	2	CH_3	CH_3
p.CH_3	3	2	2	CH_3	CH_3
m.CH_3	3	2	2	CH_3	CH_3
H	3	2	2		
H	3	3	1	CH_3	CH_3
p.CH_3	3	3	1	CH_3	CH_3
H	4	2	2	CH_3	CH_3
p.CH_3	4	2	2	CH_3	CH_3
H	6	2	2	CH_3	CH_3

d) Preparation of compounds of the general formula II:

50 g (0.145 mol) of 5-(3-phenylpropyl)-2-(3,3-dimethylglutaryl)-thiophene are dissolved in 250 ml of triethylene glycol.

The temperature is adjusted to 70°C and 28.5 mg

(0.536 mol) of hydrazine hydrate (80 %) are added.

The temperature is increased to 100°C and 24.4 g (0.435 mol) of potassium hydroxide are added. Refluxing is maintained for 45 minutes, then the water is distilled off until the temperature reaches 210-220°C.

Refluxing is then continued for 2 hours.

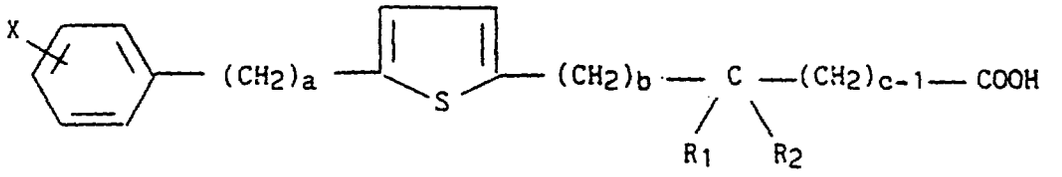
The reaction mixture is hydrolysed with 300 ml of water to which 35 ml of concentrated HCl have been added, and is then extracted three times with 100 ml of ether each time.

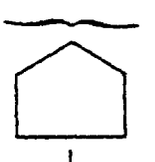
The organic phase is washed with aqueous N HCl then with water, dried over $MgSO_4$ and decolourised with animal black.

The solvent is distilled off leaving 41.5 g of colourless oil which slowly crystallises to give 5-(3-phenylpropyl)-2-(4-carboxy-3,3-dimethylbutyl)-thiophene.

The products listed in the following Table 4 were prepared in this manner:

Table 4 : Compounds of formula :



X	a	b	c	R_1	R_2
H	2	2	2	CH_3	CH_3
p.CH_3	2	2	2	CH_3	CH_3
H	3	2	2	H	H
p.CH_3	3	2	2	H	H
H	3	2	2	CH_3	H
p.CH_3	3	2	2	CH_3	H
H	3	2	2	CH_3	CH_3
p.CH_3	3	2	2	CH_3	CH_3
m.CH_3	3	2	2	CH_3	CH_3
H	3	2	2		
H	3	3	1	CH_3	CH_3
p.CH_3	3	3	1	CH_3	CH_3
H	4	2	2	CH_3	CH_3
p.CH_3	4	2	2	CH_3	CH_3
H	6	2	2	CH_3	CH_3

B) Second method :

a) Preparation of compounds of the general formula D:

42.07 g (0.5 mol) of thiophene and 71.07 g (0.55 mol) of 3,3-dimethylglutaric anhydride are

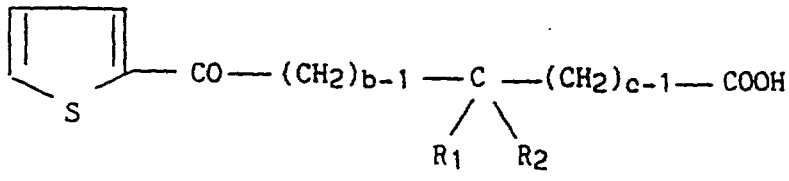
dissolved in 1500 ml of nitrobenzene. The reaction mixture is cooled to 0-2°C with a brine bath and 166.67 g (1.25 mol) of aluminium chloride are added in portions while stirring vigorously and maintaining the temperature of the reaction mixture at a value lower than 5°C. The reaction is continued for 30 minutes at a temperature of 0-5°C and is then completed at room temperature over a period of 10 hours.

The reaction mixture is hydrolysed with 31 ml of a water/ice mixture. After the addition of 217 ml of concentrated HCl, the organic phase is decanted off, the nitrobenzene is distilled off with steam and the residual aqueous phase is extracted 3 times with 200 ml of ethyl ether each time. The combined ethereal phases are washed with a normal aqueous solution of HCl and then with water. After treating with magnesium sulphate and animal black, the solvents are distilled off leaving 106.5 g of a pale-yellow oil which slowly crystallises (yield : 94 %).

The product can be recrystallised in water to yield, after filtration and drying, 2-(3,3-dimethylglutaryl)-thiophene in the form of a white solid, b.p. : 70°C.

The products listed in the following Table 5 were prepared in this manner:

Table 5 : Compounds of formula :



b	c	R_1	R_2
2	2	CH_3	CH_3
2	2	CH_3	H
2	2	H	H
1	3	CH_3	CH_3
3	1	CH3	CH3

b) Preparation of compounds of the general formula E :

17.5 g (0.0773 mol) of 2-(3,3-dimethylglutaryl)-thiophene are suspended in 100 ml of triethylene glycol. The temperature is adjusted to 70°C and stirring is continued until dissolution is complete. 10.83 g (0.27 mol) of 80 % hydrazine hydrate are added. The temperature is increased to 100°C then 13 g (0.23 mol) of potassium hydroxide pellets are added.

Refluxing is maintained for 30 minutes then the water that has formed is distilled off over approximately one hour; the temperature rises to 200-210°C, and the reaction is complete after one hour at that temperature.

