

Description

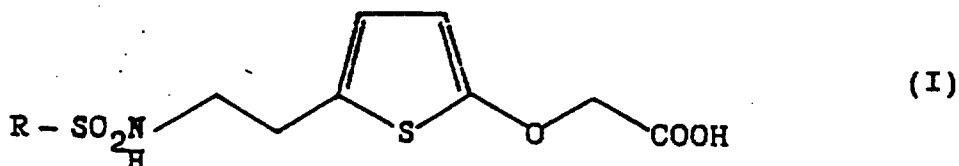
The invention relates to novel 2-thienyloxyacetic acid derivatives, a process for their preparation and pharmaceutical preparations containing these substances.

Substances with an antithrombotic action have already been known for a relatively long time. Thus, for example, acetylsalicylic acid (Aspirin) also has an antithrombotic action in high doses. However, in many cases it can cause gastritis in this high dosage. Sulphated polysaccharides, such as, for example, heparins, also have an antithrombotic activity. Since these substances can cause haemorrhages, however, their use in human medicine presents problems.

It is also known that substances which inhibit thromboxane A₂ synthesis or block thromboxane A₂ receptors have an antithrombotic action. Such substances are described, for example, in US-PS 4,602,016, where phenoxyalkylimidazoles with an antithrombotic action are disclosed. However, since the pharmacological action profile of these substances has not yet been tested and it is therefore not clear whether these substances can also really be used in human therapy, there continues to be a need for novel compounds with an antithrombotic action.

It has now been found that certain 2-thienyloxyacetic acid derivatives can block thromboxane A₂ receptors.

The invention thus relates to novel derivatives of 2-thienyloxyacetic acid of the general formula I



in which R denotes a phenyl or thienyl group which is optionally mono- or polysubstituted by halogen, trifluoromethyl or C₁-C₄ alkyl, and pharmaceutically usable salts thereof, a process for their preparation and pharmaceutical preparations containing these compounds.

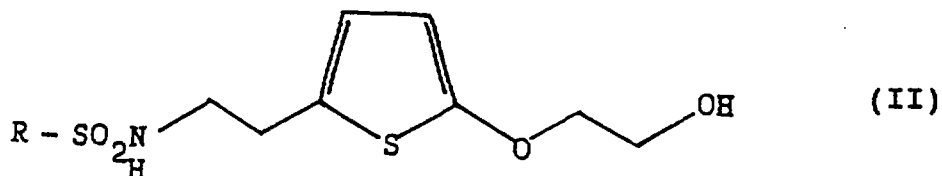
Halogen is understood as being, preferably, fluorine, chlorine or bromine, in particular chlorine.

5 The expression "C₁-C₄ alkyl" used in this description designates straight-chain or branched hydrocarbon groups with 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert.butyl.

Preferred compounds of the general formula I are those in which R denotes phenyl or 4-chlorophenyl.

10 Particularly preferred individual compounds are: 5-(2-(benzenesulphonylamino)-ethyl)-2-thienyloxyacetic acid and 5-(2-(4-chloro-benzenesulphonylamino))-ethyl)-2-thienyloxyacetic acid.

According to the invention, the compounds of the general formula I and salts thereof are prepared by
15 a) oxidizing a compound of the formula II



in which R has the above meaning, with silver oxide in an aqueous alkaline medium to give the acid and
20 b) if desired converting a free acid obtained in process step a), of the general formula I, into a pharmaceutically tolerated salt using an inorganic or organic base.

