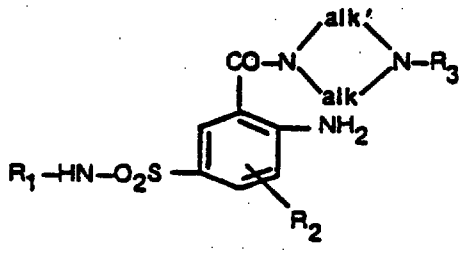
Substituted anthranilamides, processes for their preparation, pharmaceutical formulations containing these compounds and the preparation thereof

The invention relates to new substituted anthranilamides of the formula



(I),

wherein R_1 denotes hydrogen, lower alkyl having up to 4 C atoms, lower alkenyl having up to 4 C atoms, cycloalkyl having 5 to 8 ring members, bicycloalkyl or tricycloalkyl having in each case 5 or 6 ring members, cycloalkyl-lower alkyl having 5 to 8 ring members and up to 4 C atoms in the lower alkylene part or bicycloalkyl-lower alkyl or tricycloalkyl-lower alkyl having in each case 5 or 6 ring members and up to 4 C atoms in the lower alkylene part, R_2 denotes hydrogen, lower alkyl having up to 4 C atoms, lower alkoxy having up to 4 C atoms, halogen up to atomic number 35 or trifluoromethyl, alk and alk' represents (sic) identical or different lower alkylene which separates the nitrogen atoms by 2 C atoms and has up to 4 C atoms, and R_3 represents hydrogen, lower alkyl having up to 4 C atoms, lower alkenyl having up to 4 C atoms or a phenyl-lower alkyl, phenyl-lower alkenyl, pyridyl-lower alkyl or thienyl-lower alkyl radical which is optionally substituted in the phenyl or pyridyl or thienyl part, respectively, by lower alkyl having up to 4 C

atoms, lower alkoxy having up to 4 C atoms, halogen up to atomic number 35 and/or trifluoromethyl, and contains up to 4 C atoms in the lower alk(en)ylene part, and salts thereof, processes for their preparation, their use as medicaments and pharmaceutical formulations containing these compounds.

Examples of cycloalkyl radicals having 5 to 8 ring members are cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. Examples of bicycloalkyl radicals in which the individual rings each contain 5 or 6 ring members are 2-bornyl, 2-norbornyl, 2-bicyclo[2,2,2]-octyl, 2-bicyclo[4,4,0]decyl or 3-bicyclo[4,4,0]decyl. Examples of tricycloalkyl radicals in which the cycloalkyl radicals contain 5 or 6 ring members are 1-adamantyl or 2-adamantyl.

Examples of optionally susbstituted phenyl-lower alkyl radicals or phenyl-lower alkenyl radicals are those which are optionally substituted in the phenyl part by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl.

Examples of optionally substituted pyridyl-lower alkyl or thienyl-lower alkyl radicals are those which are optionally substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl.

In the preceding and following text, "lower" organic radicals and compounds are to be understood preferentially as those which contain up to and including 7, in particular up to and including 4, carbon atoms (C atoms).

Examples of lower alkyl are methyl, ethyl, propyl, isopropyl, n-butyl, sec.-butyl isobutyl or tert.-butyl and also pentyl, hexyl or heptyl.

Examples of lower alkoxy are methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec.-butoxy, isobutoxy or tert.-butoxy and also pentyloxy, hexyloxy or heptyloxy.

Examples of halogen are halogen up to and including atomic number 35, such as fluorine, chlorine or bromine.

Examples of lower alkylene which separates the nitrogen atoms in formula I by or 3 chain members (sic), are ethylene or 1,3-propylene and also 1,2-propylene, 1,3-butylene

or 2,3-butylene.

Examples of lower alkenyl are vinyl, allyl or methallyl.

Examples of phenyl-lower alkyl are benzyl, 1-phenylethyl, 2-phenylethyl, 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl, 1-phenylisopropyl, 2-phenylisopropyl, 3-phenylbutyl or 4-phenylbutyl.

An example of phenyl-lower alkenyl is 3-phenylpropen-2-yl.

Examples of pyridyl-lower alkyl are 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 1-(2-, 3- or 4-pyridyl)-ethyl, 2-(2-, 3- or 4-pyridyl)-ethyl, 3-(2-, 3- or 4-pyridyl)-propyl, 1-(2-, 3- or 4-pyridyl)-isopropyl, 2-(2-, 3- or 4-pyridyl)-isopropyl, 3-(2-, 3- or 4-pyridyl)-butyl or 4-(2-, 3- or 4-pyridyl)-butyl.

Examples of thienyl-lower alkyl are 2-thienylmethyl, 3-thienylmethyl, 1-(2- or 3-thienyl)-ethyl, 2-(2- or 3-thienyl)-ethyl, 1-(2- or 3-thienyl)-propyl, 2-(2- or 3-thienyl)-propyl, 3-(2- or 3-thienyl)-propyl, 1-(2- or 3-thienyl)-isopropyl, 2-(2- or 3-thienyl)-isopropyl, 3-(2- or 3-thienyl)-butyl or 4-(2- or 3-thienyl)-butyl.

The compounds of the formula I have valuable pharmacological properties. In particular, they possess a pronounced antinociceptive (analgesic) action which can be demonstrated, for example, by means of the acetic acid writhing syndrome on mice in a dosage range of about 100 to 300 mg/kg administered orally and on rats in a dosage range of about 10 to about 100 mg/kg administered orally. They also display a marked anti-inflammatory action which can be demonstrated, for example, on rats by means of turpentine pleurisy in a dosage range of about 10 to about 300 mg/kg administered orally. They also display a pronounced anti-allergic action which is demonstrated, for example, on rats by means of a passive, cutaneous anaphylaxis in a dosage range of about 3 to about 30 mg/kg administered orally. The compounds of the formula I can, accordingly, be used as

analgesics, anti-inflammatory agents and/or anti-allergic agents.

The new compounds display a markedly superior pharmacological, for example anti-inflammatory, action, compared with the compounds described in the state of the art (German Auslegeschrift 1,445,629 and German Offenlegungsschrift 2,431,609).

The invention relates particularly to compounds of the formula I wherein R_1 denotes hydrogen, lower alkyl having up to 4 C atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl or secondary butyl, lower alkenyl having up to 4 C atoms, such as allyl, cycloalkyl having 5 to 8 ring members, such as cyclopentyl, cyclohexyl or cycloheptyl, bicycloalkyl or tricycloalkyl having in each case 5 or 6 ring members, such as 2-bornyl, 2-norbornyl, 2-bicyclo-[2,2,2]octyl, 1-adamantyl or 2-adamantyl, cycloalkyl-lower alkyl having 5 to 8 ring members and up to 4 C atoms in the lower alkylene part, such as cyclopentylmethyl, cyclohexylmethyl or cycloheptylmethyl, or bicycloalkyl-lower alkyl or tricycloalkyl-lower alkyl having in each case 5 or 6 ring members and having up to 4 C atoms in the lower alkylene part, such as 2-bornylmethyl, 2-norbornylmethyl or 2-bicyclo[2,2,2]octylmethyl, R_2 denotes hydrogen, lower alkyl having up to 4 C atoms, such as methyl, lower alkoxy having up to 4 C atoms, such as methoxy, halogen up to atomic number 35, such as chlorine, or trifluoromethyl, alk and alk' represents (sic) identical or different lower alkylene which separates the nitrogen atoms by 2 C atoms and has up to 4 C atoms, such as ethylene, 1,2-propylene or 2,3-butylene, and R_3 represents hydrogen, lower alkyl having up to 4 C atoms, such as methyl, lower alkenyl having up to 4 C atoms, such as allyl, or a phenyl-lower alkyl radical, such as benzyl, 2-phenylethyl or 3-phenylpropyl radical, phenyl-lower alkenyl radical, such as 3-phenylpropen-2-yl radical, pyridyl-lower alkyl radical, such as 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)-ethyl or 3-(2-, 3- or 4-

pyridyl)-propyl radical, or thienyl-lower alkyl radical, such as 2-thienylmethyl, 3-thienylmethyl, 2-(2- or 3-thienyl)-ethyl or 3-(2- or 3-thienyl)-propyl radical, each of which is optionally substituted in the phenyl or pyridyl or thienyl part, respectively, by lower alkyl having up to 4 C atoms, such as methyl, lower alkoxy having up to 4 C atoms, such as methoxy, halogen up to atomic number 35, such as chlorine, and/or trifluoromethyl, and contains up to 4 C atoms in the lower alk(en)ylene part, and salts thereof.