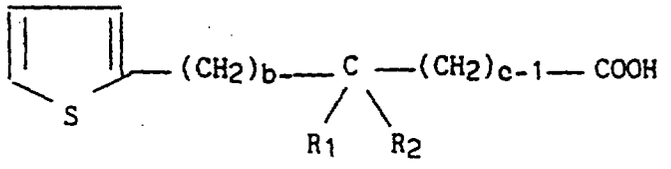
After the reaction mixture has been cooled to 20°C, it is hydrolysed with 300 ml of water and neutralised with concentrated hydrochloric acid.

The aqueous phase is extracted 3 times with 100 ml of ethyl ether each time and then the ethereal phases are

washed with a normal aqueous solution of HCl, then with water. After treatment with anhydrous magnesium sulphate and animal black, the solvent is distilled off leaving 14.37 g of a pale-yellow oil which slowly crystallises to give 5-(2-thienyl)-3,3-dimethylpentanoic acid. Yield : 80 %.

The products listed in the following Table 6 were prepared in this manner:

Table 6 : Compounds of formula



b	c	R_1	R_2
2	2	CH_3	CH_3
2	2	CH_3	H
2	2	H	H
1	3	CH_3	CH_3
3	1	CH_3	CH_3

c) Preparation of compounds of the general formula F :

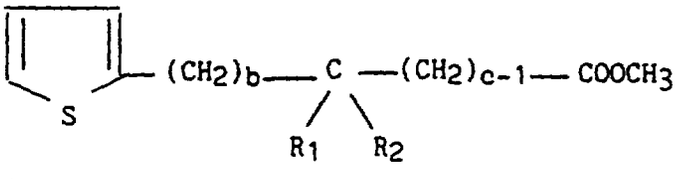
13 g (0.0612 mol) of 5-(2-thienyl)-3,3-dimethyl-pentanoic acid are dissolved in 200 ml of anhydrous methanol in the presence of a catalytic amount (0.025 g) of p-toluenesulphonic acid.

The mixture is heated to and then maintained at

reflux for 20 hours. After verifying the absence of the starting acid (by thin layer chromatography), the methanol is distilled off and the residue is taken up in ethyl ether. After washing the ethereal phase with water, treating with anhydrous $MgSO_4$ and then animal black, the solvent is distilled off leaving a crude oil which is chromatographed (SiO_2/CH_2Cl_2) to yield 12.25 g of a colourless oil. Yield : 88 %.

The methyl esters of the acids of Table 6, that is to say the products listed in the following Table 7, were prepared in this manner:

Table 7 : Compounds of formula



b	c	R_1	R_2
2	2	CH_3	CH_3
2	2	CH_3	H
2	2	H	H
1	3	CH_3	CH_3
3	1	CH_3	CH_3

c) Preparation of compounds of the general formula G :

7 g (0.0309 mol) of 5-(2-thienyl)-3,3-dimethyl-pentanoic acid methyl ester and an equivalent of p-fluorophenylpropanoic acid chloride - prepared from 5.2 g (0.0309 mol) of p-fluorophenylpropanoic acid and 3.36 ml of $SOCl_2$ - are dissolved in 175 ml of anhydrous methylene chloride. 4.52 ml (0.0386 mol) of tin chloride are added

dropwise, with vigorous stirring, to the solution maintained at 0°C. The reaction is complete after 30 minutes at 0°C and then one night at room temperature.

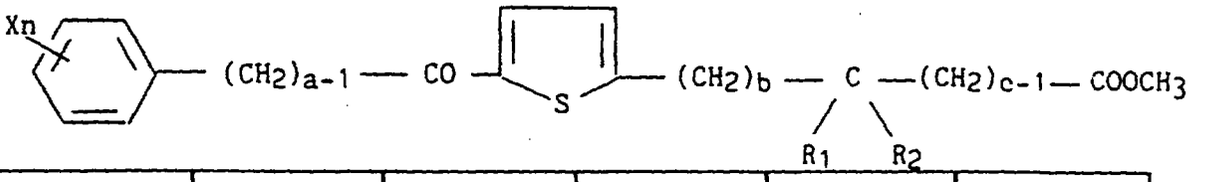
The reaction mixture is hydrolysed with 500 ml of a water/ice mixture acidified with 50 ml of concentrated HCl. After stirring for 4 hours, the organic phase is decanted off and the aqueous phase is extracted 3 times with 100 ml of dichloromethane each time.

The organic phases are washed with a normal aqueous solution of HCl, a saturated aqueous solution of sodium bicarbonate and then water, and are then treated with $MgSO_4$ and animal black and concentrated to dryness leaving 11.06 g of a crude oil which, after chromatography (SiO_2/CH_2Cl_2), yields 10.48 g of a colourless oil.

Yield : 90.5 %.

The products listed in the following Table 8 were prepared in this manner:

Table 8 : Compounds of formula



X	a	b	c	R_1	R_2
H	3	2	2	CH_3	CH_3
p.F	3	2	2	CH_3	CH_3
p.F	3	2	2	CH_3	H
m.F	3	2	2	CH_3	CH_3
o.Cl	3	2	2	CH_3	CH_3
H	6	2	2	CH_3	CH_3
2,4 diCH_3	3	2	2	CH_3	H
2,4 diCH_3	3	2	2	CH_3	CH_3
m.F	3	2	2	CH_3	H
p.CH_3	4	2	2	CH_3	H
p.CH_3	4	2	2	CH_3	CH_3
2,5 diCH_3	3	2	2	CH_3	CH_3
2,5 diCH_3	3	2	2	CH_3	H
p.CH_3	3	2	2	H	H
p.CH_3	3	1	3	CH_3	CH_3
p.CH_3	3	3	1	CH_3	CH_3
p.-$CH(CH_3)_2$	3	2	2	CH_3	H
p.-$CH(CH_3)_2$	3	2	2	CH_3	CH_3
p.-$(CH_2)_4$-CH_3	3	2	2	CH_3	H
p.-$(CH_2)_4$-CH_3	3	2	2	CH_3	CH_3
3-F,4-CH_3	3	2	2	CH_3	H
3-F,4-CH_3	3	2	2	CH_3	CH_3

e) Preparation of compounds of the general formula II :

10.48 g (0.0278 mol) of methyl 5-[5-(3-p-fluorophenylpropionyl)-2-thienyl]-3,3-dimethyl pentanoate are dissolved in 80 ml of triethylene glycol heated to 70°C. 3.12 g (0.0974 mol) of 80 % hydrazine hydrate are added.