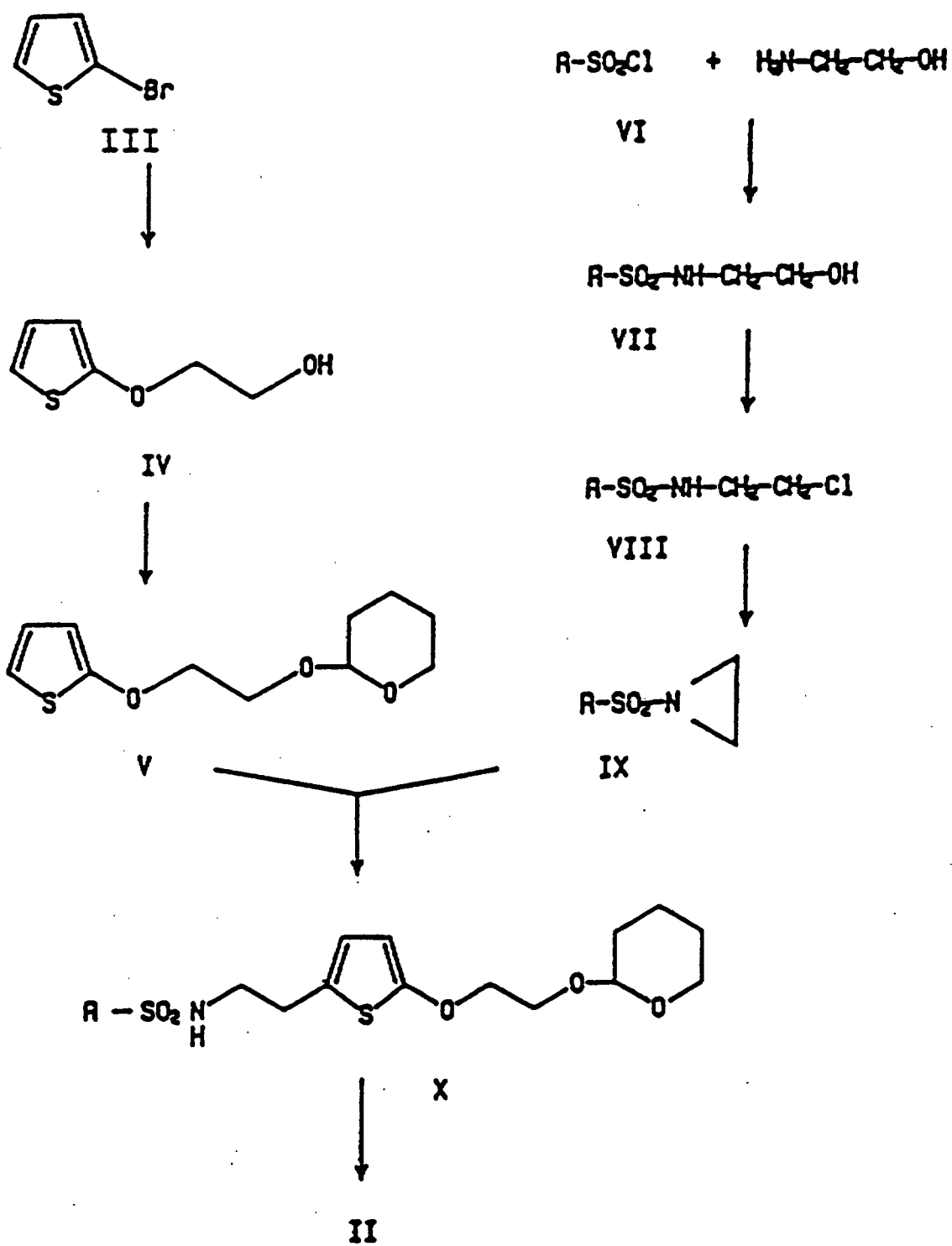
The reaction in the process according to the invention is most advantageously carried out by dissolving the sulphonamide alcohol of the formula II in 0.5-
25 4.0N, preferably in 2N, alkali metal hydroxide solution, adding at least 2 equivalents of Ag₂O and heating the suspension at a temperature of about 75-85°C, with stirring. The reaction time is about 2 - 3 hours.

30 The acids of the general formula I can be converted into their pharmaceutically usable salts in the customary manner using inorganic or organic bases. The salt formation can be carried out, for example, by dissolving the compounds of the formula I mentioned in a suitable solvent, for example water or a lower aliphatic
35 alcohol, for example methanol, ethanol, propanol or

isopropanol, adding an equivalent amount of the desired base, ensuring good thorough mixing and, when the salt formation has ended, distilling off the solvent in vacuo. If appropriate, the salts can be recrystallized after being isolated.

Pharmaceutically usable salts are, for example, metal salts, in particular alkali metal or alkaline earth metal salts, such as sodium, potassium, magnesium or calcium salts. Other pharmaceutically usable salts are furthermore, for example, ammonium salts which crystallize readily. The latter are derived from ammonia or organic amines, for example mono-, di- or tri-lower (alkyl, cycloalkyl or hydroxyalkyl)-amines, lower alkylenediamines or (hydroxy-lower alkyl or aryl-lower alkyl)-lower alkylammonium bases, such as, for example, methylamine, diethylamine, triethylamine, dicyclohexylamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)-aminomethane, benzyl trimethylammonium hydroxide and the like.

The starting compounds of the general formula II used for the process according to the invention can be prepared from known products in a manner which is known per se. In particular, they can be synthesized in accordance with the following equation and the specific information in the examples.



The novel compounds of the general formula I block thromboxane A₂ receptors in vitro and in vivo.

On the basis of these pharmacological properties, the novel compounds can be used as a medicament, by themselves or as a mixture with other active substances in the form of customary galenical formulations, on diseases caused by thromboxane A₂, such as, for example, thrombosis, inflammations, high blood pressure, apoplexy, asthma, shock and angina pectoris.

To determine the antithrombotic action, the substance of Example 1, 5-(2-(benzenesulphonylamino)-ethyl)-2-thienyloxyacetic acid, was compared with dazoxiben (4-(2-(1H-imidazol-1-yl)ethoxy)benzoic acid hydrochloride), an antithrombotic undergoing clinical trials, as described in Example A. This comparison showed that the antithrombotic action of the substance of Example 1 is clearly superior to the action of dazoxiben.

The compounds of the general formula I are intended for use on humans and can be administered in the customary manner, such as, for example, orally or parenterally. They are preferably administered orally, the daily dose being about 0.05 to 20 mg/kg of body weight, preferably 0.5 to 5.0 mg/kg of body weight. However, the attending doctor can also prescribe doses above or below these, depending on the general state and age of the patient, the appropriate substance of the formula I, the nature of the disease and the nature of the formulation.

If the substances according to the invention are used for prophylaxis, the doses vary approximately within the same margins as in treatment cases. Oral administration is also preferred for prophylaxis.

