

SPECIFICATION

Phenylaminothiophenacetic acids, processes for their preparation and medicaments containing them

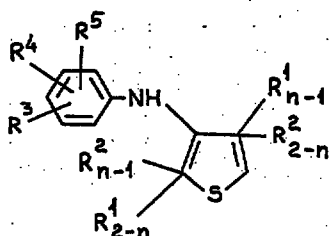
The invention relates to phenylaminothiophenacetic acids, processes for their preparation and medicaments containing them.

The compounds according to the invention are used in the pharmaceutical industry and for the preparation of medicaments.

3-Phenylaminothiophen-4-carboxylic acids, to which good antiphlogistic and antipyretic properties are attributed, are described in German Patent Specification 1,493,705. The antiphlogistic action of the 2,3-dimethylphenyl compound proved comparable to that of phenylbutazone, and its antipyretic action provided to be superior. Further interesting representatives of this class of compounds are the 2,6-dichlorophenyl derivative and the 2-methyl-3-chlorophenyl derivative [H. G. Alpermann; *Arzneim.-Forsch. (Drug Res.)* 20 (1970)293—94] and the 2-chloro-3-methylphenyl derivative [H. G. Alpermann et al., *Arzneim.-Forsch. (Drug Res.)* 22 (1972)2146—47], the actions of which are superior to those of phenylbutazone. Fibrinolytic properties are also attributed to various thiophencarboxylic acids [K. N. von Kaulla, *Arzneim.Forsch.* 25, 152—55 (1975) K. N. von Kaulla, D. Thilo, *Klin. Wochensch.* 48, 668—73 (1970); and D. Thilo, K. N. von Kaulla, *J.Med.Chem.* 13, 503—10 (1970)].

It has now been found that phenylaminothiophenacetic acids (=phenylaminothiénylacetic acids) and their salts have an outstanding pharmacological activity, and that the corresponding nitriles or esters are predominantly valuable intermediate products for the preparation of the pharmacologically active phenylaminothiophenacetic acids and their salts.

The invention relates to phenylaminothiophenacetic acids of the general formula I



wherein

R^1 denotes a hydrogen atom, a chlorine atom, a bromine atom or a methyl group,

R^2 denotes a $-\text{CH}_2-\text{COOH}$ group or a $-\text{CH}_2-\text{COOR}^6$ group,

R^3 denotes a hydrogen atom, a halogen atom, an alkyl group, an alkoxy group or a trifluoromethyl group,

R^4 has one of the meanings of R^3 ,

R^5 denotes a hydrogen atom, a halogen atom or an alkyl group,

R^6 denotes an alkyl group with 1 to 5 carbon atoms which is optionally substituted by hydroxyl, hydroxyalkoxy or alkanoyloxy groups, or a benzyl group and n denotes 1 or 2,

and salts of the acids.

Possible halogen atoms may be the fluorine or bromine atom, preferably the chlorine atom.

Preferred alkyl or alkoxy groups are those with 1 to 5 carbon atoms. Examples which may be mentioned are those with straight-chain alkyl groups, such as the pentyl, butyl, propyl, ethyl or methyl group, and those with branched alkyl groups, such as the neopentyl, tert.-butyl, sec.-butyl or isopropyl group. Preferred alkyl or alkoxy groups are the methyl group and the methoxy group.

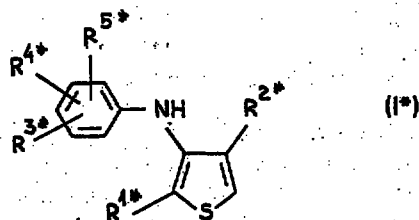
Preferred hydroxyalkoxy groups are those with up to four carbon atoms and up to three hydroxyl groups. Preferred alkanoyloxy groups are those with one to four carbon atoms. Examples which may be mentioned are the 2-hydroxyethoxy group, the 2,3-dihydroxypropoxy group, the 2-hydroxypropoxy group, the acetoxy group and the butyryloxy group. Preferred substituted alkyl groups R^6 are the 2-hydroxy-ethoxy-ethyl group and the acetoxymethyl group.

Preferred salts of the invention are the pharmacologically acceptable salts, that is to say biologically tolerated salts. Cations which are used for the salt formation are, above all, the cations of the alkali metals, alkaline earth metals and earth metals, or the ammonium ion, as well as the corresponding cation acids of univalent or polyvalent organic nitrogen bases, in particular of organic amines.

Possible examples are the cations of the metals lithium, sodium, potassium, magnesium, calcium and aluminium, or mixtures thereof, such as in basic magnesium aluminium complex salts, and of copper, and the cation acids of ethanolamine, diethanolamine, triethanolamine, ethylenediamine, dimethylamine, diethylamine, morpholine, piperazine, methylcyclohexylamine, glucosamine, N-methylglucamine and N-methylglucosamine, and furthermore of tert.-butylamine, dibutylamine,

diisopropylamine, triethylamine, isopropylamine, 2-amino-2-thiazoline, quinoline or ammonia, or amino-acids, such as alanine, lysine, arginine or asparagine.

Phenylaminothiophenacetic acids of the general formula I*



5 wherein

R^{1*} denotes a hydrogen atom, a chlorine atom, a bromine atom or a methyl group,

R^{2*} denotes a —CH₂—COOH group or a —CH₂—COOR^{6*} group,

R^{3*} denotes a hydrogen atom, a chlorine atom, a methyl group or a trifluoromethyl group,

R^{4*} has one of the meanings of R^{3*},

R^{5*} denotes a hydrogen atom or a chlorine atom and

R^{6*} denotes an alkyl group with 1 to 4 carbon atoms which is optionally substituted by an acetoxy group or a 2-hydroxyethoxy group, or a benzyl group,

and salts of the acids form an embodiment of the invention.

Preferred representatives of embodiment I* are those in which

R^{1*} denotes a hydrogen atom or a chlorine atom,

R^{2*} denotes a —CH₂—COOH group or a —CH₂—COOR^{6*} group,

R^{3*} denotes a chlorine atom, a methyl group or a trifluoromethyl group,

R^{4*} denotes a chlorine atom or a methyl group,

R^{5*} denotes a hydrogen atom or a chlorine atom and

R^{6*} denotes a 2-(2-hydroxyethoxy)-ethyl group,

and the pharmacologically tolerated salts of the acids.

Particularly preferred representatives of embodiment I* are those in which

R^{1*} denotes a hydrogen atom,

R^{2*} denotes a —CH₂—COOH group,

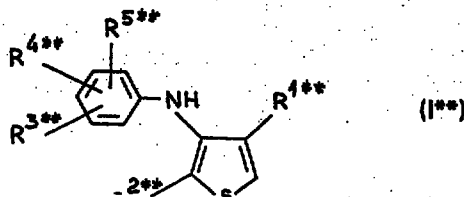
R^{3*} denotes a chlorine atom or a methyl group,

R^{4*} denotes a chlorine atom and

R^{5*} denotes a hydrogen atom,

and their pharmacologically tolerated salts.

Phenylaminothiophenacetic acids of the general formula I**



wherein

R^{1**} denotes a hydrogen atom or a methyl group,

R^{2**} denotes a —CH₂—COOH group or a —CH₂—COOR^{6**} group,

R^{3**} denotes a hydrogen atom, a chlorine atom, a methyl group or a trifluoromethyl group,

R^{4**} has one of the meanings of R^{3**},

R^{5**} denotes a hydrogen atom or a chlorine atom and

R^{6**} denotes an alkyl group with 1 to 4 carbon atoms which is optionally substituted by an acetoxy group or a 2-hydroxyethoxy group, or a benzyl group,

and salts of the acids form a further embodiment of the invention.

Preferred representatives of embodiment I** are those

in which

R^{1**} denotes a hydrogen atom,

R^{2**} denotes a —CH₂—COOH group or a —CH₂—COOR^{6**} group,

R^{3**} denotes a chlorine atom, a methyl group or a trifluoromethyl group,

R^{4**} denotes a chlorine atom or a methyl group,

R^{5**} denotes a hydrogen atom or a chlorine atom and

R^{6**} denotes a 2-(2-hydroxyethoxy)-ethyl group,

and the pharmacologically tolerated salts of the acids.

Particularly preferred representatives of embodiment I** are those in which

R^{1**} denotes a hydrogen atom,

R^{2**} denotes a —CH₂—COOH group,

5 R^{3**} denotes a chlorine atom or a methyl group,

R^{4**} denotes a chlorine atom and

R^{5**} denotes a hydrogen atom,

and their pharmacologically tolerated salts.

Representatives of the formula I* are preferably to those of the formula I**.

10 Examples of representatives of the compounds according to the invention are 4-(2,3-dimethylanilino)-3-thiophenacetic acid, 4-(2,3-dimethylanilino)-3-thiophenacetic acid benzyl ester, 4-(2-fluoro-6-trifluoromethylanilino)-3-thiophenacetic acid, 4-(2-chloro-6-methylanilino)-3-thiophenacetic acid, 4-(2-chloro-6-methylanilino)-3-thiophenacetic acid 2-(2-hydroxyethoxy)-ethyl ester, 4-(2-chloro-6-methylanilino)-3-thiophenacetic acid benzyl ester, 4-(2,4,6-trimethylanilino)-3-thiophenacetic acid, 4-(2,4,6-trichloroanilino)-3-thiophenacetic acid, 4-(2,4,6-trimethylanilino)-3-thiophenacetic acid 3-acetoxy-propyl ester, 4-(2-bromoanilino)-3-thiophenacetic acid, 4-(2-methyl-4-trifluoromethylanilino)-3-thiophenacetic acid, 4-(4-fluoroanilino)-3-thiophenacetic acid, 4-(2,3-dichloroanilino)-3-thiophenacetic acid, 4-(2,3-dichloroanilino)-3-thiophenacetic acid methyl ester, 4-(2,3-dichloroanilino)-3-thiophenacetic acid 2-(2-hydroxyethoxy)ethyl ester, 4-(2,3-dichloroanilino)-3-thiophenacetic acid benzyl ester, 4-(2-chloro-5-methylanilino)-3-thiophenacetic acid, 4-(2-chloro-5-methylanilino)-3-thiophenacetic acid 2-acetoxy-ethyl ester, 4-(2-chloro-3-methylanilino)-3-thiophenacetic acid 3-acetoxy-propyl ester, 4-(2-chloro-3-methylanilino)-3-thiophenacetic acid benzyl ester, 4-(2,4-dichloro-3-methylanilino)-3-thiophenacetic acid, 4-(2,4-dichloro-3-methylanilino)-3-thiophenacetic acid n-propyl ester, 4-(2-dichloro-5-methylanilino)-3-thiophenacetic acid, 4-(2,4-dichloro-5-methylanilino)-3-thiophenacetic acid sec.-butyl ester, 3-(2,3-dimethylanilino)-2-thiophenacetic acid, 3-(2,3-dimethylanilino)-2-thiophenacetic acid 2-(2-hydroxyethoxy)-ethyl ester, 3-(2,4,6-trimethylanilino)-2-thiophenacetic acid, 3-(2,4,6-trichloroanilino)-2-thiophenacetic acid, 3-(2-chloroanilino)-2-thiophenacetic acid, 3-(2-chloroanilino)-2-thiophenacetic acid 3-acetoxy-propyl ester, 3-(2-chloroanilino)-2-thiophenacetic acid benzyl ester, 3-(2,3-dichloroanilino)-2-thiophenacetic acid, 3-(2,3-dichloroanilino)-2-thiophenacetic acid 2-butyryloxy-ethyl ester, 3-(2,3-dichloroanilino)-2-thiophenacetic acid benzyl ester, 3-(3-methylanilino)-2-thiophenacetic acid, 3-(3-methylanilino)-2-thiophenacetic acid isopropyl ester, 3-(3-methylanilino)-2-thiophenacetic acid benzyl ester, 3-(2,4-dichloro-3-methylanilino)-2-thiophenacetic acid, 3-(2,4-dichloro-3-methylanilino)-2-thiophenacetic acid 2-(2-hydroxyethoxy)-ethyl ester, 3-(2,4-dichloro-3-methylanilino)-2-thiophenacetic acid benzyl ester, 3-(2-methyl-4-trifluoromethylanilino)-3-thiophenacetic acid, 3-(2-methyl-4-trifluoromethylanilino)-2-thiophenacetic acid n-butyl ester, 3-(2-methyl-4-trifluoromethylanilino)-2-thiophenacetic acid 2-acetoxy-ethyl ester, 3-(2,4-dichloroanilino)-2-thiophenacetic acid benzyl ester, 3-(2,5-dichloroanilino)-2-thiophenacetic acid, 4-(2,5-dichloroanilino)-3-thiophenacetic acid benzyl ester, 4-(2,3-dimethylanilino)-5-chloro-3-thiophenacetic acid, 4-(2,3-dimethylanilino)-5-chloro-3-thiophenacetic acid 2-(2-hydroxyethoxy)-ethyl ester, 4-(2-chloro-6-methylanilino)-5-chloro-3-thiophenacetic acid, 4-(2-bromoanilino)-5-chloro-3-thiophenacetic acid, 4-(2,3-dichloroanilino)-5-methyl-3-thiophenacetic acid, 4-(2,3-dichloroanilino)-5-methyl-3-thiophenacetic acid benzyl ester, 4-(2-chloro-5-methylanilino)-5-methyl-3-thiophenacetic acid, 4-(2,4-dichloro-3-methylanilino)-5-chloro-3-thiophenacetic acid, 4-methyl-3-(2,3-dimethylanilino)-2-thiophenacetic acid, 4-methyl-3-(2,3-dimethylanilino)-2-thiophenacetic acid 2-acetoxy-ethyl ester, 3-(2-chloroanilino)-4-methyl-2-thiophenacetic acid, 3-(2-chloroanilino)-4-methyl-2-thiophenacetic acid benzyl ester, 3-(2,3-dichloroanilino)-4-methyl-2-thiophenacetic acid, 5-chloro-4-(2-methyl-4-trifluoromethylanilino)-3-thiophenacetic acid, 4-(2,4,6-trichloroanilino)-5-methyl-3-thiophenacetic acid and 5-chloro-4-(2,4,6-trichloroanilino)-3-thiophenacetic acid and salts of the acids.