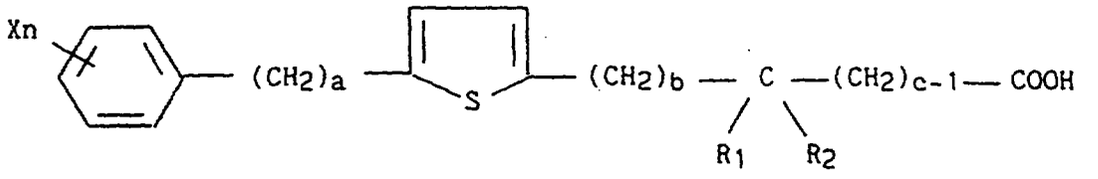
The temperature is increased to 100°C and 4.68 g (0.083 mol) of potassium hydroxide pellets are added in one batch. After refluxing for 30 minutes, the water that has formed is distilled off over a period of one hour during which the temperature rises to 210-220°C After one hour at that temperature the reaction is complete.

After having been cooled to 20°C, the reaction mixture is hydrolysed with 200 ml of water, acidified by 30 ml of concentrated HCl, and extracted 3 times with 100 ml of sulphuric ether each time. The combined ethereal phases are washed with a normal HCl solution and then with water, and treated with anhydrous $MgSO_4$ then animal black and concentrated to dryness.

10.5 g of crude oil are obtained which are chromatographed (SiO_2/CH_2Cl_2) to yield 9.10 g of a colourless oil. Yield : 94 %.

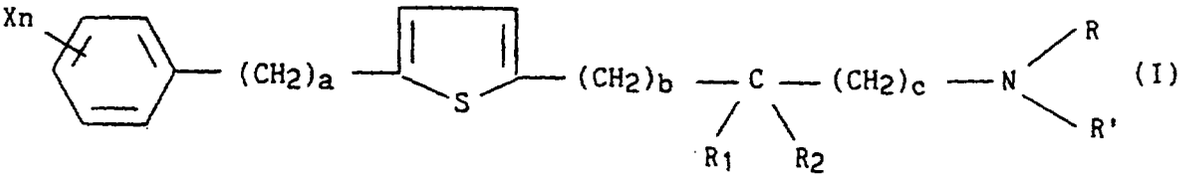
The products listed in the following Table 9 were prepared in this manner:

Table 9 : Compounds of formula



X	a	b	c	R_1	R_2
H	3	2	2	CH_3	CH_3
p.F	3	2	2	CH_3	CH_3
p.F	3	2	2	CH_3	H
m.F	3	2	2	CH_3	CH_3
o.Cl	3	2	2	CH_3	CH_3
H	6	2	2	CH_3	CH_3
2,4-diCH_3	3	2	2	CH_3	H
2,4-diCH_3	3	2	2	CH_3	CH_3
m.F	3	2	2	CH_3	H
p.CH_3	4	2	2	CH_3	H
p.CH_3	4	2	2	CH_3	CH_3
2,5-diCH_3	3	2	2	CH_3	CH_3
2,5-diCH_3	3	2	2	CH_3	H
p.CH_3	3	2	2	H	H
p.CH_3	3	1	3	CH_3	CH_3
p.CH_3	3	3	1	CH_3	CH_3
p.-$CH(CH_3)_2$	3	2	2	CH_3	H
p.-$CH(CH_3)_2$	3	2	2	CH_3	CH_3
p.-$(CH_2)_4$-CH_3	3	2	2	CH_3	H
p.-$(CH_2)_4$-CH_3	3	2	2	CH_3	CH_3
3-F, 4-CH_3	3	2	2	CH_3	H
3-F, 4-CH_3	3	2	2	CH_3	CH_3

II) <u>Synthesis of compounds of the general formula I :</u>



A) Preparation of compounds of the general formula V :

16.5 g (0.05 mol) of 5-(3-phenylpropyl)-2-(4-carboxy-3,3-dimethylbutyl)-thiophene and 6.5 g (0.055 mol) of thionyl chloride are dissolved in 300 ml of anhydrous chloroform and stirring is maintained until the evolution of gas has ceased. The solvent and excess thionyl chloride are then distilled off under reduced pressure.

The acid chloride so-obtained dissolved in 250 ml of anhydrous ether, and 8.71 g (0.1 mol) of morpholine dissolved in 150 ml of anhydrous ether, are simultaneously poured onto 100 ml of anhydrous ether agitated magnetically.

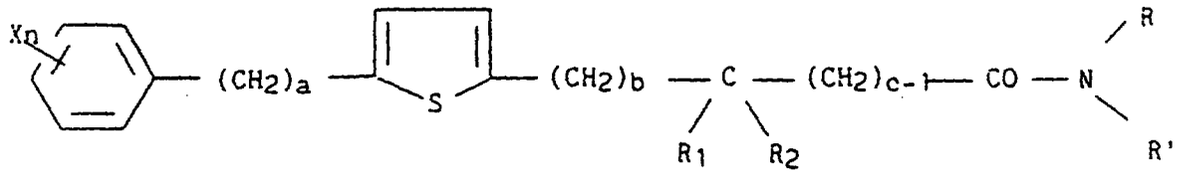
After 20 minutes, the morpholinium hydrochloride formed is filtered off and washed with ether.