The invention relates above all to compounds of the formula I wherein R_1 denotes hydrogen, lower alkyl having up to 4 C atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl or secondary butyl, cycloalkyl having 5 to 8 ring members, such as cyclopentyl, cyclohexyl or cycloheptyl, or tricycloalkyl having in each case 5 or 6 ring members, such as 1-adamantyl or 2-adamantyl, R_2 denotes hydrogen, lower alkyl having up to 4 C atoms, such as methyl, lower alkoxy having up to 4 C atoms, such as methoxy, halogen up to atomic number 35, such as chlorine, or trifluoromethyl, alk and alk' represents (sic) identical lower alkylene which separates the nitrogen atoms by 2 C atoms and has up to 4 C atoms, such as ethylene, 1,2-propylene or 2,3-butylene, and R_3 represents hydrogen, lower alkyl having up to 4 C atoms, such as methyl, or a phenyl-lower alkyl radical, such as benzyl, 2-phenylethyl or 3-phenylpropyl radical, which is optionally substituted in the phenyl part by lower alkyl having up to 4 C atoms, such as methyl, lower alkoxy having up to 4 C atoms, such as methoxy, halogen up to atomic number 35, such as chlorine, and/ or trifluoromethyl, and contains up to 4 C atoms in the lower alkylene part, and salts thereof.

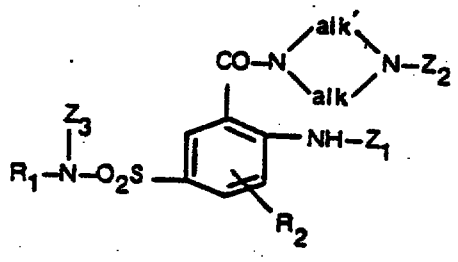
The invention relates first and foremost to compounds of the formula I wherein R_1 denotes lower alkyl having up to 4 C atoms, such as methyl, ethyl, propyl, isopropyl, butyl, secondary butyl or isobutyl, R_2 is hydrogen, alk and alk' denote ethylene and R_3 denotes hydrogen,

lower alkyl having up to 4 C atoms, such as methyl, or a phenyl-lower alkyl radical, such as benzyl or 2-phenylethyl radical, which is optionally substituted in the phenyl part by lower alkyl having up to 4 C atoms, such as methyl, lower alkoxy having up to 4 C atoms, such as methoxy, and/or halogen, and contains up to 10 C atoms, and salts thereof.

The invention relates in particular to the compounds of the formula I mentioned in the examples, and salts thereof.

The compounds of the formula I can be prepared by methods which are in themselves known.

A preferred procedure is characterized in that, in a compound of the formula



(II)

wherein at least one of the radicals Z_1, Z_2 and Z_3 .... (sic) a radical Z which can be replaced by hydrogen and a radical Z_1, Z_2 and/or Z_3 which is optionally different from Z represents hydrogen or, in the case of a radical Z_2, represents a group R_3 which is different from hydrogen, the radical Z is replaced by hydrogen and, if desired, the compound thus obtainable is converted into another compound of the formula I and/or a resulting free compound is converted into a salt, or a resulting salt is converted into the free compound or into another salt.

Examples of radicals Z which can be replaced by hydrogen are radicals which can be replaced by hydrogen by reduction or solvolysis.

Examples of radicals which can be replaced by hydrogen by reduction are optionally substituted benzyloxycarbonyl radicals, for example benzyloxycarbonyl or

p-nitrobenzyloxycarbonyl, or 2-halogeno-lower alkoxycarbonyl radicals, for example 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl or 2,2,2-trichloro-tert.-butoxycarbonyl. Further radicals Z_1 which can be replaced by hydrogen are hydroxyl or amino which is optionally substituted by an aromatic radical, such as optionally substituted phenyl, for example anilino, and further radicals Z_1 or Z_3 which can be replaced are α-aralkyl radicals, for example benzyl.

The reductive replacement by hydrogen of the radicals mentioned is carried out in a customary manner, for example by treatment with hydrogen in the presence of a hydrogenation catalyst, such as a nickel, platinum, rhodium, ruthenium or palladium catalyst, for example Raney nickel, platinum or platinum oxide, optionally on charcoal, a complex of rhodium chloride or ruthenium chloride and a phosphene, such as triphenylphosphine or triethylphosphine, or palladium-on-charcoal, or, if starting from compounds of the formula II wherein Z_1 is hydroxyl, in the presence of a copper catalyst, for example copper-I oxide. It is advantageous to carry out the reaction in an inert solvent, such as a lower alkanol, for example in methanol or ethanol, or a lower alkanoic acid, such as acetic acid, if necessary under elevated pressure, at elevated temperature and/or in a closed vessel. Z_1 which is 2-halogeno-lower alkoxycarbonyl and/or hydroxyl can also be replaced by hydrogen by reaction with a base metal, such as zinc, in acetic acid, or with a transition metal compound of lower valency, such as cobalt-II chloride, and Z_1 as hydroxyl groups can also be replaced by hydrogen by reaction with a suitable di-light metal hydride, for example lithium borohydride or sulfurised sodium borohydride.

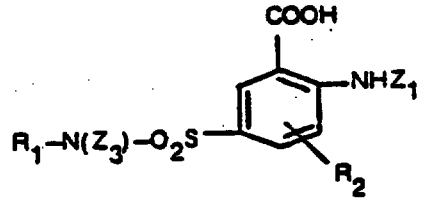
Examples of radicals Z which can be replaced by hydrogen by solvolysis are acyl radicals, such as acyl radicals derived from optionally halogenated lower alkanoic acids or optionally substituted benzoic acid, for example formyl, acetyl, trifluoroacetyl or benzoyl, acyl radicals

derived from monofunctional derivatives of carbonic acid, such as lower alkoxycarbonyl radicals which are optionally substituted by halogen, lower alkanesulfonyl or lower alkylthio, optionally substituted benzenesulfonyl or phenylthio, or silyl radicals, for example ethoxycarbonyl, 2-iodoethoxycarbonyl or 2,2,2-trichloro-tert.-butoxycarbonyl, 2-lower alkanesulfonylethoxycarbonyl, 2-lower alkyl-thioethoxycarbonyl or 2-trimethylsilylethoxycarbonyl, optionally substituted 2-(benzenesulfonyl)-ethoxycarbonyl or 2-(phenylthio)-ethoxycarbonyl, for example 2-(p-toluenesulfonyl)-ethoxycarbonyl or 2-(p-methylphenylthio)-ethoxycarbonyl, optionally substituted benzyloxycarbonyl radicals, for example benzyloxycarbonyl or p-nitrobenzyloxycarbonyl, cycloalkoxycarbonyl radicals, for example isobornyloxycarbonyl, or halogenocarbonyl, for example chlorocarbonyl, and also cyano or silyl radicals, such as trimethylsilyl. Further radicals Z_1 which can be replaced by hydrogen by solvolysis are hydrocarbon radicals which are optionally further substituted and are substituted by hydroxyl in the α-position, such as α-hydroxy-lower alkyl, for example 1-hydroxyethyl or 2-(2-hydroxy)-propyl, α-hydroxycycloalkyl radicals, such as 1-hydroxycyclohexyl, or optionally substituted α-(hydroxy)-α-phenyl-lower alkyl radicals, such as α-(hydroxy)-α-benzyl radicals.