50 Preferred compounds are: 4-(2,6-dichloroanilino)-3-thiophenacetic acid, 4-(2-chloro-6-methylanilino)-3-thiophenacetic acid, 4-(2,6-dichloro-3-methylanilino)-3-thiophenacetic acid, 3-(2,6-dichloroanilino)-2-thiophenacetic acid, 4-(2-chloro-3-methylanilino)-3-thiophenacetic acid, 4-(3-chloro-2-methylanilino)-3-thiophenacetic acid, 4-(2,6-dimethylanilino)-3-thiophenacetic acid, 5-chloro-4-(2,6-dichloroanilino)-3-thiophenacetic acid and 3-(2-chloro-6-methylanilino)-2-thiophenacetic acid and salts thereof.

55 In addition to analgesic and antipyretic properties, the compounds according to the invention and their salts have pronounced antiphlogistic properties, as can be demonstrated, for example, by various tests in which the influence of the compounds on acute inflammatory reactions (carrageenin edema of the hind paw of rats [Winter et al.: Proc.Soc.exp.Biol.Med. 111 (1962) 544]) and on chronic inflammatory processes (Cotton pellet test on rats [Winter et al.: J.Pharmacol.exp.Therap. 141 (1963) 369]) and on adjuvant arthritis [based on the method of Perrine et al., Brit.J.Pharmacol. 21 (1963) 127] is determined. In these tests, they prove to be superior to the compounds of the prior art, for example those of the German Patent Specification 1,493,705 mentioned, and to the commercially available medicaments, such as indomethacin. Moreover, they are distinguished by a comparably low toxicity.

65 When administered in a therapeutically active and pharmacologically tolerated amount, the compounds

according to the invention are thus suitable for the treatment of a number of mammalian illnesses in which one or more symptoms of inflammation, pain and fever occur. Examples of such illnesses are the most diverse inflammatory and degenerative illnesses of the rheumatic type and of other inflammatory illness processes, for example acute and chronic polyarthritis, osteoarthritis, psoriatic arthritis,

5 ankylosing spondylitis, polyarthroses, spondyloses, articular rheumatism and rheumatic fever; rheumatism of soft tissues, for example sciatica; painful post-operative swellings and inflammations; pain and swellings after hydrarthroses, sprains and breaks; pain and inflammations in connection with dental surgery; attacks of pain of the most diverse origins, for example neuritides, headaches and spasms; and human and animal illnesses which result in the above symptoms and require the use of an
10 antiinflammatory, analgesic and/or antipyretic medicament.

The invention furthermore relates to medicaments which are characterised in that they contain one or more of the new active compounds. If appropriate, the new medicaments contain, in addition to the new active compounds, pharmaceutical excipients for these active compounds. The content of active compound in these medicaments is 1 to 95, preferably 10 to 85, per cent by weight, relative to
15 the finished medicament.

The medicaments are preferably administered orally, and furthermore rectally, or parenterally, for example subcutaneously, intramuscularly or intravenously, as solutions of salts, or are applied topically (percutaneously). The pharmaceutical formulation of the active compound is advantageously in the form of unit doses which are adjusted to the desired administration. A unit dose can be, for example, a tablet,
20 a capsule, a suppository or a measured volume of a powder, of granules, of a solution, of an emulsion, of a suspension, of a gel or of a cream. "Unit dose" for the purpose of the present invention is understood as a physically determined unit which contains an individual amount of the active constituent mixed with a pharmaceutical diluent for the constituent or together with a pharmaceutical excipient. The amount of active compound is chosen so that one or more units are usually required for an individual
25 therapeutic administration. However, the unit can also be divisible, for example in the case of tablets provided with breaking grooves, if only a fraction, such as a half or one-quarter, of the divisible unit is required for an individual therapeutic administration.

The pharmaceutical formulations according to the invention, when in the form of a unit dose for administration to humans, contain 0.5 to 500 mg; advantageously 2.5 to 250 mg and in particular 5 to
30 125 mg, of active compound.

The unit doses for administration to lighter or heavier mammals are to be chosen appropriately smaller or larger; thus, for example, unit doses for administration to large animals such as cattle or horses, contain 50 to 5,000 mg, advantageously 100 to 3,000 mg and in particular 150 to 2,000
35 mg, of active compound. The pharmaceutical formulations can be administered therapeutically 1 to 4 times daily, for example after each mealtime and/or in the evening. The dose administered depends on the frequency of administration, the period of treatment, the nature and severity of the illness and the weight, age and state of health of the patient. In general, the daily dose for mammals is between 0.01 to 35 mg/kg of body weight, preferably below 10 mg/kg of body weight. An appropriate daily dose for
40 administration to humans is between 0.5 and 5 mg/kg of body weight.

The pharmaceutical formulations as a rule consist of the active compounds according to the invention and non-toxic, pharmaceutically acceptable medicinal excipients which are used as an admixture in solid, semi-solid or liquid form, or as a means of encasing, for example in the form of a capsule, a tablet coating, a sachet or some other container for the therapeutically active constituent. An excipient can for example serve as a promoter of the absorption of the medicament by the body, as a
45 formulation auxiliary, as a sweetener, as a flavouring agent, as a dyestuff or as a preservative.

Examples of forms which may be administered orally are tablets, dragees, hard and soft capsules, for example made of gelatine, dispersible powders, granules, aqueous and oily suspensions, emulsions, solutions or syrups.

Tablets may contain inert diluents, for example calcium carbonate, calcium phosphate, sodium
50 phosphate or lactose; granulating agents and dispersing agents, for example maize starch or alginates; binders, for example starch, gelatine or gum acacia; and lubricants, for example aluminium stearate or magnesium stearate, talc or silicone oil. The tablets may in addition be provided with a coating, which can also be such that delayed dissolution and resorption of the medicament in the gastrointestinal tract and hence, for example, better toleration or a long period of action, are achieved. Gelatine capsules may
55 contain the medicament mixed with a solid diluent, for example calcium carbonate or kaolin, or with an oily diluent, for example olive oil, groundnut oil or paraffin oil.

Aqueous suspensions may contain suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth or gum acacia; dispersing agents and wetting agents, for example polyoxyethylene
60 stearate, heptadecaethyleneoxycetanol, polyoxyethylene-sorbitol-monooleate, polyoxyethylene-sorbitan-monooleate or lecithin; preservatives, for example methylhydroxybenzoate or propylhydroxybenzoate; flavouring agents; and sweeteners, for example sucrose, lactose, dextrose or invert sugar syrup.

Oily suspensions may contain, for example, groundnut oil, olive oil, sesame oil, coconut oil or
65 paraffin oil, and thickeners, such as, for example, beeswax, hard paraffin or cetyl alcohol; and

furthermore sweeteners, flavouring agents and antioxidants.

Water-dispersible powders and granules may contain the medicaments mixed with dispersing agents, wetting agents and suspending agents, for example those mentioned above, as well as with sweeteners, flavouring agents and dyestuffs.

- 5 Emulsions may contain, for example, olive oil, groundnut oil or paraffin oil, in addition to emulsifying agents, such as, for example, gum acacia, gum tragacanth, phosphatides, sorbitan, monooleate or polyoxyethylene-sorbitan-monooleate, and sweeteners and flavouring agents. 5

Suppositories which are prepared with the aid of binders which melt at the rectal temperature, for example cacao butter or polyethylene glycols, are used for rectal administration of the medicaments.

- 10 Sterile injectable aqueous solutions, isotonic salt solutions or other solutions, which may contain dispersing agents or wetting agents and/or pharmacologically tolerated diluents, for example propylene glycol or butylene glycol, are used for parenteral administration of the medicaments. 10

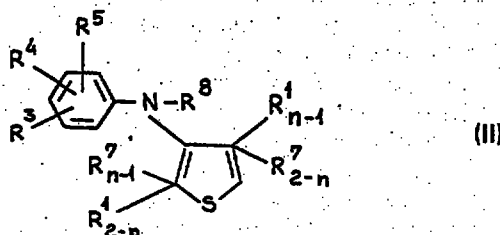
In addition to the new phenylaminothiophenacetic acids, the pharmaceutical formulations can contain, for example, one or more pharmacologically active constituents from other groups of

- 15 medicaments, for example corticosteroids which have an antiphlogistic action (for example prednisone, prednisolone, dexamethasone and derivatives thereof); analgesics, such as, for example, pyrazolone derivatives, propoxyphene, phenacetin, and salicylic acid derivatives; muscle relaxants, such as pyridazine derivatives, carbamates (for example phenprobamate); substances with an antitumorogenic action; antacids (such as, for example, magnesium trisilicate and aluminium hydroxide); 15
20 substances which stimulate local blood flow, such as, for example, nicotinic acid derivatives and dimethylsulphoxide; local anaesthetics (such as, for example, lidocaine) and vitamins (such as, for example, vitamin B₁ chloride hydrochloride, vitamin B₆ hydrochloride, vitamin B₁₂ cyano complex and thiamine disulphide). 20

The invention furthermore relates to a process for the preparation of phenylaminothiophenacetic acids of the general formula I or of embodiments I* or I**, wherein 25

R¹, R², R³, R⁴, R⁵, R⁶ and n or the substituents in the embodiments have the meaning indicated for these formulae, and salts thereof with organic and inorganic bases.

- 30 The process is characterised in that functional carboxylic acid derivatives of the general formula II 30

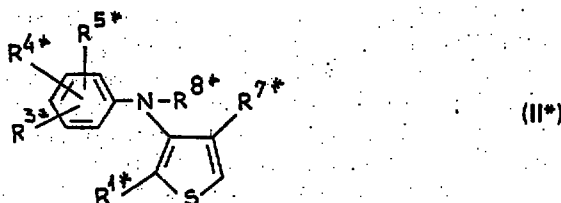


wherein

- 35 R¹ denotes a hydrogen atom, a chlorine atom, a bromine atom or a methyl group.
R³ denotes a hydrogen atom, a halogen atom, an alkyl group, an alkoxy group or a trifluoromethyl group,
R⁴ has one of the meanings of R³, 35
R⁵ denotes a hydrogen atom, a halogen atom or an alkyl group,
R⁷ denotes a —CH₂—G group or, together with R⁸, a —CH₂—CO— group,
R⁸ denotes a hydrogen atom or, together with R⁷, a —CO—CH₂— group,
40 G denotes a functional derivative of a carboxylic acid group and
n denotes 1 or 2, 40

are lyoyised, that is to say split by solvolysis, hydrolygenolysis or thermolysis, to give compounds of the general formula I or salts thereof, and the resulting acids or esters of the general formula I are then optionally converted into one another and/or into salts in the customary manner.