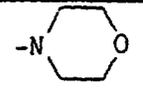
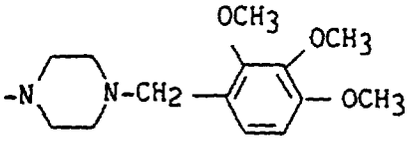
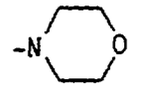
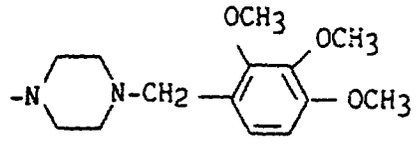
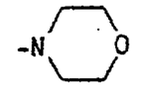
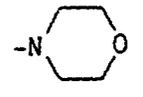
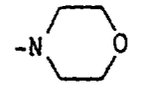
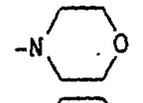
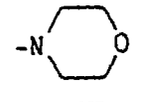
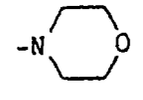
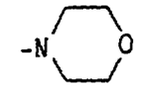
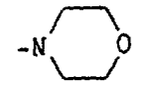
The ethereal phase is washed twice with 30 ml of water each time, dried over $MgSO_4$ and decolourised with animal black.

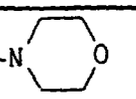
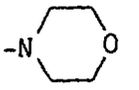
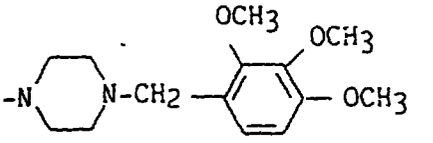
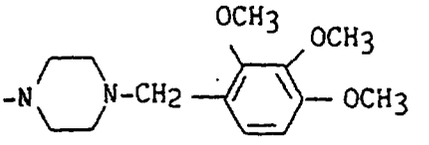
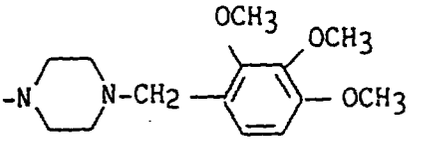
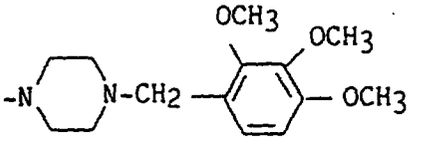
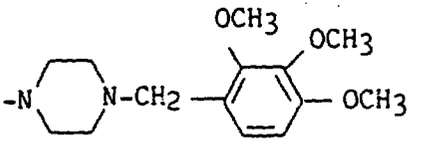
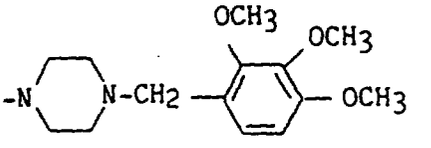
The solvent is evaporated off to leave 18.8 g of a colourless oil : 5-(3-phenylpropyl)-2-(3,3-dimethyl-4-N-morpholinocarbonylbutyl)-thiophene.

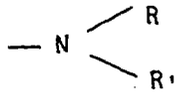
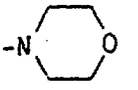
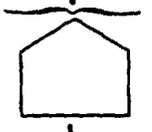
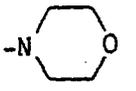
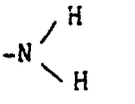
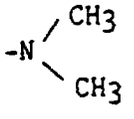
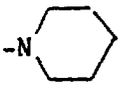
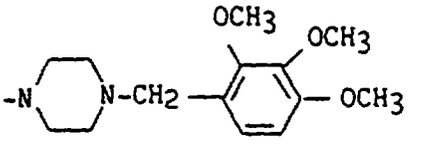
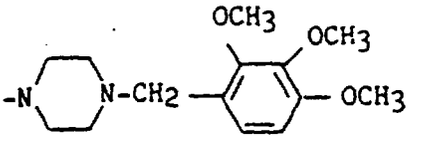
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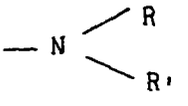
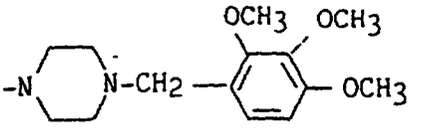
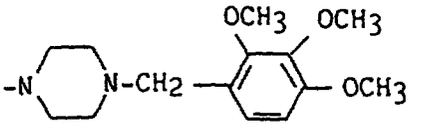
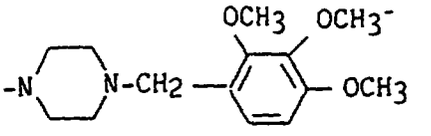
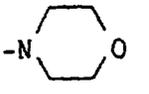
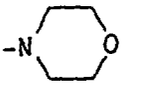
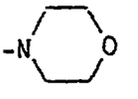
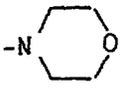
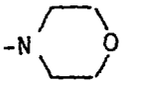
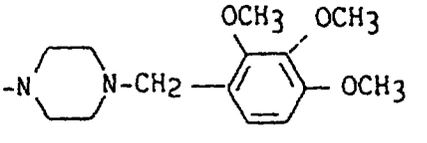
Table 10 : Compounds of formula