The solvolytic replacement by hydrogen of the solvolysable groups Z mentioned is carried out in a customary manner, for example by hydrolysis, if necessary in the presence of an acid or basic hydrolytic agent and/or a solvent, preferably a water-miscible solvent, such as a lower alkanol, for example ethanol, a di-lower alkyl ketone, for example acetone, or a lower alkanoic acid amide, for example dimethylformamide, and/or at elevated temperature. Examples of acid hydrolytic agents are proton acids, such as mineral acids, for example hydrochloric acid, sulfuric acid or phosphoric aicd, or organic carboxylic acids, such as optionally halogenated lower alkanoic acids, for example formic acid,

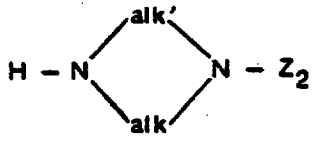
acetic acid, chloroacetic acid or trichloroacetic acid. Examples of basic hydrolytic agents are alkali metal hydroxides or alkaline earth metal hydroxides, such as sodium hydroxide, potassium hydroxide or calcium hydroxide, alkali metal carbonates, such as sodium carbonate or potassium carbonate, ammonia or organic nitrogen bases, such as tribenzylmethylammonium hydroxide. Tertiary lower alkoxycarbonyl groups, such as tert.-butoxycarbonyl, can also be replaced by hydrogen by solvolysis under anhydrous conditions by reaction with a suitable carboxylic acid, such as trifluoroacetic acid, or, in the case of silyl groups and 2-silylethoxycarbonyl groups, by reaction with a salt of hydrofluoric acid, for example with potassium fluoride in acetonitrile.

The starting materials of the formula II can be prepared by methods which are in themselves known, for example by reacting an acid of the formula



(IIa)

or a reactive functional derivative thereof with an amine of the formula

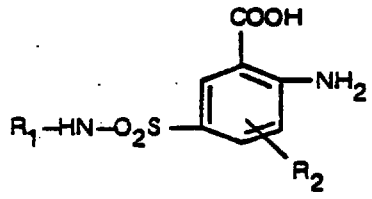


(IIb)

or a reactive derivative or salt thereof, for example a 5-(R_1-sulfamoyl)-N-Z_1-anthranilic acid with the N-chlorocarbonyl derivative or an N-lower alkanoic, such as N-methanoic, or N-benzenesulfenic acid derivative of a compound of the formula IIb, or a 5-(R_1-sulfamoyl)-isatic anhydride with a compound of the formula IIb in which Z_2 denotes a radical Z. The reaction is carried out in a customary manner, in particular as indicated below for the reaction of compounds of the formulae III and IV or their reactive derivatives.

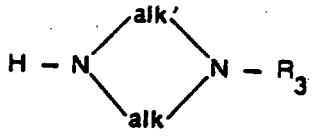
Starting materials of the formula II wherein Z_1 denotes hydroxyl as a radical which can be replaced by hydrogen by reduction, are advantageously prepared in situ by reduction from the corresponding 5-(R_1-sulfamoyl)-2-nitrobenzamides or their salts, under the conditions of the reduction. These compounds in turn are accessible by reacting corresponding 5-(chlorosulfonyl)-2-nitrobenzoic acids with a compound of the formula R_1-NH_2, if appropriate converting the 5-(R_1-sulfamoyl)-2-nitrobenzoic acid thus obtainable into a reactive derivative, for example into the acid chloride by means of thionyl chloride, and a subsequent customary condensation reaction with the amine of the formula IIb or a reactive derivative or salt thereof. Analogously, compounds of the formula II in which Z denotes a hydrocarbon radical which is substituted by hydroxyl in the α-position, are advantageously prepared in situ by acid hydrolysis of of the corresponding 5-(R_1-sulfamoyl)-anthranilamides which are substituted on the anilino N atom by a divalent hydrocarbon radical which is optionally substituted. These anthranilamides are obtained, for example, by reacting the corresponding 5-chlorosulfonyl-2-chlorobenzoic acids with an amine R_1-NH_2, then subjecting the product to aminolysis, subjecting the 5-(R_1-sulfamoyl)-anthranilic acid of the latter, thus obtainable, to a condensation reaction with α-oxo-hydrocarbons, for example benzaldehyde or acetaldehyde, converting the product into the chloride and reacting the 5-(R_1-sulfamoyl)-anthraniloyl chloride which is substituted on the anilino N atom and which is thus obtainable, for example 5-(R_1-sulfamoyl)-2-benzylideneaminobenzoyl chloride, with a compound of the formula IIb.

The compounds of the formula I can also be prepared by reacting an acid of the formula



(III)

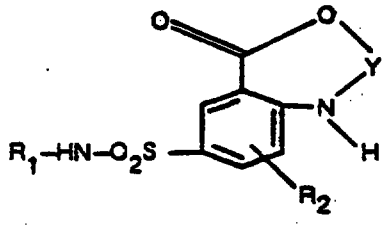
or a reactive functional derivative thereof with an amine of the formula



(IV)

or a reactive derivative or salt thereof and, if desired, converting the compound thus obtainable into another compound of the formula I and/or converting a resulting free compound into a salt, or a resulting salt into the free compound or into another salt.

Examples of reactive functional derivatives of acids of the formula III are reactive esters, such as optionally substituted phenyl esters, for example phenyl, p-nitrophenyl or 2,4-dinitrophenyl esters, reactive amides, such as 1-imidazolides, or anhydrides thereof, such as open-chain anhydrides with a mineral acid, for example acid chlorides, anhydrides with phosphinous or phosphorous acids, for example with diphenylphosphinous acid, or with carbonic acid half-esters or acid phosphorous acid esters, such as carbonic acid monophenyl esters or carbonic acid monoethyl esters or phosphorous acid diethyl esters, or cyclic anhydrides thereof, such as compounds of the formula



(IIIa),

wherein Y represents a carbonyl, thiocarbonyl or sulfinyl group or a group of the formulae >P-R, >P(=O)-R or >P(=O)(R_2) in which R denotes an organic radical, such as lower alkyl, for example methyl or denotes optionally substituted phenyl.

Examples of reactive derivatives of compounds of the formula IV are acyl derivatives of the latter derived from

half-esters of carbonic acid or halogenoformic acid, such as lower alkoxycarbonyl or halogenocarbonyl derivatives, for example chlorocarbonyl derivatives, or sulfenylamides thereof with organic sulfenic acids, such as lower alkanesulfenic acids, or optionally substituted benzenesulfenic acids, for example with methanesulfenic acid or benzenesulfenic acid.

The reaction of compounds of the formulae III and IV or of reactive derivatives thereof is carried out in the manner which is customary for the particular case.

The reaction of acids of the formula III with amines of the formula IV or salts thereof is advantageously carried out in the presence of a water-binding agent, preferably phosphorus pentoxide or an ester of pyrophosphorous acid, for example tetraethyl pyrophosphite, or by removing the water of reaction by distillation, preferably azeotropic distillation, if necessary in an inert solvent, such as toluene, and/or at elevated temperature, for example at about 50 to 200°C.

The reaction of reactive esters or amides or anhydrides of acids of the formula III with amines of the formula IV or salts thereof is advantageously carried out in a solvent which is inert towards the reactants, for example in toluene, xylene, tetrahydrofuran or dioxane, if necessary in the presence of a basic condensation agent, such as a tertiary organic nitrogen base, such as triethylamine or pyridine, and/or at reduced or elevated temperature, for example in the temperature range from about 0° to about 150°.

The reaction of acids of the formula III with acyl derivatives of amines of the formula IV is preferably carried out with the application of heat, for example at about 100 to 250°C, if necessary in a solvent which is inert towards the reactants, such as xylene, while the reaction with sulfenylamides derived from amines of the formula IV is preferably carried out at normal temperature,

for example at about 0 to 50°C, preferably in an inert solvent, such as an N,N-di-lower alkylamide, for example dimethylformamide, or N-methylpyrrolidone, in pyridine, in an ether, for example diethyl ether, dioxane or tetrahydrofuran, or in benzene, toluene or xylene.

The starting materials of the formula III and IV can be prepared in a manner which is in itself known.

Acids of the formula III are obtained, for example, by reacting a corresponding 5-chlorosulfonyl-2-chlorobenzoic acid with an amine R_1-NH_2 and subjecting the resulting 5-(R_1-sulfamoyl)-2-chlorobenzoic acid to ammonolysis in a customary manner.

Reactive esters of acids of the formula III are obtained, for example, by esterification in a customary manner, such as reaction with the corresponding alcohol in the presence of a mineral acid, such as sulfuric acid or hydrochloric acid.