- 45 An embodiment of the invention is a process for the preparation of phenylaminothiophenacetic acids of the general formula I* where the substituents have the same meaning as above and their salts which is characterised in that functional phenylaminothiophenacetic acid derivatives of the general formula II* 45



wherein

R^{1*} denotes a hydrogen atom, a chlorine atom, a bromine atom or a methyl group,

R^{3*} denotes a hydrogen atom, a chlorine atom, a methyl group or a trifluoromethyl group,

R^{4*} has one of the meanings of R^{3*},

R^{5*} denotes a hydrogen atom or a chlorine atom,

R^{7*} denotes a —CH₂—G* group or, together with R^{8*}, a —CH₂—CO— group,

R^{8*} denotes a hydrogen atom or, together with R^{7*}, a —CO—CH₂— group and

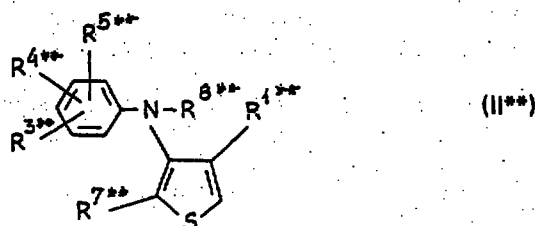
G* denotes a functional derivative of a carboxylic acid group,

are lyolysed to give compounds of the general formula I* or salts thereof, and the resulting acids or esters of the general formula I* are then optionally halogenated and/or, in the customary manner, converted into one another and/or into salts.

In a preferred embodiment of the process, compounds of the formula II* in which G* represents a nitrile group, a carboxylic acid alkyl ester group with 1 to 7 carbon atoms in the alkyl radical, a carboxylic acid benzyl ester group or a carboxylic acid amide group are used as the starting substances.

A further embodiment of the invention is a process for the preparation of phenylaminothiophenacetic acids of the general formula I** where the substituents have the same meaning as above and their salts which is characterised in that

a) functional phenylaminothiophenacetic acid derivatives of the general formula II**



wherein

R^{1**} denotes a hydrogen atom or a methyl group,

R^{3**} denotes a hydrogen atom, a chlorine atom, a methyl group or a trifluoromethyl group,

R^{4**} has one of the meanings of R^{3**},

R^{5**} denotes a hydrogen atom or a chlorine atom,

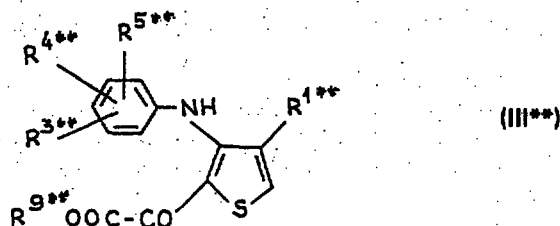
R^{7**} denotes a —CH₂—G** group or, together with R^{8**}, a —CH₂—CO— group,

R^{8**} denotes a hydrogen atom or, together with R^{7**}, a —CO—CH₂— group and

G** denotes a functional derivative of a carboxylic acid group,

are lyolysed to give compounds of the general formula I** or salts thereof, and the resulting acids or esters of the general formula I** are then optionally converted into one another and/or into salts in the

customary manner, or b) a phenylaminothiophenacetic acid derivative of the general formula III**



wherein

R^{1**} denotes a hydrogen atom or a methyl group,

R^{3**} denotes a hydrogen atom, a chlorine atom, a methyl group or a trifluoromethyl group,

R^{4**} has one of the meanings of R^{3**},

R^{5**} denotes a hydrogen atom or a chlorine atom,

R^{9**} denotes a hydrogen atom or an alkyl group with 1 to 5 carbon atoms,

or a salt thereof is reduced, and the resulting acids or esters of the general formula I** are then optionally converted into one another and/or into salts in the customary manner.

In a preferred embodiment of process a), compounds of the formula II** in which R^{7**} represents a —CH₂—G** group, R^{8**} represents a hydrogen atom and G** represents a nitrile group, a carboxylic acid alkyl ester group with 1 to 7 carbon atoms in the alkyl radical, a carboxylic acid benzyl ester group or a carboxylic acid amide group, are used as starting substances. Process b) is preferred over variant a).

By lyolysis of carboxylic acid derivatives there is understood solvolytic, hydrogenolytic or

thermolytic splitting. Solvolytic splitting is, above all, hydrolysis and alcoholysis. A water-supplying medium, which consists completely or partly of water or of agents which split off water or OH ions under the reaction conditions, is used for hydrolytic splitting of functional carboxylic acid derivatives of the general formula II, II* or II**. The reaction can be carried out as a homogeneous reaction, in which case it is usually carried out in the presence of a polar organic solvent or a solubilising agent. Examples of solvents which are advantageously used are low-molecular alcohols, dioxan, acetone, low-molecular carboxylic acid, N-methyl-pyrrolidone, sulpholane, or dimethylsulphoxide. However, it is also possible to carry out the reaction as a heterogeneous reaction. The pH of the water-supplying medium depends on the chemical nature of the phenylaminothiophenacetic acid derivative employed, but also on the nature of the desired compound of the general formula I, I* or I**; it can thus be neutral, acid or basic. It is adjusted to the desired value with acids, bases or buffers. The reaction temperatures are between 0°C and the boiling point of the water-supplying medium, in general between 0° and 150°C and in particular between 20° and 120°C. They also depend specifically on whether the reaction is carried out under pressure or under atmospheric pressure. The reaction times are between 10 minutes and 20 hours, depending on the mixture, the reaction temperature and other reaction parameters. When the hydrolytic splitting has ended, the phenylaminothiophenacetic acids are isolated by customary methods, for example by recrystallisation or by acidification of their solutions, if appropriate with concentration of their solutions. For their purification, an alkaline solution thereof can be extracted with an organic solvent which is immiscible with the alkaline solution, for example ether, benzene, chlorobenzene, chloroform or methylene chloride.

The alcoholysis is preferably carried out in the case of carboxylic acid derivatives of the general formula II, II* or II** in which G, G* or G** represents a nitrile group. A medium which consists completely or partly of the alcohol concerned and a proton donor, for example methanol saturated with hydrochloric acid gas, is used for the alcoholysis. The reaction temperatures are between -20° and 50°C, in particular between 0° and 20°C. The reaction times are between 30 minutes and 10 hours (depending on the reaction temperature and other parameters). When the alcoholysis has ended, the esters formed are isolated by customary methods.

Lyolysis in the form of hydrogenolysis is carried out in the case of compounds of the formula II, II* or II** in which G, G* or G** represents a carboxylic acid benzyl ester group. It is effected under the customary conditions, for example with hydrogen on palladium-on-charcoal or platinum, at -10° to 50°C, preferably at room temperature, under a pressure of 1—200, preferably 1—10, bars and in an inert solvent, such as methanol or acetic acid ethyl ester, or, preferably, in the presence of glacial acetic acid.

Lyolysis in the form of thermolysis is carried out in the case of phenylaminothiophenacetic acid derivatives of the formula II, II* or II** in which G, G* or G** represents a carboxylic acid tert.-alkyl ester group, preferably a tert.-butyl ester group.

This reaction is carried out under the customary conditions, if appropriate in an inert organic solvent, for example chlorobenzene, xylene or toluene, without or preferably in the presence of an acid catalyst, such as p-toluenesulphonic acid, by heating to 30 to 200°C, preferably 70—150°C.

The phenylaminothiophenacetic acid of the general formula I, I* or I** can be converted into their salts by direct alkaline solvolysis with hydroxyl ions from the phenylaminothiophenacetic acid derivatives of the general formula II, II* or II**. The alkaline reaction partner used is appropriately that inorganic or organic base, the salt of which is desired. However, the salts are also obtained by reacting phenylaminothiophenacetic acids of the general formula I, I* or I** with the stoichiometric equivalent of a corresponding base, or by converting readily soluble salts into sparingly soluble salts by double decomposition or converting any desired salts into pharmacologically tolerated salts.

The phenylaminothiophenacetic acid derivatives of the formula II, II* and II** employed as starting materials or intermediate products are likewise new compounds. They are prepared by known methods. Thus, nitriles of the formulae II, II* and II** are obtained from the corresponding halogenomethyl compounds, that is to say from compounds of the formula II, II* or II** in which G denotes a halogen atom, preferably a bromine or chlorine atom, by reaction with alkali metal cyanides or alkaline earth metal cyanides, such as sodium cyanide, potassium cyanide or barium cyanide. The reaction is appropriately carried out in an aprotic, dipolar solvent, for example dimethylformamide, or in a two-phase system in the presence of a phase transfer catalyst, such as benzyltrimethylammonium chloride, at temperatures of from 0° to 80°C.

Phenylaminothiophenacetic acid esters of the general formula II, II* and II** are readily accessible from the nitriles by alcoholysis; and furthermore from the free acids of the general formula I, I* and I** by reaction with alcohols under conditions to split off water, or by reaction of acids and salts with alkylating agents, for example benzyl esters are obtained by reacting silver salts with benzyl halides.

Halogenomethyl compounds are obtained by reducing corresponding phenylthiophene-carboxylic acids or -carboxylic acid esters and subsequently halogenating the products. Examples of suitable reducing agents are sodium boranate, sodium/ethanol or lithium aluminium hydride. The reaction is preferably carried out in inert solvents, such as open-chain or cyclic ethers, for example diethyl ether or tetrahydrofuran, at temperatures between 0° and 25°C. The hydroxymethyl compounds formed are converted into the halogenomethyl compounds by reaction with hydrogen halides, such as hydrogen

chloride or hydrogen bromide. The reaction is effected in a polar, preferably aqueous medium, for example in concentrated hydrochloric acid, at temperatures between 10 and 50°C.

4-Phenylaminothiophen-3-carboxylic acids are obtained according to German Patent Specification 1,493,705. The corresponding esters are obtained by reaction of these acids with alcohols

5 in a manner which is known per se. 3-Phenylaminothiophen-2-carboxylic acids or their esters are obtained by a process analogous to that in German Patent Specification 1,493,705 by reaction of 3-oxo-tetrahydrothiophen-2-carboxylic acid methyl ester or ethyl ester [E. E. Moore and M. B. Moore, J. Am. Chem. Soc. 68 (1946) 910; Erastov, O. A. and Ignat'eva, S. N., Khim. Geterosikl. Soedin. 1971, 7(11)1473—80] with anilines substituted by R³, R⁴ and R⁵, and subsequent dehydrogenation and, if
10 appropriate, hydrolysis.

The subsequent halogenation of resulting compounds of the general formula I* which may be carried out is effected by processes which are known per se. Examples of possible halogenating agents for the halogenation of the thiophen ring are the free halogens chlorine or bromine, N-halogeno-amides and -imides, sulphuryl chloride or phosphorus pentachloride. The reaction with the halogenating agent
15 can be carried out in a known manner, for example in an inert, non-aqueous solvent, such as a chlorinated hydrocarbon or glacial acetic acid (for example using chlorine, bromine or sulphuryl chloride), at temperatures of -40°C to 20°C, preferably at -20° to 0°C, using excess or preferably equivalent amounts of the halogenating agent. As a rule, the reaction has ended 10 minutes to 2 hours after the addition of the halogenating agent.

20 The hydrolysis of phenylaminothiophenacetic acid lactams of the general formula II, II* or II**, that is to say of compounds in which R⁷, R^{7*} or R^{7**}, together with R⁸, R^{8*} or R^{8**} respectively, denote a —CH₂—CO— group and R⁸, R^{8*} or R^{8**}, together with R⁷, R^{7*} or R^{7**} respectively, denote a —CO—CH₂— group, is effected in a manner which is known per se by alkaline or acid saponification in polar solvents, such as alcohols, for example methanol, at temperatures of 20°C up to the boiling point
25 of the solvent.

In general, the reaction has ended after 2 hours, depending on the reaction temperature.

The reduction of the phenylaminothiophenacetic acid derivatives of the general formula III** is effected in a manner which is known per se, by reaction with a suitable reducing agent, for example sodium borohydride, in inert solvents, such as tetrahydrofuran or dimethylformamide, at temperatures
30 of 0° up to the boiling point of the solvent, preferably at 50° to 80°C. The reaction time is 1 to 5 hours, depending on the temperature.