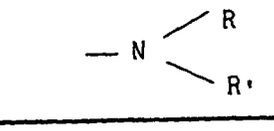
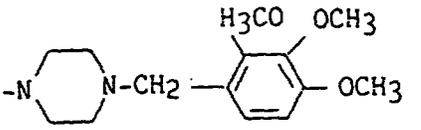
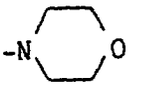
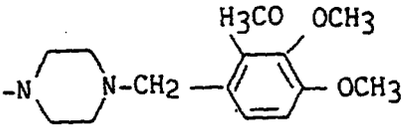
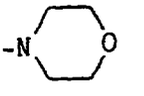
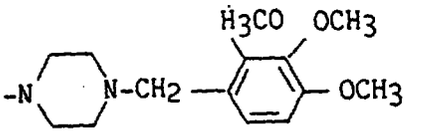
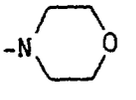
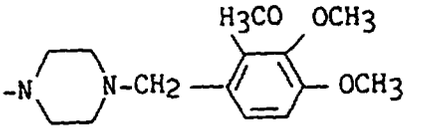


Xn	a	b	c	R_1	R_2	$-N(R)(R')$
H	2	2	2	CH_3	CH_3	
p.CH_3	2	2	2	CH_3	H	
p.CH_3	2	2	2	CH_3	CH_3	
p.CH_3	2	2	2	CH_3	CH_3	
H	3	2	2	H	H	
p.CH_3	3	2	2	H	H	
H	3	2	2	CH_3	H	
p.CH_3	3	2	2	CH_3	H	
p.F	3	2	2	CH_3	H	
H	3	2	2	CH_3	CH_3	
p.CH_3	3	2	2	CH_3	CH_3	
m.CH_3	3	2	2	CH_3	CH_3	

Xn	a	b	c	R_1	R_2	— N(R)(R')
p.F	3	2	2	CH_3	CH_3	
m.F	3	2	2	CH_3	CH_3	
2,4 diCH_3	3	2	2	CH_3	H	
2,4 diCH_3	3	2	2	CH_3	CH_3	
2,5 diCH_3	3	2	2	CH_3	H	
2,5 diCH_3	3	2	2	CH_3	CH_3	
p.CH_3	4	2	2	CH_3	H	
p.CH_3	4	2	2	CH_3	CH_3	

Xn	a	b	c	R_1	R_2	
O.cl	3	2	2	CH_3	CH_3	
H	3	2	2			
H	3	2	2	CH_3	CH_3	
H	3	2	2	CH_3	CH_3	
H	3	2	2	CH_3	CH_3	
H	3	2	2	CH_3	CH_3	
m.F	3	2	2	CH_3	CH_3	

Xn	a	b	c	R_1	R_2	
m.F	3	2	2	CH_3	H	
p.F	3	2	2	CH_3	CH_3	
p-CH_3	3	2	2	CH_3	CH_3	
H	3	3	1	CH_3	CH_3	
p.CH_3	3	3	1	CH_3	CH_3	
H	4	2	2	CH_3	CH_3	
p.CH_3	4	2	2	CH_3	CH_3	
H	6	2	2	CH_3	CH_3	
H	6	2	2	CH_3	CH_3	

Xn	a	b	c	R_1	R_2	
p.CH_3	3	2	2	H	H	
p.CH_3	3	1	3	CH_3	CH_3	"
p.CH_3	3	3	1	CH_3	CH_3	"
p.CH_3	3	1	3	CH_3	CH_3	
p.-$CH(CH_3)_2$	3	2	2	CH_3	H	
p.-$CH(CH_3)_2$	3	2	2	CH_3	CH_3	"
p.-$CH(CH_3)_2$	3	2	2	CH_3	H	
p.-$CH(CH_3)_2$	3	2	2	CH_3	CH_3	"
3-F, 4-CH_3	3	2	2	CH_3	H	
3-F, 4-CH_3	3	2	2	CH_3	CH_3	"
p.-$(CH_2)_4$-CH_3	3	2	2	CH_3	H	
p.-$(CH_2)_4$-CH_3	3	2	2	CH_3	CH_3	"
p.-$(CH_2)_4$-CH_3	3	2	2	CH_3	H	
p.-$(CH_2)_4$-CH_3	3	2	2	CH_3	CH_3	"

B) Preparation of compounds of the general formula I :

18 g (0.045 mol) of 5-(3-phenylpropyl)-2-(3,3-dimethyl-4-N-morpholinocarbonylbutyl)-thiophene dissolved in 150 ml of ether are poured dropwise onto a suspension of 4 g (0.1 mol) of lithium aluminium hydride in 200 ml of ether at reflux.

Refluxing is maintained for 2 hours after the addition, then the reaction mixture is cooled to 20°C and carefully hydrolysed with 4 ml of water, 4 ml of 4N aqueous sodium hydroxide solution, then 8 ml of water. The solid formed is filtered off and washed with ether.

The ethereal phase is washed 3 times with 50 ml of water, dried over $MgSO_4$, decolourised with animal black and concentrated to dryness.

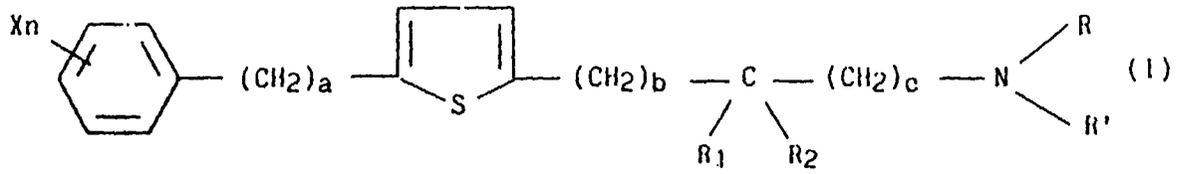
The residue is chromatographed on SiO_2 (solvent : CH_2Cl_2 - $CH_3COOC_2H_5$, 95:5).