Reactive amides of acids of the formula III can be obtained, for example, by reacting the acid in a customary manner with a corresponding urea, such as bis-(1-imidazolyl)-urea, with a dihalide, diester or ester-halide of carbonic acid, such as a halogenoformic acid lower alkyl ester, with an ester or halide of a phosphinous acid of the formula $(R)_2$ P-OH, such as a benzenephosphinous acid lower alkyl ester, for example benzenephosphinous acid ethyl ester, or benzenephosphinous acid chloride, a diester, ester-halide or dihalide of a phosphonous acid of the formula R-P$(OH)_2$, for example benzenephosphonous acid dichloride, or a diester, ester-halide or halide of a phosphonic acid of the formula R-P(=O)$(OH)_2$, for example with benzenephosphonic acid dichloride. Isatic acid dichlorides of the formula III wherein Y is carbonyl are advantageously prepared by reacting 5-chlorosulfonylisatic acid in a customary manner with an amine of the formula R_1-NH_2.

Open-chain anhydrides of acids of the formula III are advantageously formed <u>in situ</u> under the conditions of

the reaction, by reacting the corresponding acid, for example, with a halogenating agent, such as thionyl chloride, or with an ester or halide of a phosphinous acid or an ester, ester-halide or dihalide of a phosphonous acid or phosphonic acid, for example with benzenephosphinous acid chloride, benzenephosphinous acid ethyl ester or the dichloride, ethyl ester-chloride or diethyl ester of benzenephosphonous acid or of benzenephosphonic acid.

Reactive derivatives of amines of the formula IV are also advantageously produced in situ under the conditions of the reaction by reacting the amine with a halogenoformic acid ester or, in the presence of a trivalent phosphorus compound, for example triphenylphosphine, with an organic disulfide, for example a di-lower alkyl disulfide.

Compounds which can be obtained in accordance with the invention can be converted into other compounds of the formula I.

Thus it is possible to introduce a radical R_3 which is different from hydrogen into compounds of the formula I in which R_3 denotes hydrogen. The radical R_3 is introduced in a customary manner, for example by reaction with a reactive ester of an aliphatic alcohol or an optionally substituted araliphatic or hetero-aryl aliphatic alcohol, such as an ester thereof with an organic sulfonic acid, such as benzenesulfonic, p-bromobenzenesulfonic, toluenesulfonic or methanesulfonic acid, or with an inorganic sulfonic acid, such as hydrochloric, hydrobromic or hydriodic acid or sulfuric acid.

The reaction is preferably carried out in the presence of an acid-binding agent, such as a tertiary organic base, for example ethyldiisopropylamine, pyridine or quinoline, or an inorganic base, such as an alkali metal hydroxide or alkaline earth metal hydroxide or an alkali metal carbonate, for example sodium hydroxide, potassium hydroxide or calcium hydroxide or potassium carbonate or sodium carbonate. The reactions described are preferably carried out in an inert organic solvent, such as an alkanol, for example

in ethanol or methanol, or a hydrocarbon, for example in benzene, toluene or xylene, an ether, such as diethyl ether, tetrahydrofuran or dioxane, or a chlorinated or nitrated hydrocarbon, for example in methylene chloride, carbon tetrachloride, nitrobenzene or nitromethane.

The introduction of a radical R_3 can, however, also be carried out by reaction with a corresponding oxo compound, for example with a corresponding aldehyde or ketone, under reducing conditions, for example in the presence of hydrogen and in the presence of a hydrogenation catalyst, such as a palladium, platinum or nickel catalyst, for example palladium on charcoal or on calcium carbonate, platinum oxide or Raney nickel, under normal or preferably increased pressure, or in the presence of an organic reducing agent, such as formic acid, or formaldehyde, if appropriate in aqueous solution, in which case it is preferable to carry out the reaction at elevated temperature or in the presence of a light metal hydride, for example di-isoamyl borohydride, or a di-light metal hydride, such as sodium cyanoborohydride or sodium borohydride, in each case advantageously in a solvent which is inert under the reaction conditions.

Conversely, it is possible to replace R_3 by hydrogen in compounds of the formula I wherein R_3 is different from hydrogen, for example by reaction with a halogenoformic acid ester, such as a chloroformic or bromoformic acid lower alkyl ester, or a cyanogen halide, such as cyanogen bromide or cyanogen chloride, with the formation of the corresponding urethane or cyanamide and subsequent hydrolysis of the latter. α-Aralkyl radicals and α-hetero-arylalkyl radicals R_3 can also be replaced by hydrogen in the presence of a hydrogenation catalyst, such as by reduction, for example by treatment with palladium-on-charcoal

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alkyl ester, or a cynaogen halide, such as cyanogen bromide or cyanogen chloride, with the formation of the corresponding urethane or cyanamide and subsequent hydrolysis of the latter. α-Aralkyl radicals and α-hetero-arylalkyl radicals R_3 can also be replaced by hydrogen by reduction, for example by treatment with hydrogen in the presence of a hydrogenation catalyst, such as palladium-on-charcoal.

It is also possible to introduce radicals R_2 which are different from hydrogen into compounds of the formula I in which R_2 denotes hydrogen. Thus halogen can be introduced in a customary manner, for example by reaction with chlorine or bromine, preferably in the presence of a catalyst, such as iron-III chloride, or with N-chlorosuccinimide. It is also possible to introduce trifluoromethyl in a customary manner, for example by reaction with trifluoroiodomethane in the presence of metals, such as copper powder. In addition, lower alkyl can be introduced in a customary manner, for example by reaction with a lower alkyl halide, advantageously in the presence of a catalyst, such as a metal halide, for example aluminium chloride or bromide.

The reactions mentioned can, if desired, be carried out simultaneously or successively and in any desired sequence.

The reactions mentioned are carried out in a customary manner in the presence or absence of diluents, condensation agents and/or catalytic agents, at a reduced, ordinary or elevated temperature, and, if appropriate, in a closed vessel.

Depending on the process conditions and the starting materials, the end products are obtained in the free form or in the form, which is also included in the invention, of their acid addition salts.

The latter are, in particular, pharmaceutically usable acid addition salts, such as appropriate mineral acid salts, for example hydrochlorides, hydrobromides or hydriodides, sulfates, bisulfates or phosphates, or appropriate

carboxylic acid salts, such as fumarates, maleates, maleates (sic), citrates, anthranilates, p-hydroxybenzoates, pyruvates or salicylates, and also appropriate sulfonic acid salts, such as cyclohexylaminesulfonates, sulfanilates or p-toluenesulfonates. Thus it is possible, for example, to obtain basic, neutral or mixed salts and, if appropriate, also hemihydrates, monohydrates, sesquihydrates or polyhydrates thereof. The acid addition salts of the new compounds can be converted into the free compound in a manner which is in itself known, for example by means of basic agents, such as alkalis or ion exchangers. On the other hand, the resulting free bases can form salts with organic or inorganic acids.

The salts of the new compounds, such as, for example, the picrates, can also be used to purify the resulting free bases, by converting the free bases into salts, isolating the latter and liberating the bases again from the salts. Because of the close relationships between the new compounds in the free form and in the form of their salts, in the preceding and following text the free compounds are, if appropriate, also to be understood in terms of general sense and intended use as the corresponding salts.

The invention also relates to those embodiments of the process in which a compound which can be obtained as intermediate products at any desired stage of the process, is used as the starting material and the missing process stages are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative thereof, if appropriate in the form of a salt.

In the process of the present invention it is preferable to use those starting materials which lead to the compounds described initially as particularly valuable.

The pharmaceutical formulations according to the invention which contain compounds of the formula I or pharmaceutically usable salts thereof are preparations for enteral

and oral or rectal administration and for parenteral administration and also for topical application to warm-blooded animal(s), and they contain the pharmacological active compound on its own or together with a pharmaceutically usable excipient. The dosage of the active compound depends on the species of the warm-blooded animal, its age and its individual condition and also on the mode of administration. In the normal case an approximate daily dose of about 15-300 mg, advantageously distributed between several equal divided doses, can be estimated for oral administration to a warm-blooded animal weighing about 75 kg.

The new pharmaceutical formulations contain, for example, from 10% to 80%, preferably from 20% to 60%, of the active compound. Pharmaceutical formulations according to the invention for enteral or parenteral administration are, for example, preparations in unit dosage forms, such as dragees, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is in itself known, for example by means of conventional mixing, granulating, dragee-making, dissolving or lyophilizing processes. Thus it is possible to obtain pharmaceutical formulations for oral administration by combining the active compound with solid excipients, if appropriate granulating a resulting mixture, and processing the mixture or the granules to give tablets or dragee cores, if desired or if necessary, after adding suitable auxiliaries.