Compounds of the formula III** are obtained by reacting corresponding 3-phenylaminothiophens with oxalic acid alkyl ester chlorides and if appropriate subsequently saponifying the products.

The reaction is effected in the presence of an auxiliary base, such as pyridine or triethylamine, in
35 inert solvents, such as cyclic or open-chain ethers, for example tetrahydrofuran or diethyl ether, at temperatures between 0 and 50°C, preferably at room temperature.

3-Phenylaminothiophens are obtained by decarboxylation of 4-phenylamino-3-thiophenecarboxylic acids, for example by heating to temperatures of 120° to 200°C.

The hydroxymethyl compounds and halogenomethyl compounds are relatively unstable
40 compounds as crude products; they are thus appropriately further reacted immediately after being obtained, purification operations being dispensed with if necessary.

The examples which follow illustrate the invention in more detail. The abbreviations m, and bp, denote melting point and boiling point respectively. d. denotes decomposition point.

EXAMPLE 1

45 31 g (0.11 mole) of 4-(2,6-dichloroanilino)-3-thiophenacetonitrile are boiled in a solution of 110 g of sodium hydroxide in 450 ml of water and 220 ml of methanol for 4 hours. The mixture is diluted with 2 litres of warm water and extracted with toluene, the aqueous phase is acidified and the precipitate of 4-(2,6-dichloroanilino)-3-thiophenacetic acid which has formed is filtered off. The precipitate is boiled
up with diisopropyl ether and dried and then melts at 179—180°C.

50 4-(2-Chloroanilino)-3-thiophenacetic acid (m. 125—126.5°C), 4-(2,6-dimethylanilino)-3-thiophenacetic acid (m. 152.5—153°C), 4-(2-chloro-6-methylanilino)-3-thiophenacetic acid (m. 168—169°C), 4-(4-methoxy-2-methylanilino)-3-thiophenacetic acid, 4-(2-chloro-3-methylanilino)-3-thiophenacetic acid (m. 105—106°C) and 4-(3-trifluoromethylanilino)-3-thiophenacetic acid (m. 108—109°C) are obtained analogously from: 4-(2-chloroanilino)-3-thiophenacetonitrile, 4-(2,6-dimethylamino)-3-thiophenacetonitrile, 4-(2-chloro-6-methylanilino)-3-thiophenacetonitrile, 4-(4-methoxy-2-methylanilino)-3-thiophenacetonitrile, 4-(2-chloro-3-methylanilino)-3-thiophenacetonitrile
55 and 4-(3-trifluoromethylanilino)-3-thiophenacetonitrile, respectively, by boiling with methanolic sodium hydroxide solution and appropriate working up of the mixture.

EXAMPLE 2

60 26.3 g (0.1 mole) of 4-(3-chloro-2-methylanilino)-3-thiophenacetonitrile are introduced into 135 ml of concentrated sulphuric acid, the mixture is stirred at 20°C for 1 hour, 49 ml of water are added dropwise and the mixture is heated to 100°C for 3 hours. It is poured onto ice and the precipitate which has formed is filtered off. Recrystallisation from diisopropyl ether gives 4-(3-chloro-2-methylanilino)-3-

thiophenacetic acid. m. 126—128°C.

- 4-(2,6-Dichloro-3-methylanilino)-3-thiophenacetic acid (m. 159—160°C), 4-(2-chloro-3-methylanilino)-3-thiophenacetic acid (m. 105—106°C), 4-(2,6-difluoroanilino)-3-thiophenacetic acid (m. 151°C), 4-(2,6-dimethylanilino)-3-thiophenacetic acid (m. 152.5—153°C), 5-chloro-4-(2,6-dichloroanilino)-3-thiophenacetic acid (d. 141—142°C), 4-(2-chloroanilino)-5-methyl-3-thiophenacetic acid (m. 196°C) and 4-(2,6-dichloroanilino)-5-methyl-3-thiophenacetic acid (m. 155—156°C) are obtained analogously from: 4-(2,6-dichloro-3-methylanilino)-3-thiophenacetonitrile, 4-(2-chloro-3-methylanilino)-3-thiophenacetonitrile, 4-(2,6-difluoroanilino)-3-thiophenacetonitrile, 4-(2,6-dimethylanilino)-3-thiophenacetonitrile, 5-chloro-4-(2,6-dichloroanilino)-3-thiophenacetonitrile, 4-(2-chloroanilino)-5-methyl-3-thiophenacetonitrile and 4-(2,6-dichloroanilino)-5-methyl-3-thiophenacetonitrile, respectively, by saponification with concentrated sulphuric acid.

EXAMPLE 3

31 g (0.11 mole) of 4-(2,6-dichloroanilino)-3-thiophenacetonitrile are dissolved in 30 ml of methanol.

- 15 The solution is saturated with hydrogen chloride gas at 10°C and left to stand at 10°C for four hours. It is then poured onto 200 ml of water, extracted with 100 ml of diethyl ether and the ethereal phase is washed with 50 ml of water, dried and concentrated. 4-(2,6-Dichloroanilino)-3-thiophenacetic acid methyl ester is obtained as an oil. 15

- 4-(2,6-dichloroanilino)-3-thiophenacetic acid ethyl ester (m. 64—65°C) is obtained analogously by dissolving the acetonitrile in ethanol instead of methanol. 20

4-(2-Chloro-6-methylanilino)-3-thiophenacetic acid methyl ester (m. 90—100°C) is obtained analogously from 4-(2-chloro-6-methylanilino)-3-thiophenacetonitrile by leaving this compound to stand in methanolic hydrochloric acid.

EXAMPLE 4

- 25 a) The nitriles listed in Examples 1—3 are obtained in the following way: 25

- 29.2 g (0.1 mole) of 3-(2,6-dichloroanilino)-4-chloromethylthiophen and 13 g (0.2 mole) of potassium cyanide are dissolved in 250 ml of dimethylformamide and 0.5 ml of water and the solution is warmed to 45°C for one hour. It is poured onto ice and extracted with acetic acid ethyl ester and the ethyl acetate phase is washed with water, dried over sodium sulphate and concentrated. 4-(2,6-Dichloroanilino)-3-thiophenacetonitrile remains as an oily residue which crystallizes out slowly (m. 82—83°C). 30

- 4-(2-Chloroanilino)-3-thiophenacetonitrile (oil), 4-(2-chloro-6-methylanilino)-3-thiophenacetonitrile (oil), 4-(2-chloro-3-methylanilino)-3-thiophenacetonitrile (oil), 4-(2,6-dichloro-3-methylanilino)-3-thiophenacetonitrile (oil), 4-(3-chloro-2-methylanilino)-3-thiophenacetonitrile (oil), 4-(2,6-difluoroanilino)-3-thiophenacetonitrile (oil), 4-(2-chloroanilino)-5-methyl-3-thiophenacetonitrile (oil) and 4-(2,6-dichloroanilino)-5-methyl-3-thiophenacetonitrile (m. 115°C) are obtained analogously by reacting 3-(2-chloroanilino)-4-chloromethylthiophen, 3-chloromethyl-4-(2-chloro-6-methylanilino)-thiophen, 3-chloromethyl-4-(2-chloro-3-methylanilino)-thiophen, 3-chloromethyl-4-(2,6-dichloro-3-methylanilino)-thiophen, 3-chloromethyl-4-(3-chloro-2-methylanilino)-thiophen, 3-chloromethyl-4-(2,6-difluoroanilino)-thiophen, 3-(2-chloroanilino)-4-chloromethyl-2-methylthiophen and 4-chloromethyl-3-(2,6-dichloroanilino)-2-methylthiophen, respectively, with potassium cyanide and appropriately working up the mixture. 40

Alternatively, the starting nitriles are obtained in the following manner:

- 2.72 g (10 mmoles) of 3-chloromethyl-4-(2-chloro-3-methylanilino)-thiophen in 15 ml of dimethylsulphoxide are added dropwise to a solution of 650 mg of sodium cyanide in 15 ml of dimethylsulphoxide at 40°C. The mixture is stirred for a further three hours, poured onto water and extracted three times with ethyl acetate. The combined extracts are washed with 50 ml each of 6 N hydrochloric acid and water, dried and concentrated. Crude 4-(2-chloro-3-methylanilino)-3-thiophenacetonitrile is obtained as an oil. 45

- 4-(2,6-Dimethylanilino)-3-thiophenacetonitrile, 4-(4-methoxy-2-methylanilino)-3-thiophenacetonitrile and 4-(3-trifluoromethylanilino)-3-thiophenacetonitrile are obtained analogously by reacting 3-chloromethyl-4-(2,6-dimethylanilino)-thiophen, 3-chloromethyl-4-(4-methoxy-2-methylanilino)-thiophen and 3-chloromethyl-4-(3-trifluoromethylanilino)-thiophen, respectively, with sodium cyanide. 50

- b) The chloromethyl compounds are obtained in the following way: 55

- 27.4 g (0.1 mole) of 4-(2,6-dichloroanilino)-3-thiophenmethanol are dissolved in 800 ml of concentrated aqueous hydrochloric acid and the solution is left to stand for eight hours, poured onto ice and extracted with toluene. The organic phase is washed with sodium bicarbonate solution, dried and concentrated. Recrystallisation of the residue from petroleum ether gives 3-(2,6-dichloroanilino)-4-chloromethylthiophen (m. 89—92°C). 60

3-(2-Chloroanilino)-4-chloromethyl-thiophen, 3-chloromethyl-4-(2,6-dimethylanilino)-thiophen (m. 149°C), 3-chloromethyl-4-(2-chloro-6-methylanilino)-thiophen, 3-chloromethyl-4-(4-methoxy-2-methylanilino)-thiophen, 3-chloromethyl-4-(2-chloro-3-methylanilino)-thiophen (m. 60—63°C), 3-

chloromethyl-4-(3-trifluoromethylanilino)-thiophen, 3-chloromethyl-4-(2,6-dichloro-3-methylanilino)-thiophen (m. 68—70°C), 3-chloromethyl-4-(3-chloro-2-methylanilino)-thiophen, 3-chloromethyl-4-(2,6-difluoroanilino)-thiophen, 3-(2-chloroanilino)-4-chloromethyl-2-methylthiophen (oil) and 4-chloromethyl-3-(2,6-dichloroanilino)-2-methylthiophen (m. 63—65°C) are obtained analogously by reacting 4-(2-chloroanilino)-3-thiophenmethanol, 4-(2,6-dimethylanilino)-3-thiophenmethanol, 4-(2-chloro-6-methylanilino)-3-thiophenmethanol, 4-(4-methoxy-2-methylanilino)-3-thiophenmethanol, 4-(2-chloro-3-methylanilino)-3-thiophenmethanol, 4-(3-trifluoromethylanilino)-3-thiophenmethanol, 4-(2,6-dichloro-3-methylanilino)-3-thiophenmethanol, 4-(3-chloro-2-methylanilino)-3-thiophenmethanol, 4-(2,6-difluoroanilino)-3-thiophenmethanol, 4-(2-chloroanilino)-5-methyl-3-thiophenmethanol and 4-(2,6-dichloroanilino)-5-methyl-3-thiophenmethanol, respectively, with aqueous hydrochloric acid.

c) The methanols are prepared in the following manner:

57.63 g (0.2 mole) of 4-(2,6-dichloroanilino)-3-thiophencarboxylic acid (dissolved in 350 ml of tetrahydrofuran) are added dropwise to a suspension of 7.59 g (0.2 mole) of lithium aluminium hydride in 170 ml of absolute tetrahydrofuran at 15°C in the course of one hour, whilst stirring and under nitrogen. Stirring is then continued at room temperature for one hour. The reaction mixture is hydrolysed with 2 litres of ice-cold water, acidified to pH 5 with dilute sulphuric acid and extracted with 1.5 litres of ethyl acetate. The extract is washed with 100 ml of 2 N sodium bicarbonate solution, dried over sodium sulphate and concentrated, 4-(2,6-dichloroanilino)-3-thiophenmethanol being obtained in almost quantitative yield as a viscous oil which slowly solidifies. Recrystallisation from cyclohexane gives pure 4-(2,6-dichloroanilino)-3-thiophenmethanol (m. 96—97°C).