The fractions containing the amine are concentrated to dryness. The residue is taken up in 600 ml of anhydrous ether and the hydrochloride is obtained by the addition of an equivalent of HCl dissolved in ether.

After stirring for one hour, the hydrochloride is filtered off, washed with ether, suction-filtered and dried in vacuo. 16 g of 5-(3-phenylpropyl)-2-(3,3-dimethyl-5-N-morpholinopentyl)-thiophene hydrochloride are obtained in the form of a white solid (cf. Example 8 of Table 11 below).

The products corresponding to Examples 1 to 51 listed in the following Table 11 were prepared in this manner:

Table 11 : Compounds of formula :



(I)

Example No.	X	n	a	b	c	R_1	R_2	— N(R)(R')	isolated form	M.p. °C (Kofler)
1	H	1	2	2	2	CH_3	CH_3	-N O	HCl	210
2	p.CH_3	1	2	2	2	CH_3	CH_3	-N O	HCl	220-222
3	H	1	3	2	2	H	H	-N O	CH_3SO_3H	81
4	p.CH_3	1	3	2	2	H	H	-N O	HCl	112-113
5	H	1	3	2	2	CH_3	H	-N O	HCl	146-148
6	p.CH_3	1	3	2	2	CH_3	H	-N O	HCl	150-152
7	p.F	1	3	2	2	CH_3	H	-N O	HCl	146
8	H	1	3	2	2	CH_3	CH_3	-N O	CH_3SO_3H	≈ 100
9	p.CH_3	1	3	2	2	CH_3	CH_3	-N O	HCl	207-208

Table 11 continuation 1

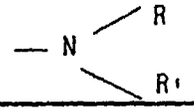
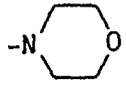
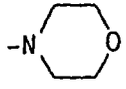
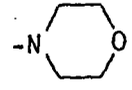
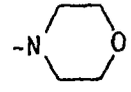
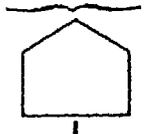
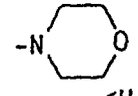
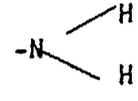
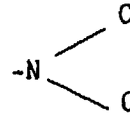
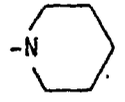
Example No.	X	n	a	b	c	R_1	R_2		isolated form	M.p. °C (Kofler)
10	m.CH_3	1	3	2	2	CH_3	CH_3		HCl	≈206
11	p.F	1	3	2	2	CH_3	CH_3		HCl	195-200
12	m.F	1	3	2	2	CH_3	CH_3		HCl	190
13	o.Cl	1	3	2	2	CH_3	CH_3		HCl	205
14	H	1	3	2	2				HCl	166-168
15	H	1	3	2	2	CH_3	CH_3		HCl	108
16	H	1	3	2	2	CH_3	CH_3		HCl	170
17	H	1	3	2	2	CH_3	CH_3		HCl	110-112

Table 11 continuation 2

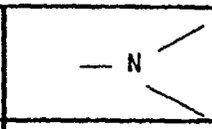
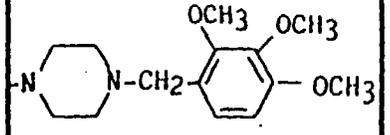
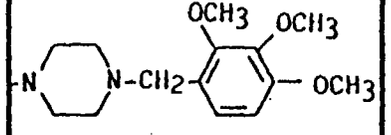
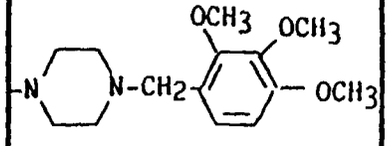
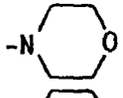
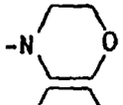
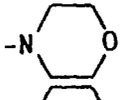
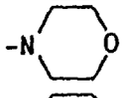
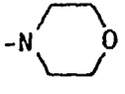
Example No.	X	n	a	b	c	R_1	R_2		isolated form	M.p. °C (Kofler)
18	H	1	3	2	2	CH_3	CH_3		2 HCl	206
19	m.F	1	3	2	2	CH_3	CH_3		2 HCl	207
20	p.F	1	3	2	2	CH_3	CH_3		2 HCl	235
21	H	1	3	3	1	CH_3	CH_3		HCl	108-110
22	p.CH_3	1	3	3	1	CH_3	CH_3		HCl	128-130
23	H	1	4	2	2	CH_3	CH_3		HCl	194-196
24	p.CH_3	1	4	2	2	CH_3	CH_3		HCl	192-194
25	H	1	6	2	2	CH_3	CH_3		HCl	197

Table 11 continuation 3

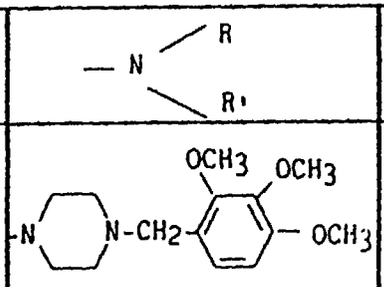
Example No.	X	n	a	b	c	R_1	R_2		isolated form	M.p. °C (capillary)
26	p.CH_3	1	3	2	2	CH_3	CH_3		2 HCl	210
27	m.F	1	3	2	2	CH_3	H	"	2 HCl	190
28	p.CH_3	1	3	2	2	CH_3	H	"	2 HCl	188-190
29	p.CH_3	1	2	2	2	CH_3	H	"	2 HCl	198-202
30	p.CH_3	1	2	2	2	CH_3	CH_3	"	2 HCl	225-230
31	H	1	6	2	2	CH_3	CH_3	"	2 HCl	> 240 (dec.)
32	2,4 diCH_3	2	3	2	2	CH_3	H	"	2 HCl	230-235
33	2,4 diCH_3	2	3	2	2	CH_3	CH_3	"	2 HCl	235
34	3,5 diCH_3	2	3	2	2	CH_3	H	"		
35	3,5 diCH_3	2	3	2	2	CH_3	CH_3	"		
36	p.CH_3	1	4	2	2	CH_3	H	"	2 HCl	227- 230