The compounds of the formula I can be administered by themselves or in combination with other pharmaceutically active substances, the content of compounds of the formula I being between 0.1 and 99 %. The pharmaceutically active compounds are in general present in a mixture with suitable inert auxiliaries and/or excipients or diluents, such as, for example, pharmaceutically acceptable solvents, gelatine, gum arabic, lactose,

starch, magnesium stearate, talc, vegetable oils, polyalkylene glycol, petroleum jelly and the like.

5 The pharmaceutical preparations can be in solid form, for example as tablets, coated tablets, suppositories, capsules and the like, in semi-solid form, for example as ointments, or in liquid form, for example as solutions, suspensions or emulsions. If appropriate, they are sterilized and contain auxiliaries, such as preservatives, stabilizers, emulsifying agents, salts for modifying the osmotic pressure and the like.

10 In particular, pharmaceutical preparations can contain the compounds according to the invention in combination with other therapeutically useful substances. The compounds according to the invention can be formulated with these, for example, together with the above-mentioned auxiliaries and/or excipients or diluents to give combination preparations.

Example 1:

20 5-(2-(Benzenesulphonylamino)-ethyl)-2-thienyloxyacetic acid

19.3 g (0.1136 mol) of silver nitrate are dissolved in 120 ml of distilled water, and a solution of 4.54 g (0.1136 mol) of sodium hydroxide in 50 ml of distilled water is slowly added dropwise, with stirring. 25 The resulting suspension of silver oxide is stirred for a further 10 minutes and the precipitate is filtered off and washed several times with distilled water.

9.3 g (0.028 mol) of N-(2-(2-(5-(2-hydroxy)ethoxy)thienyl)-ethyl)-benzenesulphonamide (II) are dissolved in 90 ml of 2N aqueous sodium hydroxide solution, the still moist silver oxide is added and the mixture is heated to 80°C, with mechanical stirring. 30 After 3 hours at this temperature, the suspension is cooled and filtered over HYFLO. The clear solution in sodium hydroxide solution is acidified with about 6 ml of concentrated hydrochloric acid and extracted three times 35 with 100 ml of ether each time.

The ethereal phase is extracted three times by

shaking with 100 ml of saturated sodium bicarbonate solution each time, and the extract is washed once with 50 ml of ether and acidified with concentrated hydrochloric acid. The aqueous phase is extracted twice with 150 ml of ether and the combined ether phases are dried over sodium sulphate, filtered and evaporated. The crystalline residue is digested with 30 ml of diisopropyl ether and filtered off.

Yield: 2.6 g of colourless crystals (26.4 % of theory)

Melting point: 110 - 113°C (ether/diisopropyl ether)

¹H-NMR: (DMSO)

delta (ppm): 9.16 (s; broad; 1H; -COOH), 7.67 - 7.88 (m; 2H; B-H₂, B-H₆), 7.47 - 7.55 (m; 3H; B-H₃, B-H₄, B-H₅), 7.27; 7.33; 7.47 (t; 1H; -NH-) 6.02; 6.06; 6.33; 6.38 (AB; 2H; Th-H₃; Th-H₄; J₃₄=3.7 Hz), 4.51 (s; 2H; O-CH₂-CO), 2.57 - 2.99 (m; 4H; -CH₂-CH₂-)

¹³C-NMR: (DMSO)

delta (ppm): 169.1 (s; -COOH), 162.0 (s; Th-C₂), 140.3 (s; B-C₁), 131.8 (s; B-C₄), 128.5 (d; B-C₃, B-C₅), 127.7 (s; Th-C₅), 126.3 (d; B-C₂, B-C₆), 122.0 (d; Th-C₄), 105.3 (d; Th-C₃), 69.5 (t; O-CH₂-CO), 43.8 (t; -NH-CH₂-), 30.2 (t; Th-CH₂-).

The starting material can be prepared as follows:

2-(2-Thienyloxy)-ethanol

323.7 ml of 5.4 M sodium methylate solution (1.75 mol) are added to 1,600 ml of absolute ethylene glycol. The reaction mixture is heated and the methanol formed is distilled off over a reflux divider, while passing through nitrogen, until the bottom temperature rises to 130°C. When the removal of methanol has ended, 187.5 g (1.15 mol) of 2-bromothiophene, 55.5 g of finely ground copper oxide and 5.6 g of sodium iodide are added, the apparatus is further flushed briefly with nitrogen and closed with a flask and the mixture is stirred at 80°C for 175 hours.

The reaction mixture is then cooled and filtered with suction over HYFLO. The filtrate is diluted with 800 ml of water and acidified slightly with concentrated hydrochloric acid.

The mixture is extracted four times with 400 ml of methylene chloride each time (1,600 ml in total). The combined organic phases are extracted once by shaking with 200 ml of water, dried over sodium sulphate, filtered and evaporated. The residue is distilled.