4-(2-Chloroanilino)-3-thiophenmethanol (oil), 4-(2,6-dimethylanilino)-3-thiophenmethanol (m. 87°C), 4-(2-chloro-6-methylanilino)-3-thiophenmethanol (m. 93—95°C), 4-(4-methoxy-2-methylanilino)-3-thiophenmethanol, 4-(2-chloro-3-methylanilino)-3-thiophenmethanol and 4-(3-trifluoromethylanilino)-3-thiophenmethanol are obtained analogously by reducing 4-(2-chloroanilino)-3-thiophencarboxylic acid, 4-(2,6-dimethylanilino)-3-thiophencarboxylic acid, 4-(2-chloro-6-methylanilino)-3-thiophencarboxylic acid, 4-(4-methoxy-2-methylanilino)-3-thiophencarboxylic acid, 4-(2-chloro-3-methylanilino)-3-thiophencarboxylic acid, 4-(3-trifluoromethylanilino)-3-thiophencarboxylic acid, respectively, with lithium aluminium hydride.

4-(2,6-Dichloro-3-methylanilino)-3-thiophenmethanol (m. 121—122°C), 4-(3-chloro-2-methylanilino)-3-thiophenmethanol (oil), 4-(2,6-difluoroanilino)-3-thiophenmethanol (m. 124—126°C), 4-(2-chloroanilino)-5-methyl-3-thiophenmethanol (oil) and 4-(2,6-dichloroanilino)-5-methyl-3-thiophenmethanol (m. 64—65°C) are obtained analogously by reducing 4-(2,6-dichloro-3-methylanilino)-3-thiophencarboxylic acid methyl ester, 4-(3-chloro-2-methylanilino)-3-thiophencarboxylic acid methyl ester, 4-(2,6-difluoroanilino)-3-thiophencarboxylic acid methyl ester, 4-(2-chloroanilino)-5-methyl-3-thiophencarboxylic acid methyl ester and 4-(2,6-dichloroanilino)-5-methyl-3-thiophencarboxylic acid methyl ester, respectively, with lithium aluminium hydride.

d) The anilinothiophencarboxylic acids and anilinothiophencarboxylic acid esters are obtained in the following way:

15.9 g (0.1 mole) of 4-oxo-tetrahydro-3-thiophencarboxylic acid methyl ester, 17.5 g of 2,6-dichloroaniline and 200 mg of p-toluenesulphonic acid are heated in 500 ml of dichloroethane for six hours using a water separator. The solution is cooled to -25°C and 52.5 g of bromine in 100 ml of dichloroethane are added dropwise. The mixture is stirred for a further 5 minutes, 100 ml of 10% strength sodium sulphite solution are added and the organic phase is separated off, washed with water and a sodium carbonate solution, dried and concentrated. Pure 4-(2,6-dichloroanilino)-3-thiophencarboxylic acid methyl ester is obtained after a bulb tube distillation (bp. 140°/10⁻² Pascal).

4-(2,6-Dichloro-3-methylanilino)-3-thiophencarboxylic acid methyl ester, 4-(3-chloro-2-methylanilino)-3-thiophencarboxylic acid methyl ester (m. 80—82°C) and 4-(2,6-difluoroanilino)-3-thiophencarboxylic acid methyl ester (m. 90—92°C) are obtained analogously as products from 4-oxo-tetrahydro-3-thiophencarboxylic acid methyl ester and 2,6-dichloro-3-methylaniline, 3-chloro-2-methylaniline and 2,6-difluoroaniline, respectively.

4-(2-Chloroanilino)-5-methyl-3-thiophencarboxylic acid methyl ester (m. 64—65°C) and 4-(2,6-dichloroanilino)-5-methyl-3-thiophencarboxylic acid methyl ester (m. 86°C) are likewise obtained from 5-methyl-4-oxo-tetrahydro-3-thiophencarboxylic acid methyl ester and 2-chloroaniline and 2,6-dichloroaniline respectively.

Alternatively, 3-(2,6-dichloroanilino)-4-methyl-2-thiophencarboxylic acid methyl ester (m. 110—112°C) is obtained from 4-methyl-3-oxo-tetrahydro-2-thiophencarboxylic acid methyl ester and 2,6-dichloroaniline.

The procedure for the preparation of the anilinothiophencarboxylic acids can also be as follows:

15.9 g (0.1 mole) of 3-oxo-tetrahydro-2-thiophencarboxylic acid methyl ester, 14.2 g of 2-chloro-3-methylaniline and 200 mg of p-toluenesulphonic acid are heated in 500 ml of toluene for six hours using a water separator. 24.6 g (0.1 mole) of chloranil are then added and the mixture is boiled for a further one hour. It is cooled and filtered, the filtrate is washed with 100 ml each of 2 N sodium hydroxide solution, sodium dithionite solution and water and concentrated and the residue is purified by column chromatography (silica gel, toluene/ethyl acetate 4/1). 3-(2-Chloro-3-methylanilino)-2-thiophencarboxylic acid methyl ester is obtained as an oil.

The following compounds: 3-(2,6-dichloroanilino)-2-thiophencarboxylic acid methyl ester, 3-(2,4-dichloro-5-methylanilino)-2-thiophencarboxylic acid methyl ester and 3-(2-chloro-5-methylanilino)-2-thiophencarboxylic acid methyl ester are obtained analogously from 3-oxo-tetrahydro-2-thiophencarboxylic acid methyl ester and 2,6-dichloroaniline, 2,4-dichloro-5-methylaniline and 2-chloro-5-methylaniline respectively.

The saponification of the anilinothiophencarboxylic acid esters is carried out as follows:

3.16 g (0.1 mole) of 3-(2,6-dichloroanilino)-4-methyl-2-thiophencarboxylic acid methyl ester are boiled in 300 ml of methanol and 100 ml of 6 N potassium hydroxide solution for six hours. Methanol is then distilled off and the mixture is taken up in water and washed with toluene. The aqueous phase is acidified and extracted with ether. The organic phase is dried, clarified with bleaching earth (for example Tonsil®) and concentrated. Recrystallisation of the residue from toluene gives 3-(2,6-dichloroanilino)-4-methyl-2-thiophencarboxylic acid (m. 157—158°C).

4-(2-Chloroanilino)-3-thiophencarboxylic acid, 4-(2,6-dimethylanilino)-3-thiophencarboxylic acid, 4-(2-chloro-6-methylanilino)-3-thiophencarboxylic acid, 4-(4-methoxy-2-methylanilino)-3-thiophencarboxylic acid, 4-(2-chloro-3-methylanilino)-3-thiophencarboxylic acid and 4-(3-trifluoromethylanilino)-3-thiophencarboxylic acid are obtained analogously from 4-(2-chloroanilino)-3-thiophencarboxylic acid methyl ester, 4-(2,6-dimethylanilino)-3-thiophencarboxylic acid methyl ester, 4-(2-chloro-6-methylanilino)-3-thiophencarboxylic acid methyl ester, 4-(4-methoxy-2-methylanilino)-3-thiophencarboxylic acid methyl ester, 4-(2-chloro-3-methylanilino)-3-thiophencarboxylic acid methyl ester and 4-(3-trifluoromethylanilino)-3-thiophencarboxylic acid methyl ester, respectively, by saponification.

e) The oxo-tetrahydro-thiophencarboxylic acids are known or are prepared as follows:

100 g (1 mole) of methacrylic acid methyl ester are added dropwise to 106 g of thioglycolic acid methyl ester and 1 ml of piperidine. The reaction mixture is added dropwise to a solution of 40 g of sodium methylate in 200 ml of methanol. The mixture is stirred for a further half an hour, poured onto water, acidified and extracted with methylene chloride and the organic phase is washed with water and dried with sodium sulphate. After distillation, 4-methyl-3-oxo-tetrahydro-2-thiophencarboxylic acid methyl ester is obtained (bp. 110—115°C/14 Pascal).

5-Methyl-4-oxo-tetrahydro-3-thiophencarboxylic acid methyl ester (bp. 112°C/14 Pascal) is obtained analogously from acrylic acid methyl ester and thiolactic acid methyl ester.

EXAMPLE 5

0.32 g (1 mmole) of 3-(2-chloro-6-methylanilino)-2-thiophenglyoxylic acid ethyl ester and 1 g of sodium boranate are warmed to 80°C in 10 ml of dimethylformamide for 2 hours. The mixture is then poured onto water and washed with ether and the aqueous phase is acidified and extracted with ethyl acetate. Concentration of the organic phase and column chromatography (silica gel/methylene chloride) give, in the first fraction, 3-(2-chloro-6-methylanilino)-2-thiophenacetic acid ethyl ester.

3-(2,6-Dichloroanilino)-2-thiophenacetic acid ethyl ester is obtained analogously from 3-(2,6-dichloroanilino)-2-thiophenglyoxylic acid ethyl ester by reduction with sodium boranate.

EXAMPLE 6

3.16 g (10 mmoles) of 3-(2,6-dichloroanilino)-2-thiophenglyoxylic acid and 2 g of sodium boranate are warmed to 80°C in 10 ml of dimethylformamide for 4 hours. The mixture is poured onto water and extracted with toluene, the aqueous phase is acidified and extracted with ethyl acetate and the organic phase is dried and concentrated. Recrystallisation of the residue from toluene gives 3-(2,6-dichloroanilino)-2-thiophenacetic acid (m. 164—168°C).

3-(2-Chloro-6-methylanilino)-2-thiophenacetic acid (m. 147—149°C) and 3-(2,6-dichloroanilino)-4-methyl-2-thiophenacetic acid (m. 126—128°C) are obtained analogously from 3-(2-chloro-6-methylanilino)-2-thiophenglyoxylic acid and 3-(2,6-dichloroanilino)-4-methyl-2-thiophenglyoxylic acid by reduction with sodium boranate and appropriate working up.

The starting compounds are obtained in the following manner:

a) 3.44 g (10 mmoles) of 3-(2,6-dichloroanilino)-2-thiophenglyoxylic acid ethyl ester are dissolved in 10 ml of ethanol with 1 g of potassium hydroxide until a homogeneous solution has formed after 10 minutes. The solution is diluted with 50 ml of water, acidified and extracted with ethyl acetate and the organic phase is dried and concentrated. Recrystallisation from cyclohexane with a little toluene gives 3-(2,6-dichloroanilino)-2-thiophenglyoxylic acid.

3-(2-Chloro-6-methylanilino)-2-thiophenglyoxylic acid (m. 127—136°C) and 3-(2,6-dichloroanilino)-4-methyl-2-thiophenglyoxylic acid (m. 126—128°C) are obtained analogously from 3-(2-chloro-6-methylanilino)-2-thiophenglyoxylic acid ethyl ester and 3-(2,6-dichloroanilino)-4-methyl-2-thiophenglyoxylic acid ethyl ester by saponification with ethanolic potassium hydroxide solution.

b) 2.44 g (10 mmoles) of 3-(2,6-dichloroanilino)-thiophen, 1.01 g of triethylamine and 1.37 g (10 mmoles) of chlorooxalic acid ethyl ester are stirred in 20 ml of tetrahydrofuran at room temperature for 10 hours. 100 ml each of water and ethyl acetate are added and the organic phase is dried and concentrated. Recrystallisation of the residue from ethanol gives 3-(2,6-dichloroanilino)-2-thiophenglyoxylic acid ethyl ester.

3-(2-Chloro-6-methylanilino)-2-thiophenglyoxylic acid ethyl ester (m. 155—156°C) and 3-(2,6-dichloroanilino)-4-methyl-2-thiophenglyoxylic acid ethyl ester are obtained analogously from 3-(2-chloro-6-methylanilino)-thiophen and 3-(2,6-dichloroanilino)-4-methylthiophen and chlorooxalic acid ethyl ester.

5 c) 2.88 g (10 mmoles) of 4-(2,6-dichloroanilino)-3-thiophencarboxylic acid (see Example 4d) are decarboxylated at 16 Pascal and 150°C in a bulb tube distillation apparatus. Pure 3-(2,6-dichloroanilino)-thiophen is obtained as the distillate.

3-(2-Chloro-6-methylanilino)-thiophen and 3-(2,6-dichloroanilino)-4-methylthiophen are obtained analogously from 4-(2-chloro-6-methylanilino)-3-thiophencarboxylic acid and 3-(2,6-dichloroanilino)-4-methyl-2-thiophencarboxylic acid, respectively.