Table 11 continuation 4

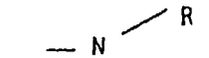
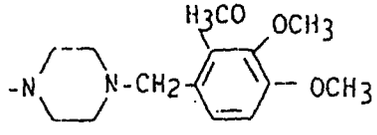
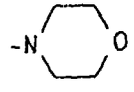
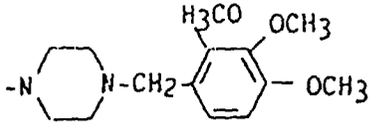
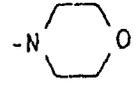
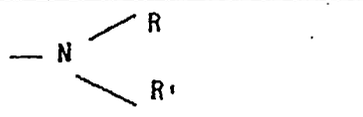
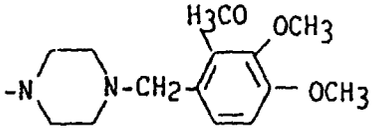
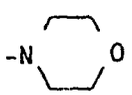
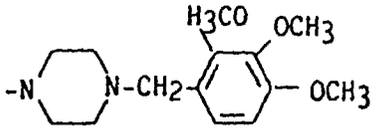
Example No.	X	n	a	b	c	R_1	R_2		isolated form	M.p. °C (capillary)
37	p.CH_3	1	4	2	2	CH_3	CH_3		2 HCl	238-240
38	p.CH_3	1	3	2	2	H	H	"	2 HCl	212-214
39	p.CH_3	1	3	1	3	CH_3	CH_3	"	2 HCl	225-230 (dec)
40	p.CH_3	1	3	3	1	CH_3	CH_3	"		
41	p.CH_3	1	3	1	3	CH_3	CH_3			
42	p.-$CH(CH_3)_2$	1	3	2	2	CH_3	H			
43	p.-$CH(CH_3)_2$	1	3	2	2	CH_3	CH_3	"		
44	p.-$CH(CH_3)_2$	1	3	2	2	CH_3	H		HCl	170
45	p.-$CH(CH_3)_2$	1	3	2	2	CH_3	CH_3	"	HCl	210

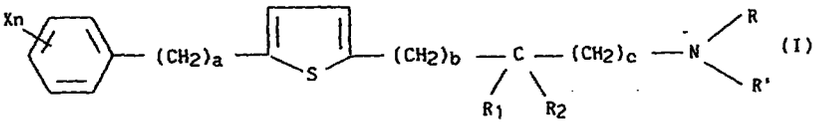
Table 11 continuation 5

Example No	X	n	a	b	c	R_1	R_2		isolated form	M.p. °C (capillary)
46	3-F,4-CH_3	2	3	2	2	CH_3	H		2 HCl	195-198
47	3-F,4-CH_3	2	3	2	2	CH_3	CH_3	"		
48	p.-$(CH_2)_4$-CH_3	1	3	2	2	CH_3	H			
49	p.-$(CH_2)_4$-CH_3	1	3	2	2	CH_3	CH_3	"		
50	p.-$(CH_2)_4$-CH_3	1	3	2	2	CH_3	H		2 HCl	220-225 (dec)
51	p.-$(CH_2)_4$-CH_3	1	3	2	2	CH_3	CH_3	"	2 HCl	> 240 (dec)

* C L M S *

CLAIMS for the Contracting States: AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Thiophene compounds of the general formula I :



in which :

- X represents a hydrogen or halogen atom, a straight-chain or branched alkyl or alkoxy radical each having from 1 to 5 carbon atoms, or a dialkylamino radical in which each alkyl group contains from 1 to 5 carbon atoms;
- n represents 1 or 2;
- a represents an integer of from 2 to 6 inclusive;
- b represents 2 or 3;
- c represents 1 or 2, and is such that b+c = 4;
- R_1 and R_2, which may be the same or different, each represents a hydrogen atom or an alkyl radical having from 1 to 5 carbon atoms, or
  R_1 and R_2 together with the carbon atom to which they are bonded form a hydrocarbon ring containing from 3 to 6 carbon atoms; and
- R and R', which may be the same or different, each represents a hydrogen atom or an alkyl radical having from 1 to 5 carbon atoms, or
  R and R' together with the nitrogen atom to which they are bonded form a pentagonal or hexagonal heterocyclic radical optionally containing an oxygen atom or a second nitrogen atom which may itself be substituted by an alkyl radical containing from 1 to 5 carbon atoms or by an arylalkyl radical in which the alkyl group contains from 1 to 5 carbon

* C L M S *

atoms and the aryl group is either unsubstituted or mono- or poly-substituted by a halogen atom or an alkyl or alkoxy radical each having from 1 to 5 carbon atoms,

and the physiologically tolerable addition salts thereof with appropriate acids.