Suitable excipients are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose formulations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes, using, for example, maize starch, wheat starch, rice starch or potato starch, gelatine, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrating agents, such as the abovementioned starches, and also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar or alginic

acid or a salt thereof, such as sodium alginate. Auxiliaries are primarily flow-regulating agents and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings, if appropriate coatings resistant to gastric juices, using, inter alia, concentrated sugar solutions which optionally contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or solvent mixtures or, for the preparation of coatings resistant to gastric juices, solutions of suitable cellulose preparaations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyestuffs or pigments can be added to the tablets or dragee coatings, for example in order to identify or characterize different doses of active compound.

Further pharmaceutical formulations which can be administered orally are push-fit capsules made of gelating and also soft, closed capsules made of gelatine and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active compound in the form of granules, for example mixed with fillers, such as lactose, binders, such as starches, and/or slip agents, such as talc or magnesium stearate, and, if appropriate, stabilizers. In soft capsules the active compound is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, and stabilizers can also be added.

Examples of suitable pharmaceutical formulations which can be administered rectally are suppositories which consist of a combination of the active compound with a suppository base composition. Examples of suitable suppository base compositions are natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Moreover, it is also possible to use gelatine rectal capsules which contain a combination of the active

compound with a base composition; examples of suitable base composition materials are liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Aqueous solutions of an active compound in a water-soluble form, for example in the form of a water-soluble salt, and also suspensions of the active compound, such as appropriate oil injection suspensions in which suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, are used, or aqueous injection suspensions which contain substances which increase the viscosity, for example sodium carboxymethylcellulose, sorbitol and/or dextran and optionally also stabilizers, are primarily suitable for parenteral administration.

Suitable pharmaceutical formulations which can be applied topically are primarily creams, ointments, pastes, foams, tinctures and solutions, which contain from 0.5 to 20% of the active compound.

The present invention also relates to the use of the compounds of formula I and of the salts of those compounds which have salt-forming properties, preferably for the treatment of inflammations, primarily inflammatory chronic diseases of the rheumatic variety, especially chronic arthritis.

The examples which follow illustrate the invention described above; they are not, however, intended to limit the scope of this invention in any way. Temperatures are quoted in degrees centrigrade.

Example 1

2.7 g of 1-methylpiperazine are added slowly at 100°, while stirring, to a suspension of 10.2 g of 5-[N-(1-adamantyl)-sulfamoyl]-isatic anhydride in 250 ml of absolute toluene. After the addition is complete, stirring is continued for 1 hour at 100°, the mixture is allowed to cool to room temperature, the precipitate is removed by decantation and the crude product thus obtained is recrystallized from ethanol. This gives 5-[N-(1-adamantyl)-

sulfamoyl]-anthranilic acid 4-methylpiperazide with a melting point of 214-215° (melting point of the hydrochloride: 298-300°).

The starting material can be obtained, for example, as follows:

30.5 g of 2-chloro-5-chlorosulfonylbenzoic acid are added in portions at room temperature, while stirring, to 165 ml of water and 36.1 g of 1-aminoadamantane, stirring is continued for 1 hour and the mixture is acidified with concentrated hydrochloric acid to pH 1 and is filtered. This gives 5-[N-(1-adamantyl)-sulfamoyl]-2-chlorobenzoic acid with a melting point of 207-210°.

350 ml of 25% strength aqueous ammonia solution and 1 g of copper powder are added to 16.9 g of this compound and the mixture is warmed at 125-130° for 12 hours in an autoclave. The mixture is then cooled to room temperature, filtered through silica gel, acidified with concentrated hydrochloric acid to pH 5 and allowed to stand overnight at 0° and the crystals which have been formed are filtered off. This gives 5-[N-(1-adamantyl)-sulfamoyl]-anthranilic acid with a melting point 168-171° (decomposition).

A suspension of 14.2 g of the above compound in 140 ml of acetic acid is warmed to 70° for 10 minutes, while stirring. It is then cooled to room temperature and phosgene is passed in until saturation is reached. In the course thereof the customary safety precautions should be taken. The mixture is then warmed at 100° for 20 minutes. It is then cooled to room temperature, a little water is added, the precipitate which is immediately deposited is filtered off and washed successively with water and diethyl ether and the crystalline product is dried in vacuo at 100°. This gives 5-[N-(1-adamantyl)-sulfamoyl]-isatic anhydride with a melting point of 164° (decomposition).

Example 2

5-[N-(2-Butyl)-sulfamoyl]-anthranilic acid 4-methylpiperazide with a melting point of 130-132° (from an

ethanol/diethyl ether mixture is obtained in a manner analogous to that described in Example 1 by reacting 5-[N-(2-butyl)-sulfamoyl]-isatic anhydride with 1-methylpiperazine. The hydrochloride melts at 246-248°.

The 5-[N-(2-butyl)-sulfamoyl]-isatic anhydride to be used as the starting material can, for example, be obtained in a manner analogous to that described in Example 1, starting from 2-chloro-5-chlorosulfonylbenzoic acid via 5-[N-(2-butyl)-sulfamoyl]-2-chlorobenzoic acid with a melting point of 118-123° and 5-[N-(2-butyl)-sulfamoyl]-anthranilic acid with a melting point of 187-188°. It melts at 228-229°.

Example 3

5-(N-Cyclohexylsulfamoyl)-anthranilic acid 4-methylpiperazide with a melting point of 167-168° (from ethanol) is obtained in a manner analogous to that described in Example 1 by reacting 5-(N-cyclohexylsulfamoyl)-isatic anhydride with 1-methylpiperazine. The hydrochloride melts at 263-264°.

The 5-(N-cyclohexylsulfamoyl)-isatic anhydride to be used as the starting material can, for example, be obtained in a manner analogous to that described in Example 1, starting from 2-chloro-5-chlorosulfonylbenzoic acid via 2-chloro-5-(N-cyclohexylsulfamoyl)-benzoic acid with a melting point of 168-175° and 5-(N-cyclohexylsulfamoyl)-anthranilic acid with a melting point of 204-206°. It melts at 232-233°.

Example 4

5-[N-(2-Methylpropyl)-sulfamoyl]-anthranilic acid 4-methylpiperazide with a melting point of 162-163° (from ethanol; melting point of the hydrochloride: 254-255°) is obtained in a manner analogous to that described in Example 1 by reacting 5-[N-(2-methylpropyl)-sulfamoyl]-isatic anhydride with 1-methylpiperazine.

The 5-[N-(2-methylpropyl)-sulfamoyl]-isatic anhydride to be used as the starting material can, for example,

be obtained in a manner analogous to that described in Example 1, starting from 2-chloro-5-chlorosulfonylbenzoic acid via 2-chloro-5-[N-(2-methylpropyl)-sulfamoyl]-benzoic acid with a melting point of 163-166° and 5-[N-(2-methylpropyl)-sulfamoyl]-anthranilic acid with a melting point of 203-205°; it melts at 270-273°.

Example 5

5-(N-Isopropylsulfamoyl)-anthranilic acid 4-methylpiperazide with a melting point of 118-122° (from methylene dichloride/diethyl ether; melting point of the methane-sulfonate: 232-234°) is obtained in a manner analogous to that described in Example 1 by reacting 5-(N-isopropylsulfamoyl)-isatic anhydride with 1-methylpiperazine. The 5-(N-isopropylsulfamoyl)-isatic anhydride to be used as the starting material can, for example, be obtained in a manner analogous to that described in Example 1, starting from 2-chloro-5-chlorosulfonylbenzoic acid via 2-chloro-5-(N-isopropylsulfamoyl)-benzoic acid with a melting point of 170-173° and 5-(N-isopropylsulfamoyl)-anthranilic acid with a melting point of 230-232°; it melts at 235-237°.

Example 6

5-(N-Methylsulfamoyl)-anthranilic acid 4-methylpiperazide is obtained in the form of an oil (melting point of the methanesulfonate: 120-123°) in a manner analogous to that described in Example 1 by reacting 5-(N-methylsulfamoyl)-isatic anhydride with 1-methylpiperazine.