EXAMPLE 7

316.2 mg (1 mmole) of 4-(2,6-dichloroanilino)-3-thiophenacetic acid methyl ester are boiled in a solution of 11 ml of 2 N sodium hydroxide solution in 4.5 ml of water and 3 ml of methanol for one hour. The mixture is then diluted with 20 ml of water and extracted with 20 ml of methylene chloride and the aqueous phase is acidified. The precipitate which has formed is filtered off and washed with 5 ml of diisopropyl ether. 4-(2,6-Dichloroanilino)-3-thiophenacetic acid (m. 179—180°C) is obtained.

5-Chloro-4-(2-chloro-6-methylanilino)-3-thiophenacetic acid (m. 143—146°C) is obtained analogously from 5-chloro-4-(2-chloro-6-methylanilino)-3-thiophenacetic acid methyl ester by boiling with methanolic sodium hydroxide solution and appropriately working up the mixture.

EXAMPLE 8

330 mg (1 mmole) of 3-(2,6-dichloroanilino)-2-thiophen-acetic acid ethyl ester are boiled with 1 g of potassium hydroxide in 5 ml of ethanol for one hour. The mixture is then diluted with 20 ml of water and extracted with 20 ml of methylene chloride. The aqueous solution is acidified and the precipitate which has formed is filtered off and washed with 3 ml of diisopropyl ether. 3-(2,6-Dichloroanilino)-2-thiophenacetic acid (m. 164—168°C) is obtained.

3-(2-Chloro-6-methylanilino)-2-thiophenacetic acid (m. 147—149°C), 3-(2,6-dichloroanilino)-2-thiophenacetic acid (m. 164—168°C) and 5-chloro-4-(2-chloro-6-methylanilino)-3-thiophenacetic acid (m. 143—146°C) are obtained analogously from 3-(2-chloro-6-methylanilino)-2-thiophenacetic acid ethyl ester, 3-(2,6-dichloroanilino)-2-thiophenacetic acid methyl ester and 5-chloro-4-(2-chloro-6-methylanilino)-3-thiophenacetic acid methyl ester, respectively, by boiling with ethanolic potassium hydroxide solution and appropriately working up the mixture.

EXAMPLE 9

357 mg (1 mmole) of 4-(2,6-dichloroanilino)-3-thiophenacetic acid tert.-butyl ester are heated to the boil with 10 mg of p-toluenesulphonic acid in toluene for 2 hours. The reaction solution is washed with water, dried and concentrated to give 4-(2,6-dichloroanilino)-3-thiophenacetic acid (m. 179—180°C).

The starting compound is obtained in the following manner:

316 mg (1 mmole) of 4-(2,6-dichloroanilino)-3-thiophenacetic acid methyl ester are warmed to 60°C in 20 ml of tert.-butanol and 2 ml of concentrated sulphuric acid for 2 hours. The excess alcohol is distilled off. Chromatography on a column (silica gel/methylene chloride) gives, in the first fraction, 4-(2,6-dichloroanilino)-3-thiophenacetic acid tert.-butyl ester.

EXAMPLE 10

393 mg (1 mmole) of 4-(2,6-dichloroanilino)-3-thiophenacetic acid benzyl ester are subjected to hydrogenolysis in a mixture of 100 ml of ethyl acetate and 10 ml of glacial acetic acid in a circulatory hydrogenation apparatus in the presence of 50 mg of 10% strength palladium-on-active charcoal at room temperature and under atmospheric pressure until the theoretical amount of hydrogen has been taken up. The catalyst is filtered off, the filtrate is concentrated in vacuo and the residue is dissolved in 1 N sodium hydroxide solution. The aqueous solution is extracted with toluene and the product phase is acidified with 1 N hydrochloric acid and extracted again with toluene. The organic phase is dried and concentrated. 4-(2,6-Dichloroanilino)-3-thiophenacetic acid (m. 179—180°C) is obtained.

The starting compound is obtained in the following manner:

316 mg (1 mmole) of 4-(2,6-dichloroanilino)-3-thiophenacetic acid methyl ester are introduced into a solution of 10 mg of potassium benzyl alcoholate in 20 ml of benzyl alcohol. The mixture is stirred at room temperature for 2 hours, excess alcohol is distilled off in vacuo and 4-(2,6-dichloroanilino)-3-thiophenacetic acid benzyl ester is obtained as the residue.

EXAMPLE 11

30.1 g (0.1 mole) of 4-(2,6-dichloroanilino)-3-thiophenacetamide are warmed to 100°C in 135 ml of concentrated sulphuric acid and 49 ml of water for 3 hours. The mixture is poured onto ice and the precipitate of 4-(2,6-dichloroanilino)-3-thiophenacetic acid which has formed is filtered off. The precipitate is boiled up with diisopropyl ether and dried and then melts at 179—180°C.

The starting compound is obtained in the following manner:

28.3 g (0.1 mole) of 4-(2,6-dichloroanilino)-3-thiophenacetonitrile are introduced into 150 ml of concentrated sulphuric acid and stirred for one hour at room temperature. It is poured onto ice and the precipitate which has formed is filtered off. Recrystallisation from ethyl acetate gives 4-(2,6-dichloroanilino)-3-thiophenacetamide (m. 172—173°C).

EXAMPLE 12

A solution of 135 mg of sulphuryl chloride in 5 ml of methylene chloride is added dropwise to a solution of 283 mg (1 mmole) of 4-(2,6-dichloroanilino)-3-thiophenacetonitrile in 20 ml of methylene chloride at -15°C. After 10 minutes, a sodium dithionite solution and 3 ml of 2 N sodium hydroxide solution are added. The organic phase is separated off, dried, clarified with bleaching earth [for example "Tonsil" (Registered Trade Mark)] and concentrated. Recrystallisation of the residue from methanol gives 5-chloro-4-(2,6-dichloroanilino)-3-thiophenacetonitrile (m. 128—128.5°C).

5-Chloro-4-(2-chloro-6-methylanilino)-3-thiophenacetic acid methyl ester is obtained analogously from 4-(2-chloro-6-methylanilino)-3-thiophenacetic acid methyl ester by chlorination with sulphuryl chloride.

EXAMPLE 13

1.35 g (10 mmoles) of sulphuryl chloride in 20 ml of methylene chloride are added dropwise to a solution of 3.02 g (10 mmoles) of 4-(2,6-dichloroanilino)-3-thiophenacetic acid in 15 ml of methylene chloride at -15°C. After 10 minutes, 10 ml each of 2 N NaOH and 10% strength sodium dithionite solution are added. The aqueous phase is separated off, acidified and extracted with ethyl acetate and the product phase is dried and concentrated. Recrystallisation of the residue from cyclohexane gives pure 5-chloro-4-(2,6-dichloroanilino)-3-thiophenacetic acid (d. 141—142°C).

5-Chloro-4-(2-chloro-6-methylanilino)-3-thiophenacetic acid is obtained analogously from 4-(2-chloro-6-methylanilino)-3-thiophenacetic acid by chlorination with sulphuryl chloride.

EXAMPLE 14

2.84 g (10 mmoles) of N-(2,6-dichlorophenyl)-2,3-dihydro-2-oxo-thieno[3,4-b]pyrrole are boiled in 40 ml of methanol and 10 ml of 6 N KOH for half an hour. The mixture is diluted with 200 ml of water and extracted with toluene, the aqueous phase is acidified and the precipitate of 4-(2,6-dichloroanilino)-3-thiophenacetic acid which has formed is filtered off. The precipitate is boiled up with diisopropyl ether and dried and then melts at 179—181°C.

The starting compound is obtained in the following manner:

1 g (0.33 mmole) of 4-(2,6-dichloroanilino)-3-thiophenacetic acid and 0.7 g (0.33 mmole) of phosphorus pentachloride are stirred in 10 ml of toluene at room temperature for half an hour. The mixture is extracted with water and sodium bicarbonate solution, clarified with bleaching earth (for example Tonsil®) and concentrated. Recrystallisation of the residue from isopropanol gives N-(2,6-dichlorophenyl)-2,3-dihydro-2-oxo-thieno[3,4-b]pyrrole (m. 187—188°C).

EXAMPLE 15

2.83 g of 4-(2,6-dichloroanilino)-3-thiophenacetonitrile are introduced into 40 ml of diethylene glycol, which has been saturated with hydrochloric acid gas at 0°C. The mixture is stirred at room temperature for one hour and poured onto water, the aqueous phase is extracted with ethyl acetate and the product phase is washed several times with water, dried and concentrated. Recrystallisation of the residue from cyclohexane gives pure 4-(2,6-dichloroanilino)-3-thiophenacetic acid 2-(2-hydroxyethoxy)-ethyl ester (m. 58°C).

EXAMPLE 16.

5.28 g (17.5 mmoles) of 4-(2,6-dichloroanilino)-3-thiophenacetic acid are dissolved in 30 ml of chloroform together with 2.6 g (17.5 mmoles) of triethanolamine, and the solution is extracted by shaking with 20 ml of water. After evaporating off the water, the residue is taken up in ethanol and is crystallised in a crystallising dish by evaporation. Triethanolammonium 4-(2,6-dichloroanilino)-3-thiophenacetate is obtained.

Piperazinium bis-[4-(2,6-dichloroanilino)-3-thiophenacetate] is obtained analogously.

EXAMPLE 17

30.2 g (0.1 mole) of 4-(2,6-dichloroanilino)-3-thiophenacetic acid are dissolved in 100 ml of a 1 N sodium hydroxide solution under the influence of heat. The solution is allowed to cool and the sodium 4-(2,6-dichloroanilino)-3-thiophenacetate which has precipitated is filtered off (m. 247—250°C).

Sodium 3-(2,6-dichloroanilino)-2-thiophenacetate (m. 229—232°C) is obtained analogously.

EXAMPLE 18

10,000 tablets with an active compound content of 30 mg are prepared as described below:

300 g of 4-(2,6-dichloro-anilino)-3-thiophenacetic acid, 800 g of maize starch, 550 g of lactose,

- 30 g of amorphous silicic acid and 40 g of sodium lauryl-sulphate are mixed and the mixture is sieved. This mixture is moistened with a solution of 50 g of polyvinylpyrrolidone in 320 ml of ethanol and granulated through a sieve with a mesh width of 1.25 mm. The granules are dried at 40°C and mixed with 160 g of pectin, 50 g of talc and 20 g of magnesium stearate. This mixture is pressed to tablets weighing 200 mg with a diameter of 8 mm.

EXAMPLE 19

10,000 capsules with an active compound content of 25 mg are prepared as described below: 250 g of 4-(2,6-dichloroanilino)-3-thiophenacetic acid, 745 g of microcrystalline cellulose and 5 g of unpressed amorphous silicic acid are mixed thoroughly and filled into size 4 hard gelatine capsules.

10 EXAMPLES 20

Preparation of a batch of 1,000 suppositories.

2.450 kg of suppository base [Suppocire[®] BM] are heated to 40 to 45°C. 0.050 kg of 4-(2,6-dichloroanilino)-3-thiophenacetic acid (in the form of the sodium salt) is stirred into the melt.

The suppository mass is homogenised and then cast in moulds.

15 EXAMPLE 21

Preparation of a batch of 100 litres of a suspension.

- 2.70 kg of Tylose[®]C 30 are added to 90 l of water, whilst stirring vigorously; 1.00 kg of 4-(2,6-dichloroanilino)-3-thiophenacetic acid, 0.11 kg of sodium cyclamate and 0.08 kg of sorbic acid are then added. "Tylose" is a Registered Trade Mark. The mixture is made up to 100 l with water. It is passed through a corundum disc mill, subsequently degassed and then filled in 5 ml fractions. Cyclamates are subject to the Artificial Sweetener Regulations, 1969.

EXAMPLE 22

Preparation of 100 litres of an injection solution.

- 25 65 l of distilled water are heated to 80°C, whilst gassing with N₂, and 2.000 kg of 4-(2,6-dichloroanilino)-3-thiophenacetic acid (in the form of the sodium salt) and 0.150 kg of prednisolone are then added. When everything has dissolved, the solution is cooled to room temperature and 0.200 kg of sodium disulphite, 0.025 kg of cysteine hydrochloride and 26.00 kg of 1,2-propylene glycol are added and the mixture is made up to 100 l with distilled water and stirred until a solution is formed.