Yield: 102.7 g of a colourless oil (62 % of theory)

Boiling point: 90 - 95°C/0.6 mbar

N-(2-(2-(5-(2-Hydroxy)-ethoxy)-thienyl)-ethyl)-benzene-sulphonamide

30 g (0.208 mol) of 2-(2-thienyloxy)-ethanol are taken in 300 ml of absolute tetrahydrofuran, and 50 mg of p-toluenesulphonic acid are dissolved therein. 18.37 g (0.218 mol) of 3,4-dihydropyran are added to the solution and the mixture is stirred for 8 hours.

The mixture is cooled to -20°C and 83.2 ml (0.208 mol) of a 2.5 M solution of n-butyllithium in n-hexane are added dropwise, with stirring, such that the temperature does not rise above -10°C. The mixture is allowed to warm to room temperature and is stirred for one hour.

The reaction mixture is cooled to 10°C and a solution of 19.05 g (0.104 mol) of N-benzenesulphonylaziridine (DRP 698,597 (1939)) in 100 ml of absolute tetrahydrofuran is added dropwise at 10 - 15°C in the course of 30 minutes. The mixture is heated to room temperature and stirred for a further 2 hours.

The mixture is emptied onto 200 ml of 2N aqueous HCl and extracted three times with 120 ml of methylene chloride each time. The combined organic phases are dried over sodium sulphate, filtered and evaporated. The residue is taken up in 300 ml of absolute methanol, 2 ml of 30 % strength methanolic hydrochloric acid are added and the mixture is stirred at room temperature for 10 minutes. After addition of 2 g of sodium carbonate, the mixture is evaporated in vacuo.

The residue is partitioned between 250 ml of 1N aqueous sodium hydroxide solution and 200 ml of ether and the ethereal phase is rinsed once with 50 ml of 1N sodium hydroxide solution. The combined aqueous phases are

washed twice with 100 ml of ether each time, acidified with about 25 ml of concentrated hydrochloric acid and extracted three times with 150 ml of methylene chloride each time. The methylene chloride phase is dried over sodium sulphate, 3 g of active charcoal are added, and the mixture is filtered and evaporated.
Yield: 33.3 g of a dark red oil (97.8 % of theory), which is used directly in the next stage.

Example 2:

5-(2-(4-Chloro-benzenesulphonylamino)-ethyl)-2-thienyl-oxyacetic acid

15 g (0.088 mol) of silver nitrate were dissolved in 90 ml of distilled water, and a solution of 3.5 g (0.088 mol) of sodium hydroxide in 45 ml of distilled water were slowly added dropwise, with stirring. The resulting suspension of silver oxide was stirred for a further 10 minutes and the precipitate was filtered off and washed several times with distilled water.

4.0 g (0.011 mol) of 4-chloro-N-(2-(2-(5-(2-hydroxy)-ethoxy)-thienyl)ethyl)-benzenesulphonamide (II) were dissolved in 40 ml of 2N aqueous sodium hydroxide solution, the still moist silver oxide was added and the mixture was heated to 80°C, with mechanical stirring. After 3.5 hours at this temperature, the suspension was cooled and filtered with suction over HYFLO and the residue was rinsed with 2N aqueous sodium hydroxide solution. The clear solution in sodium hydroxide solution was acidified with concentrated hydrochloric acid and extracted three times with 80 ml of ether each time.

The ethereal phase was extracted twice by shaking with 50 ml of saturated sodium bicarbonate solution each time, washed once with 50 ml of ether and acidified with concentrated hydrochloric acid. The aqueous phase was extracted twice with 150 ml of ether and the combined ether phases were dried with sodium sulphate, filtered and evaporated. The crude product was recrystallized from toluene.

Yield: 1.3 g of colourless crystals (31.7 % of theory)

Melting point: 125 - 127°C (toluene)

¹H-NMR: (CDCl₃)

delta (ppm): 7.81; 7.71; 7.51; 7.42 (AB; 4H; Bz-H;
J_{AB}=8.0 Hz), 6.39; 6.35; 6.10; 6.06 (AB; 2H; Th-H₃; Th-H₄;
5 J_{AB}=3.8 Hz), 4.85 (t; 1H; -NH-), 4.61 (s; 2H;
-O-CH₂-COO-), 3.13 (t; 2H; N-CH₂-; J=6Hz), 2.80 (t; 2H;
Th-CH₂-; J=6Hz)

¹³C-NMR: (DMSO)

delta (ppm): 169.0 (s; -COOH), 161.9 (s; Th-C₂), 139.3
10 (s; Bz-C₁), 137.1 (s; Bz-C₄), 129.1 (d; Bz-C₃, B-C₅), 128.2
(d; Bz-C₂, Bz-C₆), 127.4 (Th-C₅), 122.4 (d; Th-C₄), 105.1
(d; Th-C₃), 69.4 (t; O-CH₂-CO), 43.8 (t; -NH-CH₂-), 29.9
(t; Th-CH₂)

The starting material can be prepared as follows:

15 4-Chloro-(2-(2-(5-(2-hydroxy)-ethoxy)-thienyl)-ethyl)-
benzenesulphonamide

18.9 g (0.137 mol) of 2-(2-thienyloxy)-ethanol
were taken in 200 ml of absolute tetrahydrofuran, and
about 50 mg of p-toluenesulphonic acid were dissolved
20 therein. 14.2 g (0.169 mol) of 3,4-dihydropyran were
added and the mixture was stirred for 8 hours.