2. The compounds of claim 1 which are:

5-(2-phenylethyl)-2-(5-N-morpholino-3,3-dimethylpentyl)-thiophene and its hydrochloride,

5-(2-p-methylphenylethyl)-2-(5-N-morpholino-3,3-dimethylpentyl)-thiophene and its hydrochloride,

5-(3-phenylpropyl)-2-(5-N-morpholinopentyl)-thiophene and its methanesulphonate,

5-(3-p-methylphenylpropyl)-2-(5-N-morpholinopentyl)-thiophene and its hydrochloride,

5-(3-phenylpropyl)-2-(5-N-morpholino-3-methylpentyl)-thiophene and its hydrochloride,

5-(3-p-methylphenylpropyl)-2-(5-N-morpholino-3-methylpentyl)-thiophene and its hydrochloride,

5-(3-p-fluorophenylpropyl)-2-(5-N-morpholino-3-methylpentyl)-thiophene and its hydrochloride,

5-(3-phenylpropyl)-2-(5-N-morpholino-3,3-dimethylpentyl)-thiophene and its methanesulphonate,

5-(3-p-methylphenylpropyl)-2-(5-N-morpholino-3,3-dimethylpentyl)-thiophene and its hydrochloride,

* C L M S *

5-(3-p-fluorophenylpropyl)-2-(5-N-morpholino-3,3-dimethylpentyl)-thiophene and its hydrochloride,

5-(3-m-fluorophenylpropyl)-2-(5-N-morpholino-3,3-dimethylpentyl)-thiophene and its hydrochloride,

5-(3-o-chlorophenylpropyl)-2-(5-N-morpholino-3,3-dimethylpentyl)-thiophene and its hydrochloride,

5-(3-phenylpropyl)-2-(5-N-morpholino-3,3-tetramethylene-pentyl)-thiophene and its hydrochloride,

5-(3-p-methylphenylpropyl)-2-(5-N-morpholino-4,4-dimethylpentyl)-thiophene and its hydrochloride.

3. The compounds of claim 1 which are:

5-(3-p-fluorophenylpropyl)-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3,3-dimethylpentyl}-thiophene and its dihydrochloride,

5-(3-phenylpropyl)-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3,3-dimethylpentyl}-thiophene and its dihydrochloride,

5-(3-m-fluorophenylpropyl)-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3,3-dimethylpentyl}-thiophene and its dihydrochloride,

5-(3-p-methylphenylpropyl)-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3,3-dimethylpentyl}-thiophene and its dihydrochloride,

5-(3-m-fluorophenylpropyl)-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3-methylpentyl}-thiophene,

* C L M S *

5-(2-p-methylphenylethyl)-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3-methylpentyl}-thiophene,

5-(2-p-methylphenylethyl)-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3,3-dimethylpentyl}-thiophene,

5-(6-phenylhexyl)-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3,3-dimethylpentyl}-thiophene,

5-[3-(2,4-dimethylphenyl)-propyl]-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3-methylpentyl}-thiophene,

5-[3-(2,4-dimethylphenyl)-propyl]-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3,3-dimethylpentyl}-thiophene,

5-[3-(3,5-dimethylphenyl)-propyl]-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3-methylpentyl}-thiophene,

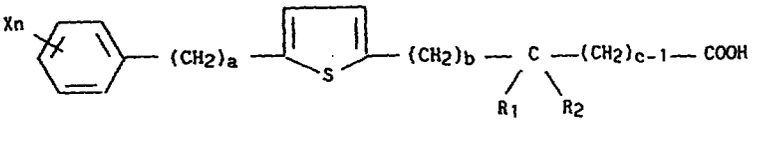
5-[3-(3,5-dimethylphenyl)-propyl]-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3,3-dimethylpentyl}-thiophene,

5-(4-p-methylphenylbutyl)-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3-methylpentyl}-thiophene,

5-(4-p-methylphenylbutyl)-2-{5-[4-(2,3,4-trimethoxybenzyl)-piperazinyl]-3,3-dimethylpentyl}-thiophene.

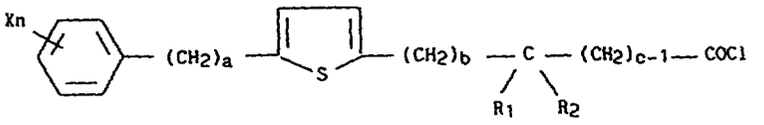
4. A process for the preparation of the compounds of claim 1, characterised in that :

an acid of the general formula II :



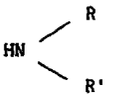
(II)

in which X, n, a, b, c, R_1 and R_2 are as defined in claim 1,
is converted into the corresponding acid chloride of the general formula III :



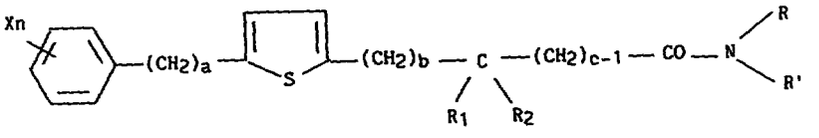
(III)

in which X, n, a, b, c, R_1 and R_2 are as defined in claim 1,
which acid chloride is used to acylate an amine of the general formula IV :



(IV)

in which R and R' are as defined in claim 1,
and the amide so-obtained of the general formula V :



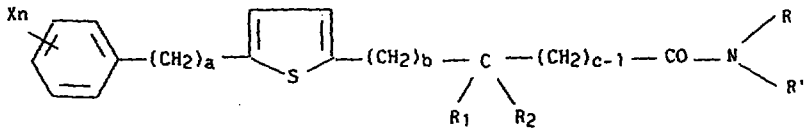
(V)

in which X, n, a, b, c, R_1, R_2, R and R' are as defined in claim 1 is reduced.

5. Pharmaceutical compositions containing as active ingredient a compound according to claims 1 to 3 together with appropriate pharmaceutical excipients.

6. Pharmaceutical compositions according to claim 5, in a form suitable in particular for the treatement of pathologies that are characterised by a loss of bone tissue.

7. The amides of the general formula V :



(V)

wherein X, n, a, b, c, R_1, R_2, R and R' are as defined in claim 1 as new industrial products that can be used in the synthesis of the compounds of formula I according to claim 1.