The 5-(N-methylsulfamoyl)-isatic anhydride to be used as the starting material can, for example, be obtained in a manner analogous to that described in Example 1, starting from 2-chloro-5-chlorosulfonylbenzoic acid via 2-chloro-5-(N-methylsuflamoyl)-benzoic acid with a melting point of 170-172° and 5-(N-methylsulfamoyl)-anthranilic acid with a melting point of 205°; it melts at 260°.

Example 7

5-(N-ethylsulfamoyl)-anthranilic acid 4-methylpiperazide with a melting point of 175-177° (from acetone/

ethanol) is obtained in a manner analogous to that described in Example 1 by reacting 5-(N-ethylsulfamoyl)-isatic anhydride with 1-methylpiperazine.

The 5-(N-ehtylsulfamoyl)-isatic anhydride to be used as the starting material can, for example, be obtained in a manner analogous to that described in Example 1, starting from 2-chloro-5-chlorosulfonylbenzoic acid via 5-(N-ethylsulfamoyl)-2-chlorobenzoic acid with a melting point of 186-190° and 5-(N-ethylsulfamoyl)-anthranilic acid with a melting point of 190-192°; it melts at 253-255°.

Example 8

99 g of 5-methylsulfamoylisatic anhydride are suspended in 1,100 ml of dioxane, the mixture is warmed to 90° and 81 g of N-[2-(p-chlorophenyl)-ethyl]-piperazine, dissolved in 1,100 ml of dioxane, are added dropwise in the course of 180 minutes. The mixture is warmed at 90° until the gas evolution is complete, is allowed to cool and is filtered and evaporated. The residue from evaporation is dissolved in acetone and is filtered through about 1,300 g of silica gel (0.06-0.2 mm). After first runnings of 600 ml the eluates are combined, evaporated and dried. 5-(N-Methylsulfamoyl)-anthranilic acid 4-[2-(p-chlorophenyl)-ethyl]-piperazide is obtained. This can be converted into its fumarate with a melting point of 224-226° by dissolving it in 2,000 ml of methanol, adding a solution of 25.5 g of fumaric acid in 1,000 ml of methanol, concentrating the mixture, cooling and filtering off the product.

The starting material can, for example, be prepared in the following way:

392 g of phosphorus pentoxide are added to 3,000 g of chlorosulfonic acid in the course of about 10 minutes and 835 g of isatic anhydride are then added in the course of about 60 minutes, the internal temperature being kept at 40 to 60°. The mixture is stirred for a further 120 minutes at 60°, cooled to room temperature and poured cautiously onto about 20,000 g of ice, the mixture is stirred

for a further 30 minutes and the product is filtered off with suction, rinsed five times with 1 litre of water each time and sucked dry. The 5-chlorosulfonylisatic anhydride which can be obtained in this way can be processed further without further purification.

210 g of 5-chlorosulfonylisatic anhydride are suspended in 780 ml of acetone. 50 g of methylamine are passed into the suspension in the course of about 50 minutes, the internal temperature being kept at 0 to 5° by vigorous cooling. The mixture is stirred for a further 3 hours at 0 to 5°, the bulk of the acetone is stripped off under reduced pressure, 1,500 ml of water are added while stirring and cooling and the product is filtered off with suction, washed with water, suspended in 500 ml of ethanol, filtered off again with suction and dried under reduced pressure. This gives 5-methylsulfamoylisatic anhydride with a melting point of 233-234°. Recrystallization from tetrahydrofuran raises the melting point to 246-247°.

Example 9

The fumarate of 5-(N-methylsulfamoyl)-anthranilic acid 4-benzylpiperazide with a melting point of 220° (decomposition) is obtained in a manner analogous to that described in Example 8 by reacting 18.3 g of 5-methyl-sulfamoylisatic anhydride with 12.5 g of 1-benzylpiperazine and chromatographing the product on silica gel with chloroform/acetone (95:5-9:1) and reacting the 5-(N-methyl-sulfamoyl)-anthranilic acid 4-benzylpiperazide which can be obtained in this way with 5.5 g of fumaric acid.

Example 10

9.2 g of 5-(N-methylsulfamoyl)-anthranilic acid 4-bensylpiperazide are dissolved in 100 ml of ethanol, the mixture is acidified with 21.6 ml of ethanolic hydrochloric acid, 1 g of palladium (5% strength on charcoal) is added and hydrogenation is carried out at room temperature and normal pressure. After filtering off the catalyst and evaporating the mixture, the hydrochloride of 5-(N-methylsulfamoyl)-anthranilic acid piperazide is obtained (melting

point 169°).

Example 11

Tablets containing 25 mg of active compound, for example 1-[5-methylsulfamoyl)-anthraniloyl]-4-[2-(p-chlorophenyl)-ethyl]-piperazine or a salt thereof, can be prepared in the following way:

Ingredients (for 1,000 tablets)

Active compound	25.0 g
Lactose	100.7 g
Wheat starch	7.5 g
Polyethylene glycol 6000	5.0 g
Talc	5.0 g
Magnesium stearate	1.8 g
Demineralized water	q.s.

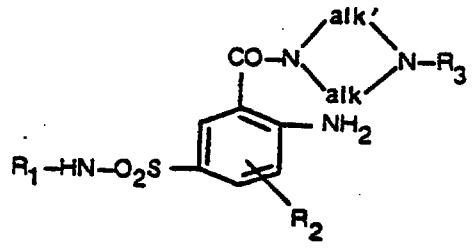
Preparation

All the solid ingredients are first forced through a sieve with a mesh width of 0.6 mm. The active compound, the lactose, the talc, the magnesium stearate and half the starch are then mixed. The other half of the starch is suspended in 40 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 ml of water, and processed with the powder mixture to give a kneadable mass, and the resulting mixture is granulated, if necessary with the addition of water. The granules are dried overnight at 35°, forced through a sieve with a mesh width of 1.2 mm and compressed for form tablets concave on both sides with a diameter of about 6 mm.

Tablets containing in each case 25 mg of another of the compounds of the formula I mentioned in Examples 1 to 10 can also be prepared in an analogous manner.

Patent claims for the contracting states:

1. Substituted anthranilamides of the formula



(I),

wherein R_1 denotes hydrogen, lower alkyl having up to 4 C atoms, lower alkenyl having up to 4 C atoms, cycloalkyl having 5 to 8 ring members, bicycloalkyl or tricycloalkyl having in each case 5 or 6 ring members, cycloalkyl-lower alkyl having 5 to 8 ring members and up to 4 C atoms in the lower alkylene part or bicycloalkyl-lower alkyl or tricycloalkyl-lower alkyl having in each case 5 or 6 ring members and up to 4 C atoms in the lower alkylene part, R_2 denotes hydrogen, lower alkyl having up to 4 C atoms, lower alkoxy having up to 4 C atoms, halogen up to atomic number 35 or trifluoromethyl, alk and alk' represents (sic) identical or different lower alkylene which separates the nitrogen atoms by 2 C atoms and has up to 4 C atoms, and R_3 represents hydrogen, lower alkyl having up to 4 C atoms, lower alkenyl having up to 4 C atoms or a phenyl-lower alkyl, phenyl-lower alkenyl, pyridyl-lower alkyl or thienyl-lower alkyl radical which is optionally substituted in the phenyl or pyridyl or thienyl part, respectively, by lower alkyl having up to 4 C atoms, lower alkoxy having up to 4 C atoms, halogen up to atomic number 35 and/or trifluoromethyl, and contains up to 4 C atoms in the lower alk(en)ylene part, and salts thereof.

2. Compounds according to claim 1, wherein R_1 denotes lower alkyl having up to 4 C atoms, R_2 is hydrogen, alk and alk' denote ethylene and R_3 denotes hydrogen, lower alkyl having up to 4 C atoms or a phenyl-lower alkyl radical which is optionally substituted in the phenyl part by lower alkyl having up to 4 C atoms and/or halogen and contains up to 10 C atoms, and salts thereof.

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3. 5-(N-Methylsulfamoyl)-anthranilic acid 4-methyl-piperazide or a salt thereof.