The mixture was cooled to -20°C and 66 ml
(0.165 mol) of a 2.5 M solution of n-butyllithium in n-
hexane were added dropwise, with stirring, such that the
25 temperature did not rise above -15°C. The mixture was
allowed to warm slowly to room temperature and stirring
was continued for one hour.

A solution of 18 g (0.083 mol) of N-(4-chloro-
benzenesulphonyl)-aziridine (V.I. Markov and D.A.
30 Danileiko, Zh.Org.Khim 1973 (6), 1357) in 100 ml of
absolute tetrahydrofuran was now added dropwise at -5 to
0°C. The reaction mixture was heated to room temperature
and stirred for a further 30 minutes.

The reaction mixture was emptied onto 200 ml of
35 2N aqueous HCl and extracted three times with 250 ml of
methylene chloride each time. The combined organic phases
were dried with sodium sulphate, filtered and evaporated.
The residue was taken up in 100 ml of absolute methanol,
10 ml of 30 % strength methanolic hydrochloric acid were

added, and the mixture was stirred at room temperature for 10 minutes. A spoonful of sodium carbonate was added and the methanol was distilled off. The residue was partitioned between 100 ml of 1N aqueous sodium hydroxide solution and 100 ml of ether and the ethereal phase was rinsed once with 100 ml of 1N sodium hydroxide solution. The combined aqueous phases were washed twice with 50 ml of ether, acidified with concentrated hydrochloric acid and extracted three times with 100 ml of methylene chloride each time. Thereafter, the extract was dried over sodium sulphate, active charcoal was added, the mixture was filtered and the filtrate was evaporated. 10.15 g of a viscous dark oil were obtained. This highly contaminated crude product was filtered over silica gel 60 (180 g of silica gel, eluting agent: ethylacetate:petroleum ether).
Yield: 4.5 g of colourless crystals (15 % of theory)
Melting point: 85 - 87°C (benzene)

Example A:

Investigation of the antithrombotic activity

Male Wistar rats (SPF) weighing 200 - 300 g were anaesthetized with pentobarbital sodium (60 mg/kg intraperitoneally). The animals were then given an intravenous injection of the substance of Example 1 ("Substance A") or dazoxiben (4-(2-(1H-imidazol-1-yl)ethoxy)benzoic acid hydrochloride) ("Substance B"). A venule of the mesenterium was exposed, clipped to the stage of a microscope and flushed with a constant 2.5 ml/min of physiological saline solution. Half an hour after injection of the test substance, a laser beam from a Coherent CR 2 supergraphite ion laser (argon laser) was directed onto the venule through the 50 x interference contrast objective of a Leitz Orthoplan microscope for a duration of 1/30 second. The initial energy under the objective of the microscope was 0.18 watt. If no platelet thrombus formed after the first laser lesion (= laser shot) or if the thrombus did not correspond to the vessel diameter in length and width, further laser shots were fired to

produce a thrombus which corresponded to the vessel diameter in length and width.

5 The number of laser shots here is a measure of the antithrombotic activity of the test substances: the higher the number of laser shots for the same vessel diameter, the greater the antithrombotic effect.

Animals which had received no test substances were used as controls.

10 The tests were carried out on 5 animals per test substance and concentration, 3 vessels with a diameter of between 20 and 30 μ m being damaged per animal. Statistical evaluation was by the Kruskal and Wallis test and by the Dunn rank sum test.

Results:

15 The results of the experiments are summarized in Table 1:

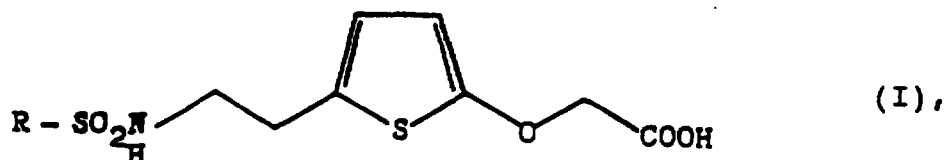
	Concentration (mg/kg)	Number of Substance A	Laser shots (mean value) Substance B
20	0 (control)	2.93 $\pm$ 0.36	2.93 $\pm$ 0.36
	1	3.12 $\pm$ 0.52	3.07 $\pm$ 0.47
	5	6.40 $\pm$ 0.56	2.89 $\pm$ 0.57
	10	6.13 $\pm$ 0.30	3.14 $\pm$ 0.66
25	15	6.33 $\pm$ 0.53	4.46 $\pm$ 0.48
	20	6.42 $\pm$ 0.41	6.35 $\pm$ 0.55

Discussion:

30 The start of the antithrombotic action is 1 mg/kg of body weight for substance A and reaches a maximum at 5 mg/kg. A further increase in concentration provides no further increase in action. In order to achieve an action comparable to the action maximum of substance A using substance B, injection of 20 mg/kg, that is to say 4 times the amount, is necessary.