Pharmacology

- 30 The pronounced antiphlogistic, analgesic and antipyretic action of the compounds according to the invention can be demonstrated in various tests. As an example, the compounds according to the invention are investigated in comparison with the commercially available compound 2 and with the compound 1 described in *Arzneim.-Forsch. (Drug Res.)* 20(1970) 293—94. Table 1 which follows shows the connection between the serial No. and the name of the compound investigated.

TABLE 1

Serial No.	Name of compound
1	3-(2,6-dichloroanilino)-thiophen-4-carboxylic acid
2	indomethacin
3	4-(2,6-dichloroanilino)-3-thiophenacetic acid
4	4-(2-chloro-6-methylanilino)-3-thiophenacetic acid
5	4-(2,6-dichloro-3-methylanilino)-3-thiophenacetic acid
6	3-(2,6-dichloroanilino)-2-thiophenacetic acid
7	4-(2-chloro-3-methylanilino)-3-thiophenacetic acid
8	4-(3-chloro-2-methylanilino)-3-thiophenacetic acid
9	4-(2,4-diethylanilino)-3-thiophenacetic acid
10	5-chloro-4-(2,6-dichloroanilino)-3-thiophenacetic acid
11	3-(2-chloro-6-methylanilino)-2-thiophenacetic acid
12	4-(2,6-difluoroanilino)-3-thiophenacetic acid

Table 2 shows the acute antiphlogistic action, the toxicity and the therapeutic quotient of the compounds investigated.

TABLE 2

Antiphlogistic action of the compound according to the invention in an acute inflammation test — measured by the influence on carrageenin edema of the hind paw of rats — after single oral administration, and the lethal action in rats.

Compound	Dose mg/kg, perorally	Maximum inhibition of carrageenin edema within 7 hours after oral administration of the substance		Therapeutic quotient LD_{50}/ED_{50}	Lethal action after administration for 7 days (rats) LD_{50} mg/kg/day perorally
		%	ED_{50} * mg/kg perorally		
1	10.0	31	56	2.1	120
	100.0	57			
	1.0	29			
2	3.0	47	4.6	1.2	5.5
	10.0	56			
	0.3	29			
3	1.0	46	1.6	6.9	11
	3.0	56			
4	3.0	50	3	>>6.7	>>20
6	3.0	52	~3	>>6.7	>>20
8	3.0	49	~3	>>10	>>30
11	3.0	49	~3	>>6.7	>>20

*) ED_{50} = dose which causes a maximum edema inhibition of 50%.

The influence of the compounds to be tested on carrageenin edema of the hind paw of rats was determined as follows:

1 hour after oral administration of the compounds to be tested, female Sprague-Dawley rats (groups of 10 animals each; weight of each animal: 140—170 g), from which the feed [Altromin (Registered Trade Mark) R, water ad libitum] had been withdrawn about 16 hours beforehand, are injected subplantarily in the right hind paw with 0.05 ml, per animal, of a 1% strength carrageenin suspension. The rats are kept at 24°C.

The paw volume of each rat is determined (2—3 individual measurements in each case) before edema provocation and at hourly intervals for 7 hours after edema provocation. The average percentage paw swelling of each treated group determined at the specified times after the carrageenin injection is related to that of the untreated control group (=100%).

The maximum percentage edema inhibition serves as a measure of the antiphlogistic action.

The paw volume is determined plethysmometrically. Measuring principle: the volume of liquid displaced through the paw of the rat is recorded digitally via an electromechanical pressure transducer (Statham P 23 V, 0—200 mm Hg).

The doses indicated for the compounds tested were administered in a volume of liquid of 20 ml/kg.

Table 3 and Table 4 show the chronic antiphlogistic action, the toxicity and the therapeutic quotient of the compounds investigated.

TABLE 3

Antiphlogistic action of the compound according to the invention in a chronic inflammation test — measured by the influence on the formation of granulation tissue after subcutaneous implantation of cotton (so-called cotton pellet test) — and the lethal action in rats after oral administration for 7 days.

Compound	Dose 7 × mg/kg/day orally	Inhibition of the formation of granulation tissue after treatment for 7 days		Therapeutic quotient LD ₅₀ /ED ₂₀	Lethal action after oral administration for 7 days (rats) LD ₅₀ mg/kg/day
		%	ED ₂₀ * mg/kg/day perorally		
2	0.1	7	~3	~1.8	5.5
	0.3	11			
	1.0	16			
	3.0	16			
	4.0	17			
	5.0	(25% dead)			
3	0.1	6	~1	~11	11
	0.3	15			
	1.0	14			
	3.0	22			
	5.0	22			
	6.0	36 (0% dead)			
5	1.0	16	1.6	5	8
	3.0	26			
7	3.0	19	~3.5	>> 5.7	>>20
	10.0	27			
9	3.0	19	~3.0	>>10	>>30

*) ED₂₀ = dose which causes an average inhibition of the formation of granulation tissue of 20%.

Experimental procedure for investigating the influence of the compounds to be tested on the formation of granulation tissue after implantation of cotton in rats (so-called cotton pellet method):

1 cotton pellet (manufacturer: Messrs. Hartmann/Heidenheim; cotton pellets size 2, No. 4865/2) which weighs 13.0 ± 0.5 mg and has been impregnated beforehand with 0.1 ml of a solution of 0.5 mg of penicillin G and 0.8 mg of streptomycin sulphate/1 ml of distilled water is in each case implanted subcutaneously into the shoulder-blade region, on both sides, of male Sprague-Dawley rats (groups of 8 animals each; weight of each animal: 150—170 g) under diethyl ether anaesthesia and under sterile conditions. The cut skin is closed by means of clamps.

The compounds to be tested (in the form of the sodium salt in aqueous solution) or the corresponding amount (5 ml/kg/day) of tapwater (=control group) are administered orally each day on seven successive days. On the eighth day, the animals are killed and the cotton granules are exposed carefully, that is to say preserving the fibrous tissue capsule, dried (15 hours at 120°C) and weighed. By subtracting the weight of the cotton pellets, the amount of newly formed granulation tissue is obtained.

The percentage reduction in the average granuloma dry weight of a treated group compared with the control group (=100%) serves as a measure of the antiproliferative action of a compound.

TABLE 4

Antiarthritic action (so-called adjuvant arthritis; rats; ED_{25} ; oral administration for 5 days) and toxicity (LD_{50} in rats after oral administration for 7 days).

Substance; Serial No.	Inhibition of adjuvant arthritis of 25% (= ED_{25}) in rats after oral administration for 5 days		LD_{50} after administration for 7 days rats mg/kg/day orally
	ED_{25} mg/kg/day perorally	therapeutic quotient LD_{50}/ED_{25}	
1	9	13.3	120
2	0.18	30.6	5.5
3	0.20	55	11

The influence of the compounds to be tested on polyarthritis in rats caused by *Mycobacterium butyricum* (so-called "adjuvant arthritis") was determined using the experimental arrangement described below: based on the method described by NEWBOULD and PERRINE et al. [NEWBOULD, B. B.: Brit.J.Pharmacol. 21, 127 (1963); and PERRINE, J. W. and TAKESUE, E. I.; Arch. int.Pharmacodyn. 174, 192—198 (1968)], so-called adjuvant arthritis, which manifests itself chiefly in a severe swelling of the tail (primary lesion) and of the paws (secondary lesion), is caused in rats by intradermal injection of a *Mycobact. butyricum* suspension in liquid paraffin into the base of the tail. Antiphlogistic agents inhibit this swelling reaction.

10 Tables 5 and 6 show the analgesic (inflammation pain) and antipyretic (yeast-induced fever) action of the compounds tested, in addition to the lethal action and therapeutic quotient. 10

TABLE 5

Analgesic action of the compound according to the invention after single oral administration—measured by the influence on the pain reaction (vocalisation) provoked in rats by bending an inflamed ankle ($AgNO_3$ arthritis; inflammation (pain) — and the toxicity in rats after administration for 7 days.

Compound	Dose mg/kg perorally	Analgesic action		Therapeutic quotients		Lethal action after oral administration for 7 days (rats) LD ₅₀ mg/kg/day
		Inhibition of the pain reaction of %	ED ₂₅ *) ED ₅₀ *) mg/kg perorally	LD ₅₀ LD ₅₀ ED ₂₅ ED ₅₀		
1	3	10				
	20	20	30	140	4 0.86	120
	100	40				
	200	60				
2	1	23				
	3	36	1.2	6	4.58 0.92	5.5
	6	50				
	1	26				
3	3	50	1	3	11 3.67	11
	10	62				

*) ED_{25} and ED_{50} = dose which completely suppresses the pain reaction at the time of maximum action in 25 and 50% of the animals respectively.

The influence of the compounds to be tested on the pain reaction provoked in rats by bending an inflamed tarsal joint (AgNO_3 inflammation) was determined as follows:

Based on the method of HOFFMEISTER et al. [Arzneim. Forsch. 24, (1974) 600], 0.2 ml of a 1% strength silver nitrate solution is injected into the ankle joint (inside) of the right hand paw of female Sprague-Dawley rats (each animal weighing 160—180 g) under ether anaesthesia. The animals are kept at 24°C and are fed Altromin[®] R and water ad libitum. After the AgNO_3 injection, almost all the animals (90—95%) can be made to cry out by moderate bending of the ankle joint. All the animals reacting positively are collected into groups of 10 animals. The compounds to be tested are administered orally in a volume of liquid of 10 ml/kg immediately after administration of the AgNO_3 ; the untreated control animals receive the corresponding amount of tapwater.

Over a period of 4 hours after administration of the substance, the number of animals reacting is determined at half hourly intervals.

The maximum percentage of the protected animals over a period of 4 hours after administration of the substance [relative to the number of animals in the control group reacting (=100%)] serves as a measure of the analgesic action.

TABLE 6

Antipyretic action of the compounds according to the invention — measured by the influence of yeast-induced fever in rats — after single oral administration, and the lethal action.

Compound	Dose mg/kg perorally	Maximum reduction in yeast- induced fever over a period of 7 hours after administration of the substance of °C		Therapeutic quotient - LD ₅₀ /ED _{1.5}	Lethal action after administration for 7 days (rats) LD ₅₀ mg/kg/day
			ED _{1.5} *) mg/kg perorally		
1	1	0			
	3	0.6			
	10	1.7	8.2	14.6	120
	30	2.1			
2	1	0.2			
	3	0.7	5.0	1.1	5.5
	6	1.8			
	0.03	0.4			
3	0.1	0.8			
	0.3	1.4	0.4	27.5	11
	1.0	1.7			
4	0.3	1.4	~0.3	>>66.7	>>20
5	0.3	1.7	<0.3	>26.7	8
6	0.3	1.7	<0.3	>>66.7	>>20
	0.1	1.0			
9	0.3	1.5	0.3	>100	>30
	1.0	2.3			
10	0.3	1.2			
	0.6	1.6	0.5	>>40	>>20
12	0.3	0.5			
	1.0	1.6	0.9	>33	>30

*) ED_{1.5} = dose which causes a maximum reduction in yeast-induced fever of 1.5°C.

The antipyretic action is determined by the influence of the compounds to be tested on yeast-induced fever in rats.

Hyperthermia is produced in female Sprague-Dawley rats (in groups of 5 animals; weight of each animal: 160—180 g) by subcutaneous injection (neck) of 10 ml/kg of a 20% strength aqueous brewer's yeast suspension (brewer's yeast "Heliosan"/Hefereformwerk Radolfzell). 24 hours after the yeast injection, the compounds to be tested are administered orally to the animals in a volume of liquid of 5 ml/kg, and a control group receives the corresponding amount of tapwater. The feed (Altromin^R R, water ad libitum) was withdrawn from the rats 18 hours beforehand. The rats are kept at approximately 23°C.

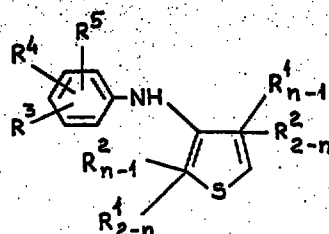
The body temperature is recorded 1 hour before administration of the substance and at hourly intervals after administration of the substance.