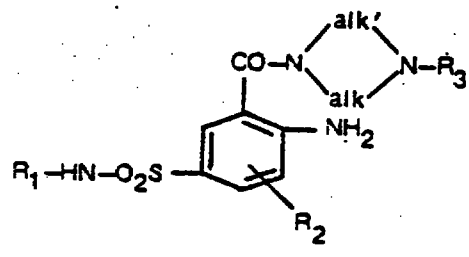
4. 5-(N-Methylsulfamoyl)-anthranilic acid 4-[2-(p-chlorophenyl)-ethyl]-piperazide or a salt thereof.

5. 5-(N-Methylsulfamoyl)-anthranilic acid 4-benzyl-piperazide or a salt thereof.

6. 5-(N-Methylsulfamoyl)-anthranilic acid piperazide or a salt thereof.

7. Pharmaceutical formulations containing a compound according to one of claims 1-6 together with customary pharmaceutical auxiliaries and/or excipients.

8. Process for the preparation of substituted anthranilamides of the formula

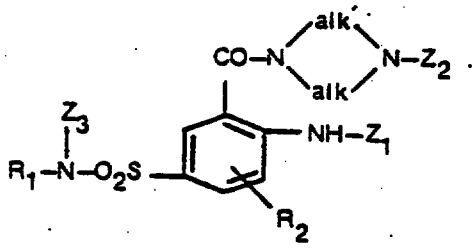


(I),

wherein R_1 denotes hydrogen, lower alkyl having up to 4 C atoms, lower alkenyl having up to 4 C atoms, cycloalkyl having 5 to 8 ring members, bicycloalkyl or tricycloalkyl having in each case 5 or 6 ring members, cycloalkyl-lower alkyl having 5 to 8 ring members and up to 4 C atoms in the lower alkylene part or bicycloalkyl-lower alkyl or tricycloalkyl-lower alkyl having in each case 5 or 6 ring members and up to 4 C atoms in the lower alkylene part, R_2 denotes hydrogen, lower alkyl having up to 4 C atoms, lower alkoxy having up to 4 C atoms, halogen up to atomic number 35 or trifluoromethyl, alk and alk' represents (sic) identical or different lower alkylene which separates the nitrogen atoms by 2 C atoms and has up to 4 C atoms, and R_3 represents hydrogen, lower alkyl having up to 4 C atoms, lower alkenyl having up to 4 C atoms or a phenyl-lower alkyl, phenyl-lower alkenyl, pyridyl-lower alkyl or thienyl-lower alkyl radical which is optionally substituted in the phenyl

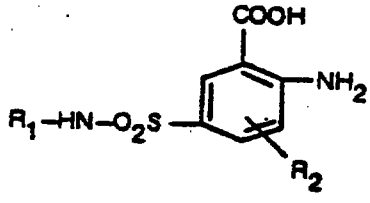
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or pyridyl or thienyl part, respectively, by lower alkyl having up to 4 C atoms, lower alkoxy having up to 4 C atoms, halogen up to atomic number 35 and/or trifluoromethyl, and salts thereof, characterized in that, in a compound of the formula



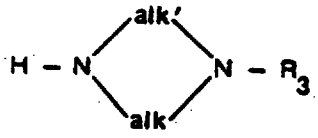
(II)

wherein at least one of the radicals Z_1, Z_2 and Z_3 ... (sic) a radical Z which can be replaced by hydrogen and a radical Z_1, Z_2 and/or Z_3 which is optionally different from Z represents hydrogen or, in the case of a radical Z_2, represents a group R_3 which is different from hydrogen, the radical Z is replaced by hydrogen, or an acid of the formula



(III)

or a reactive functional derivative is reacted with an amine of the formula



(IV)

or a reactive derivative or salt thereof and, if desired, the compound thus obtainable is converted into another compound of the formula I and/or a resulting free compound is converted into a salt, or a resulting salt is converted into the free compound or into another salt.

* C L M S *

9. Compounds of the formula I according to one of claims 1-6 having an analgesic, anti-inflammatory and/or anti-allergic action.

10. The use of compounds of the formula I according to one of claims 1-6 for the preparation of medicaments.

11. The use of compounds of the formula I according to one of claims 1-6 for the preparation of analgesics, anti-inflammatory agents and/or anti-allergic agents.

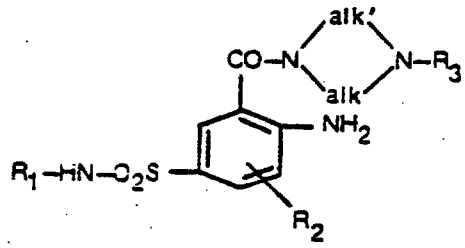
12. Compounds of the formula I according to one of claims 1-6 and 9 for use in a process for the therapeutic treatment of the human species or a warm-blooded animal species.

13. The compounds obtainable by the process according to claim 8.

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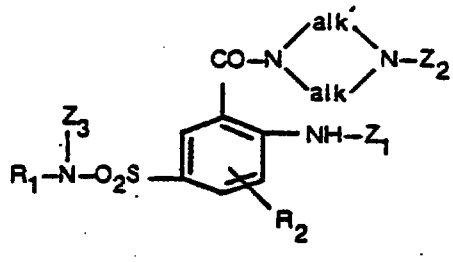
Patentansprüche für den Vertragsstaat: AT (as printed)

1. Verfahren zur Herstellung substituierter Anthranilsäureamide der Formel



(I),

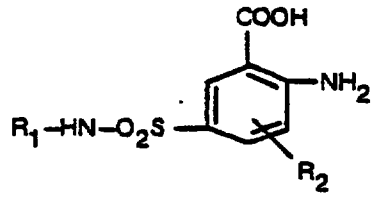
worin R_1 Wasserstoff, Niederalkyl mit bis zu 4 C-Atomen, Niederalkenyl mit bis zu 4 C-Atomen, Cycloalkyl mit 5 bis 8 Ringgliedern, Bicyclo- oder Tricycloalkyl mit jeweils 5 oder 6 Ringgliedern, Cycloalkylniederalkyl mit 5 bis 8 Ringgliedern und mit bis zu 4 C-Atomen im Niederalkylenteil oder Bicyclo- oder Tricycloalkylniederalkyl mit jeweils 5 oder 6 Ringgliedern und mit bis zu 4 C-Atomen im Niederalkylenteil bedeutet, R_2 Wasserstoff, Niederalkyl mit bis zu 4 C-Atomen, Niederalkoxy mit bis zu 4 C-Atomen, Halogen bis Atomnummer 35 oder Trifluormethyl bedeutet, alk und alk' gleiches oder verschiedenes, die Stickstoffatome durch 2 C-Atome trennendes Niederalkylen mit bis zu 4 C-Atomen, darstellt und R_3 Wasserstoff, Niederalkyl mit bis zu 4 C-Atomen, Niederalkenyl mit bis zu 4 C-Atomen, oder einen gegebenenfalls im Phenyl- bzw. Pyridyl- oder Thienylteil durch Niederalkyl mit bis zu 4 C-Atomen, Niederalkoxy mit bis zu 4 C-Atomen, Halogen bis Atomnummer 35 und/oder Trifluormethyl substituierten und im Niederalk(en)ylenteil bis zu 4 C-Atome aufweisenden Phenylniederalkyl-, Phenylniederalkenyl- Pyridylniederalkyl- oder Thienylniederalkylrest darstellt und ihre Salze, dadurch gekennzeichnet, dass man in einer Verbindung der Formel



(II)

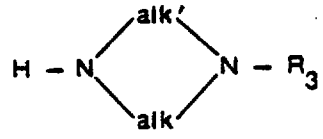
worin mindestens einer der Reste Z_1, Z_2 und Z_3 einen durch Wasserstoff ersetzbaren Rest Z und ein gegebenenfalls von Z verschiedener Rest Z., Z_2 bzw. Z_3 für Wasserstoff oder im Falle eines Restes Z_2 für eine von Wasserstoff verschiedene Gruppe R_3 steht, den Rest Z durch Wasserstoff ersetzt, oder eine Säure der Formel

* C L M S *



(III)

oder ein reaktionsfähiges funktionelles Derivat davon mit einem Amin der Formel



(IV)

oder einem reaktionsfähigen Derivat oder Salz davon umsetzt und gewünschtenfalls die so erhältliche Verbindung in eine andere Verbindung der Formel I umwandelt und/oder eine erhaltene freie Verbindung in ein Salz oder ein erhaltenes Salz in die freie Verbindung oder in ein anderes Salz überführt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, dass man eine Verbindung der allgemeinen Formel I, worin R_1 Niederalkyl mit bis zu 4 C-Atomen bedeutet, R_2 Wasserstoff ist, alk und alk' Aethylen bedeuten und R_3 Wasserstoff, Niederalkyl mit bis zu 4 C-Atomen oder einen im Phenylteil gegebenenfalls durch Niederalkyl mit bis zu 4 C-Atomen, Niederalkoxy mit bis zu 4 C-Atomen und/oder Halogen substituierten, bis zu 10 C-Atomen aufweisenden Phenylniederalkylrest, bedeutet, oder ein Salz davon herstellt.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, dass man 5-(N-Methylsulfamoyl)-anthranilsäure-(4-methyl)-piperazid oder ein Salz davon herstellt.