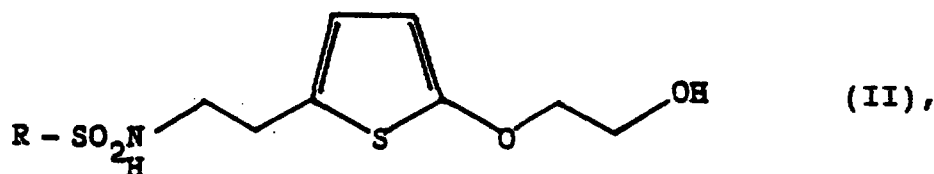
Patent Claims for the Contracting States; AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. 2-Thienyloxyacetic acid derivatives of the general formula I



in which R denotes a phenyl or thienyl group which is optionally mono- or polysubstituted by halogen, tri-fluoromethyl or C₁-C₄ alkyl, and pharmaceutically usable salts thereof.

2. Compounds of the general formula I according to Claim 1, in which R denotes phenyl.
3. Compounds of the general formula I according to Claim 1, in which R denotes 4-chlorophenyl.
4. The compound 5-(2-(benzenesulphonylamino)-ethyl)-2-thienyloxyacetic acid, according to Claim 1.
5. The compound 5-(2-(4-chloro-benzenesulphonylamino)-ethyl)-2-thienyloxyacetic acid, according to Claim 1.
6. Process for the preparation of compounds of the general formula I defined in Claim 1 and of salts thereof, characterized in that a) a compound of the formula II



in which R has the above meaning, is oxidized with silver oxide in an aqueous alkaline medium to give the acid, and b) if desired converting a free acid of the general formula I, obtained in process step a), into a pharmaceutically tolerated salt using inorganic or organic bases.

7. Pharmaceutical preparations containing compounds of the general formula I according to Claim 1 or a salt



thereof in combination with customary galenical auxiliaries, excipients and/or diluents.

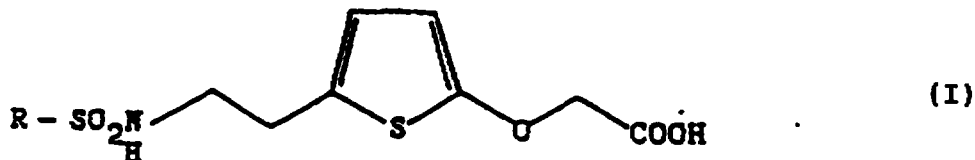
8. Pharmaceutical preparations containing compounds of the general formula I according to Claim 1 or a salt thereof in combination with other therapeutic active compounds and customary galenical auxiliaries, excipients and/or diluents.

9. Compounds according to Claim 1 for use as active substances for medicaments for the treatment and prophylaxis of diseases caused by thromboxane A₂.



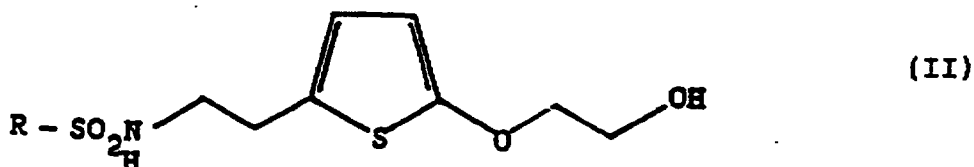
Patentansprüche für die Vertragsstaaten: ES, GR

1. Verfahren zur Herstellung neuer 2-Thienyloxyessigsäure-Derivate der Formel I



in der R eine gegebenenfalls ein-oder mehrfach durch Halogen, Trifluormethyl oder C₁ - C₄ Alkyl substituierte Phenyl-oder Thienylgruppe bedeutet, sowie von pharmazeutisch verwendbaren Salzen von Verbindungen der Formel I, dadurch gekennzeichnet, daß man

a) eine Verbindung der Formel II



in der R wie oben definiert ist, im wäßrigen alkalischen Medium mit Silberoxid zur Säure oxidiert und b) gewünschtenfalls eine im Verfahrensschritt a) erhaltene freie Säure der Formel I mit anorganischen oder organischen Basen in ein pharmazeutisch verträgliches Salz überführt.

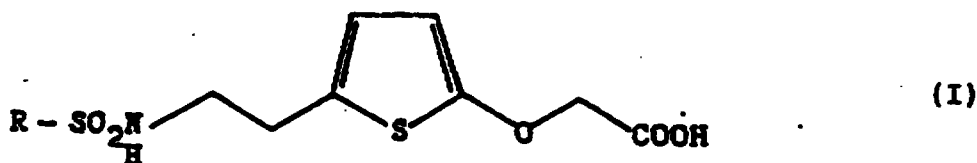
2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man eine Verbindung der Formel II in 0,5 - 4n Alkalihydroxidlösung löst und mit mindestens 2 Äquivalenten Ag₂O bei einer Temperatur von 75 - 85 °C für 2 - 3 Stunden zur Säure oxidiert.

3. Verfahren nach einem der Ansprüche 1 oder 2, dadurch gekennzeichnet, daß man eine Verbindung der Formel II in 2n NaOH- oder KOH-Lösung löst.

4. Verfahren nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß man das zur Oxidation benötigte Ag₂O kurz vor der Oxidation durch Lösen von Silbernitrat in destilliertem Wasser und Zugabe von äquimolaren Mengen von NaOH-Lösung herstellt.