The maximum reduction in temperature (relative to the temperature before administration of the substance) in the course of 6 hours serves as a measure of the antipyretic action. The body temperature is measured with a temperature probe (Tastomed H, Braun electronic).

The superiority of the compounds according to the invention over those of the prior art is shown from the above data of Tables 2—6.

CLAIMS

1. Phenylaminothiophenacetic acids of the general formula



(II)

wherein

R¹ denotes a hydrogen atom, a chlorine atom, a bromine atom or a methyl group,

R² denotes a —CH₂—COOH group or a —CH₂—COOR⁶ group,

R³ denotes a hydrogen atom, a halogen atom, an alkyl group, an alkoxy group or a trifluoromethyl group,

R⁴ has one of the meanings of R³,

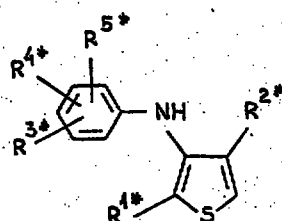
R⁵ denotes a hydrogen atom, a halogen atom or an alkyl group,

R⁶ denotes an alkyl group with 1 to 5 carbon atoms which is optionally substituted by hydroxyl, hydroxyalkoxy or alkanoyloxy groups, or a benzyl group and

n denotes 1 or 2

and salts of the acids.

2. Phenylaminothiophenacetic acids of the general formula I*



(I*)

wherein

R^{1*} denotes a hydrogen atom, a chlorine atom, a bromine atom or a methyl group,

R^{2*} denotes a —CH₂—COOH group or a —CH₂—COOR^{6*} group,

R^{3*} denotes a hydrogen atom, a chlorine atom, a methyl group or a trifluoromethyl group,

R^{4*} has one of the meanings of R^{3*},

R^{5*} denotes a hydrogen atom or a chlorine atom and

R^{6*} denotes an alkyl group with 1 to 4 carbon atoms which is optionally substituted by an acetoxy group or a 2-hydroxyethoxy group, or a benzyl group,

and salts of the acids.

3. Compounds according to Claim 2,

in which

R^{1*} denotes a hydrogen atom or a chlorine atom,

R^{2*} denotes a —CH₂—COOH group or a —CH₂—COOR^{6*} group,

R^{3*} denotes a chlorine atom, a methyl group or a trifluoromethyl group,

R^{4*} denotes a chlorine atom or a methyl group,

R^{5*} denotes a hydrogen atom or a chlorine atom and

R^{6*} denotes a 2-(2-hydroxyethoxy)-ethyl group,

and the pharmacologically tolerated salts of the acids.

4. Compounds according to Claim 2,

in which

R^{1*} denotes a hydrogen atom,

R^{2*} denotes a —CH₂—COOH group,

R^{3*} denotes a chlorine atom or a methyl group,

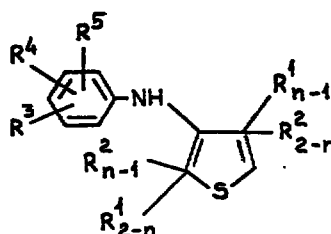
The body temperature is recorded 1 hour before administration of the substance and at hourly intervals after administration of the substance.

The maximum reduction in temperature (relative to the temperature before administration of the substance) in the course of 6 hours serves as a measure of the antipyretic action. The body temperature is measured with a temperature probe (Tastomed H, Braun electronic).

The superiority of the compounds according to the invention over those of the prior art is shown from the above data of Tables 2—6.

CLAIMS

1. Phenylaminothiophenacetic acids of the general formula



(II)

wherein

R¹ denotes a hydrogen atom, a chlorine atom, a bromine atom or a methyl group,

R² denotes a —CH₂—COOH group or a —CH₂—COOR⁶ group,

R³ denotes a hydrogen atom, a halogen atom, an alkyl group, an alkoxy group or a trifluoromethyl group,

R⁴ has one of the meanings of R³,

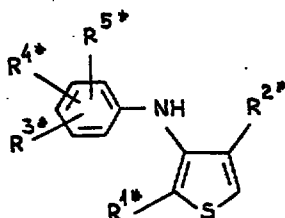
R⁵ denotes a hydrogen atom, a halogen atom or an alkyl group,

R⁶ denotes an alkyl group with 1 to 5 carbon atoms which is optionally substituted by hydroxyl, hydroxyalkoxy or alkanoyloxy groups, or a benzyl group and

n denotes 1 or 2

and salts of the acids.

2. Phenylaminothiophenacetic acids of the general formula I*



(I*)

wherein

R^{1*} denotes a hydrogen atom, a chlorine atom, a bromine atom or a methyl group,

R^{2*} denotes a —CH₂—COOH group or a —CH₂—COOR^{6*} group,

R^{3*} denotes a hydrogen atom, a chlorine atom, a methyl group or a trifluoromethyl group,

R^{4*} has one of the meanings of R^{3*},

R^{5*} denotes a hydrogen atom or a chlorine atom and

R^{6*} denotes an alkyl group with 1 to 4 carbon atoms which is optionally substituted by an acetoxyl group or a 2-hydroxyethoxy group, or a benzyl group,

and salts of the acids.

3. Compounds according to Claim 2,

in which

R^{1*} denotes a hydrogen atom or a chlorine atom,

R^{2*} denotes a —CH₂—COOH group or a —CH₂—COOR^{6*} group,

R^{3*} denotes a chlorine atom, a methyl group or a trifluoromethyl group,

R^{4*} denotes a chlorine atom or a methyl group,

R^{5*} denotes a hydrogen atom or a chlorine atom and

R^{6*} denotes a 2-(2-hydroxyethoxy)-ethyl group,

and the pharmacologically tolerated salts of the acids.

4. Compounds according to Claim 2,

in which

R^{1*} denotes a hydrogen atom,

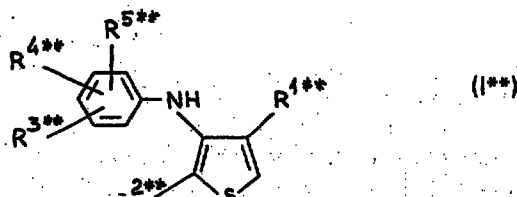
R^{2*} denotes a —CH₂—COOH group,

R^{3*} denotes a chlorine atom or a methyl group,



R^{4*} denotes a chlorine atom and
R^{5*} denotes a hydrogen atom,
and their pharmacologically tolerated salts.
5. Phenylaminothiophenacetic acids of the general formula I^{**}

5



5

wherein

- R^{1**} denotes a hydrogen atom or a methyl group,
R^{2**} denotes a —CH₂—COOH group or a —CH₂—COOR^{6**} group,
R^{3**} denotes a hydrogen atom, a chlorine atom, a methyl group or a trifluoromethyl group,
10 R^{4**} has one of the meanings of R^{3**},
R^{5**} denotes a hydrogen atom or a chlorine atom and
R^{6**} denotes an alkyl group with 1 to 4 carbon atoms which is optionally substituted by an
acetoxymethyl group or a 2-hydroxyethoxymethyl group, or a benzyl group,
and salts of the acids.

10

- 15 6. Compounds according to Claim 5,
in which

15

- R^{1**} denotes a hydrogen atom,
R^{2**} denotes a —CH₂—COOH group or a —CH₂—COOR^{6**} group,
R^{3**} denotes a chlorine atom, a methyl group or a trifluoromethyl group,
20 R^{4**} denotes a chlorine atom or a methyl group;
R^{5**} denotes a hydrogen atom or chlorine atom and
R^{6**} denotes a 2-(2-hydroxyethoxy)-ethyl group,
and the pharmaceutically tolerated salts of the acids.

20

- 25 7. Compounds according to Claim 5,
in which

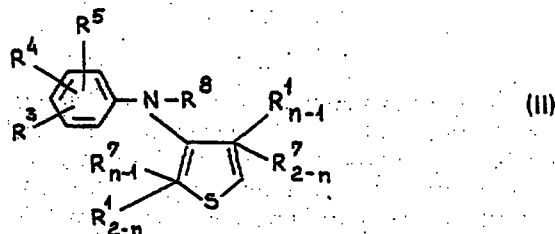
25

- R^{1**} denotes a hydrogen atom,
R^{2**} denotes a —CH₂—COOH group,
R^{3**} denotes a chlorine atom or a methyl group,
R^{4**} denotes a chlorine atom and
30 R^{5**} denotes a hydrogen atom,
and their pharmacologically tolerated salts.

30

8. 4-(2,6-Dichloro-anilino)-3-thiophenacetic acid and its pharmacologically tolerated salts.
9. Medicaments containing as active ingredient one or more compounds according to Claims 1 to
8.

- 35 10. Process for the preparation of phenylaminothiophenacetic acids of the general formula I
according to Claim 1 and salts of the acids, characterised in that functional carboxylic acid derivatives of
the general formula II



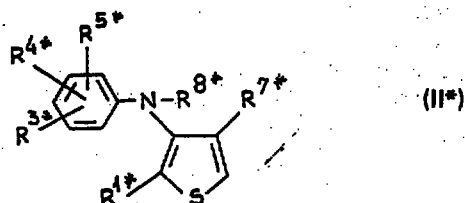
wherein

- 40 R¹, R³, R⁴, R⁵ and n have the meanings indicated above,
R⁷ represents a —CH₂—G group or, together with R⁸, a —CH₂—CO— group,
R⁸ represents a hydrogen atom or, together with R⁷, a —CO—CH₂— group and
G represents a functional derivative of a carboxylic acid group,
are hydrolysed and the resulting acids or esters of the general formula I are then optionally converted into
45 one another and/or into salts in the customary manner.

40

45

11. Process for the preparation of phenylaminothiophenacetic acids of the general formula I^{*}
according to Claim 2 and salts of the acids, characterised in that functional phenylaminothiophenacetic
acid derivatives of the general formula II^{*}



wherein

R1*, R3*, R4* and R5* have the meanings indicated above,

R7* represents a —CH₂—G* group or, together with R8*, a —CH₂—CO— group,

R8* represents a hydrogen atom, or together with R7*, a —CO—CH₂— group and

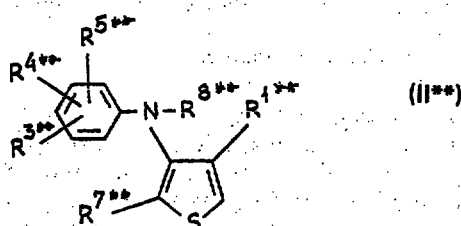
G* represents a functional derivative of a carboxylic acid group,

are hydrolysed and the resulting acids or esters of the general formula I* are then optionally halogenated and/or, in the customary manner, converted into one another and/or into salts.

12. Process for the preparation of phenylaminothiophenacetic acids of the general formula I**

according to Claim 5 and salts of the acids, characterised in that

a) functional phenylaminothiophenacetic acid derivatives of the general formula II**



wherein

R1**, R3**, R4** and R5** have the meanings indicated above,

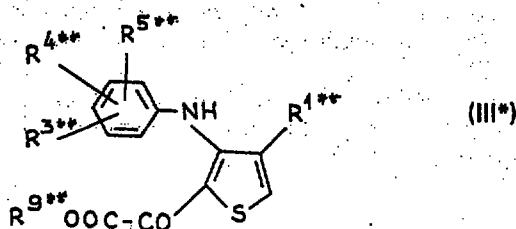
R7** represents a —CH₂—G** group or, together with R8**, a —CH₂—CO— group,

R8** represents a hydrogen atom, or together with R7**, a —CO—CH₂— group and

G** represents a functional derivative of a carboxylic acid group,

and hydrolysed and the resulting acids or esters of the general formula I** are then optionally converted into one another and/or into salts in the customary manner, or

b) a phenylaminothiophenacetic acid derivative of the general formula III**



wherein

R1**, R3**, R4** and R5** have the meanings indicated above and

R9** represents a hydrogen atom or an alkyl group with 1 to 5 carbon atoms,

or a salt thereof, is reduced and the resulting acids or esters of the general formula I** are then optionally converted into one another and/or into salts in the customary manner.

13. Pharmaceutical compositions containing from 1% to 95% by weight of the total mixture of at least one compound according to claims 1 to 8 in admixture with one or more solid or liquid pharmaceutically acceptable inert carriers.

14. A process for the preparation of phenylaminothiophenacetic acids of the general formula I according to claim 1 substantially as described with reference to the specific examples hereinbefore set forth.