Revendications pour les états contractants: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1 - Dérivés de l'acide 2-thiényloxyacétique de formule générale I:



dans laquelle R est un groupe phényle ou thiényle substitué le cas échéant, une ou plusieurs fois, par un atome d'halogène, un groupe trifluorométhyle ou alkyle de 1 à 4 atomes de carbone, ainsi que leurs sels utilisables pharmaceutiquement.

2. Composé de formule générale I ou R représente un groupe phényle.

3. Composé de formule générale I ou R représente un groupe 4-chlorophényle.

4. Composé selon la revendication 1 constitué par l'acide 5-(2-(benzènesulfonylamido)-éthyl)-2-thiényloxyacétique.

5. Composé selon la revendication 1 constitué par l'acide 5-(2-(4-chloro-benzènesulfonylamino))-éthyl)-2-thiényloxyacétique.

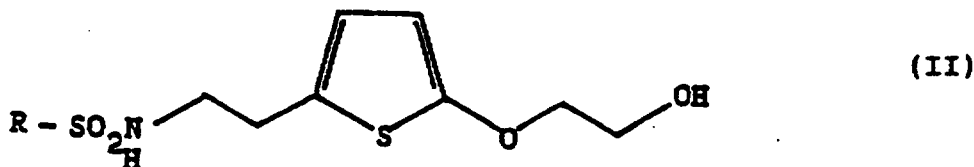
6. Procédé de fabrication de composés de formule générale I définie dans la revendication 1 et de



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leurs sels, caractérisés en ce qu'on oxyde:

a) un composé de la formule II



dans laquelle R est défini comme précédemment, dans un milieu aqueux alcalin avec l'oxyde d'argent, en acide, et

b) on convertit le cas échéant un acide libre de formule générale I, obtenu dans l'étape a) du procédé avec des bases organiques ou non en un sel pharmaceutiquement utilisable.

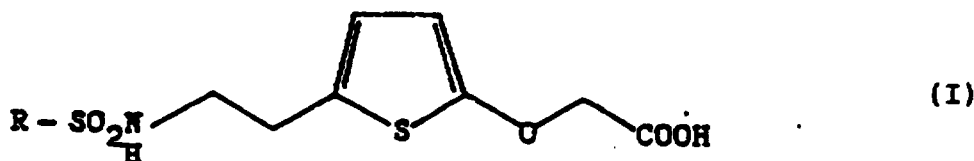
7. Préparations pharmaceutiques renfermant des composés la formule générale I selon la revendication 1 ou un sel en combinaison avec des adjuvants, des substances vecteurs ou agents de dilution galéniques.

8. Préparations pharmaceutiques renfermant des composés de formule générale I d'après la revendication 1 ou un sel en combinaison avec d'autres agents thérapeutiques, ainsi que des adjuvants et des substances vecteurs ou des agents diluants galéniques usuels.

9. Composés selon la revendication 1 utilisés comme principe actif dans des médicaments pour le traitement et la prophylaxie de maladies provoquées par le thromboxane-A₂.

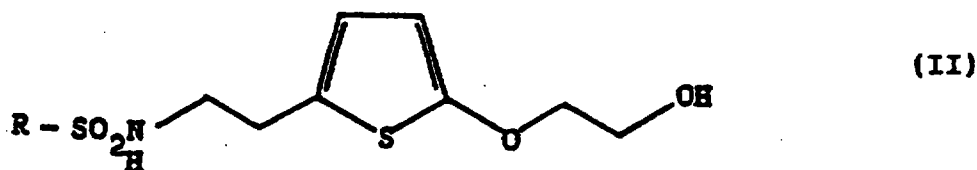
Revendications pour les états contractants: ES, GR

1.- Procédé de préparation de nouveaux dérivés de l'acide 2-thiényloxyacétique de formule (I)



dans laquelle R signifie un groupe phényle ou thiényle substitué le cas échéant une ou plusieurs fois par un atome d'halogène, un groupe trifluorométhyle ou un groupe alkyle de 1 à 4 atomes de carbone, ainsi que les sels utilisables pharmaceutiquement des composés de formule (I), caractérisés en ce que:

(a) on oxyde un composé de formule (II)



dans laquelle R est défini comme précédemment dans un milieu alcalin aqueux, avec l'oxyde d'argent en acide, et

(b) on convertit le cas échéant un acide libre de formule générale (I) obtenu dans l'étape (a) du procédé en un sel pharmaceutiquement acceptable à l'aide de bases organiques ou non.

2.- Procédé selon la revendication 1, caractérisé en ce qu'on dissout un composé de formule (II) dans une solution 0,5 - 4 N d'hydroxyde alcalin et qu'on oxyde un acide avec au moins deux équivalents de Ag₂O, à une température de 75 - 85°C pendant 2 à 3 heures.

3.- Procédé selon l'une des revendications 1 ou 2, caractérisé en ce qu'on dissout un composé de formule générale (II) dans une solution 2 N de NaOH ou KOH.

4.- Procédé selon l'une des revendications 1 à 3, caractérisé en ce que l'oxyde d'argent Ag₂O nécessaire à l'oxydation est préparé juste avant l'oxydation à l'aide d'une solution de nitrate d'argent dans l'eau distillée additionnée d'une quantité équimolaire de solution de NaOH.

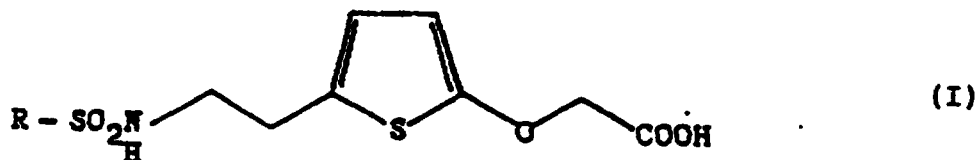


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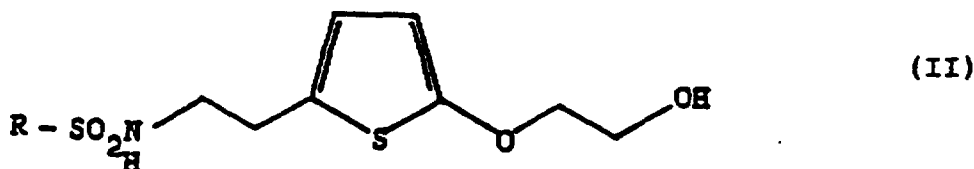
Claims for the Contracting States: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. 2-Thienyloxyacetic acid derivatives of the general formula I



in which R denotes a phenyl or thienyl group which is optionally mono- or polysubstituted by halogen, trifluoromethyl or C₁-C₄ alkyl, and pharmaceutically usable salts thereof.

2. Compounds of the general formula I according to Claim 1, in which R denotes phenyl.
3. Compounds of the general formula I according to Claim 1, in which R denotes 4-chlorophenyl.
4. The compound 5-(2-(benzenesulphonylamino)-ethyl)-2-thienyloxyacetic acid, according to Claim 1.
5. The compound 5-(2-(4-chloro-benzenesulphonylamino)-ethyl)-2-thienyloxyacetic acid, according to Claim 1.
6. Process for the preparation of compounds of the general formula I defined in Claim 1 and of salts thereof, characterized in that
 - a) a compound of the formula II

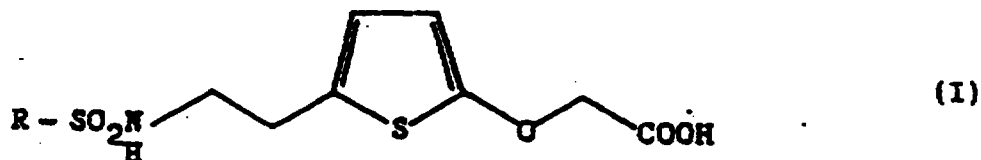


in which R has the above meaning, is oxidized with silver oxide in an aqueous alkaline medium to give the acid, and

- b) if desired converting a free acid of the general formula I, obtained in process step a), into a pharmaceutically tolerated salt using inorganic or organic bases.
7. Pharmaceutical preparations containing compounds of the general formula I according to Claim 1 or a salt thereof in combination with customary galenical auxiliaries, excipients and/or diluents.
8. Pharmaceutical preparations containing compounds of the general formula I according to Claim 1 or a salt thereof in combination with other therapeutic active compounds and customary galenical auxiliaries, excipients and/or diluents.
9. Compounds according to Claim 1 for use as active substances for medicaments for the treatment and prophylaxis of diseases caused by thromboxane A₂.

Claims for the Contracting States: ES, GR

1. Process for the preparation of novel 2-thienyloxyacetic acid derivatives of the general formula I

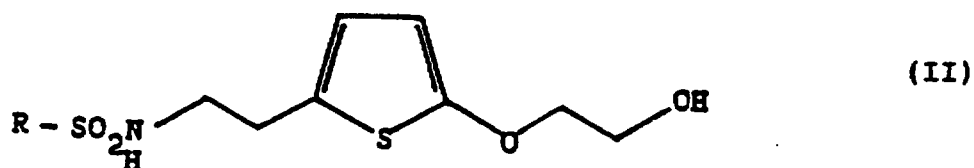


in which R denotes a phenyl or thienyl group which is optionally mono- or polysubstituted by halogen, trifluoromethyl or C₁-C₄ alkyl, and of pharmaceutically usable salts of compounds of the formula I; characterized in that

- a) a compound of the formula II



As printed



in which R has the above meaning, is oxidized with silver oxide in an aqueous alkaline medium to give the acid, and

b) if desired converting a free acid of the formula I, obtained in process step a), into a pharmaceutically tolerated salt using inorganic or organic bases.

2. Process according to Claim 1, characterized in that a compound of the formula II is dissolved in 0.5-4n alkali metal hydroxide solution and oxidized with at least 2 equivalents of Ag₂O at a temperature of 75-85°C for 2-3 hours to give the acid.

3. Process according to either of Claims 1 or 2, characterized in that a compound of the formula II is dissolved in 2n NaOH or KOH solution.

4. Process according to one of Claims 1 to 3, characterized in that the Ag₂O necessary for oxidation is prepared shortly before the oxidation by dissolving silver nitrate in distilled water and adding equimolar amounts of NaOH solution.