4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, dass man 5-(N-Aethylsulfamoyl)-anthranilsäure-(4-methyl)-piperazid oder ein Salz davon herstellt.

5. Verfahren nach Anspruch 1, dadurch gekennzeichnet, dass man 5-(N-Methylsulfamoyl)-anthranilsäure-4-[2-(p-chlorphenyl)äthyl]-piperazid oder ein Salz davon herstellt.

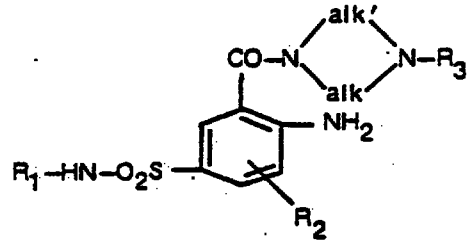
6. Verfahren nach Anspruch 1, dadurch gekennzeichnet, dass man 5 - (N - Methylsulfamoyl) - anthranilsäure - (4 - benzyl) - piperazid oder ein Salz davon herstellt.

7. Verfahren nach Anspruch 1, dadurch gekennzeichnet, dass man 5-(N-Methylsulfamoyl)-anthranilsäurepiperazid oder ein Salz davon herstellt.

8. Verfahren zur Herstellung eines pharmazeutischen Präparates enthaltend eine Verbindung gemäss einem der Ansprüche 1—7, dadurch gekennzeichnet, dass man diese mit üblichen pharmazeutischen Hilfs- und/oder Trägerstoffen verarbeitet.

Claims for the Contracting States: BE CH DE FR GB IT LU NL SE (as printed)

1. A substituted anthranilamide of the formula



(I),

in which R_1 is hydrogen, lower alkyl having not more than 4 C atoms, lower alkenyl having not more than 4 C atoms, cycloalkyl having 5 to 8 ring members, bicyclo- or tricyclo-alkyl having 5 or 6 ring members in each ring, cycloalkyl-lower alkyl having 5 to 8 ring members and having not more than 4 C atoms in the lower alkylene moiety, or bicyclo- or tricyclo-alkyl-lower alkyl having 5 or 6 ring members in each ring and having not more than 4 C atoms in the lower alkylene moiety, R_2 is hydrogen, lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35, or trifluoromethyl, alk and alk' are identical or different lower alkylene which separates the nitrogen atoms by 2 C atoms and has not more than 4 C atoms, and R_3 is hydrogen, lower alkyl having not more than 4 C atoms, lower alkenyl having not more than 4 C atoms or a phenyl-lower alkyl radical which can be substituted in the phenyl moiety by lower alkyl having not

* C L M S *

more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35 and/or trifluoromethyl and has not more than 4 C atoms in the lower alkylene moiety, a phenyl-lower alkenyl radical which can be substituted in the phenyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35 and/or trifluoromethyl and has not more than 4 C atoms in the lower alkenylene moiety, a pyridyl-lower alkyl radical which can be substituted in the pyridyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35 and/or trifluoromethyl, and has not more than 4 C atoms in the lower alkylene moiety, or a thienyl-lower alkyl radical, which can be substituted in the thienyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35, and/or trifluoromethyl and has not more than 4 C atoms in the lower alkylene moiety, or a salt thereof.

2. A compound as claimed in claim 1, in which R_1 is lower alkyl having not more than 4 C atoms, R_2 is hydrogen, alk and alk' are ethylene and R_3 is hydrogen, lower alkyl having not more than 4 C atoms or a phenyl-lower alkyl radical which can be substituted in the phenyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms and/or halogen, and has not more than 10 C atoms, or a salt thereof.

3. 5-(N-Methylsulfamoyl)-anthranilic acid-(4-methyl)-piperazide or a salt thereof.

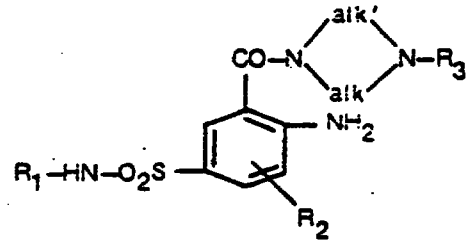
4. 5-(N-Methylsulfamoyl)-anthranilic acid-4-[2-(p-chlorophenyl)-ethyl]-piperazide or a salt thereof.

5. 5-(N-Methylsulfamoyl)-anthranilic acid-(4-benzyl)-piperazide or a salt thereof.

6. 5-(N-Methylsulfamoyl)-anthranilic acid piperazide or a salt thereof.

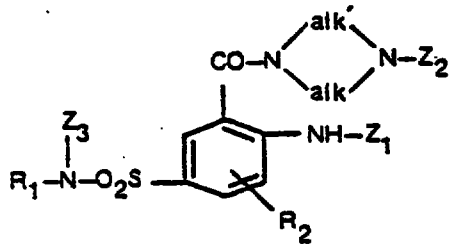
7. A pharmaceutical preparation containing a compound according to any one of claims 1—6, together with customary pharmaceutical auxiliaries and carriers.

8. A process for the manufacture of a substituted anthranilamide of the formula



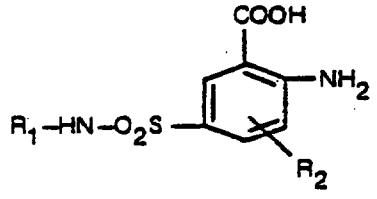
(I),

in which R_1 is hydrogen, lower alkyl having not more than 4 C atoms, lower alkenyl having not more than 4 C atoms, cycloalkyl having 5 to 8 ring members, bicyclo- or tricyclo-alkyl having 5 or 6 ring members in each ring, cycloalkyl-lower alkyl having 5 to 8 ring members and having not more than 4 C atoms in the lower alkylene moiety, or bicyclo- or tricyclo-alkyl-lower alkyl having 5 or 6 ring members in each ring and having not more than 4 C atoms in the lower alkylene moiety, R_2 is hydrogen, lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35, or trifluoromethyl, alk and alk' are identical or different lower alkylene which separates the nitrogen atoms by 2 C atoms and has not more than 4 C atoms, and R_3 is hydrogen, lower alkyl having not more than 4 C atoms, lower alkenyl having not more than 4 C atoms or a phenyl-lower alkyl radical which can be substituted in the phenyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35 and/or trifluoromethyl and has not more than 4 C atoms in the lower alkylene moiety, a phenyl-lower alkenyl radical which can be substituted in the phenyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35 and/or trifluoromethyl and has not more than 4 C atoms in the lower alkenylene moiety, a pyridyl-lower alkyl radical which can be substituted in the pyridyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35 and/or trifluoromethyl, and has not more than 4 C atoms in the lower alkylene moiety, or a thienyl-lower alkyl radical, which can be substituted in the thienyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35, and/or trifluoromethyl and has not more than 4 C atoms in the lower alkylene moiety, or of a salt thereof, which comprises effecting, in a compound of the formula



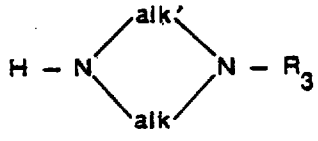
(II)

in which at least one of the radicals Z_1, Z_2 and Z_3 is a radical Z which is replaceable by hydrogen, and a radical Z_1, Z_2 or Z_3 which may differ from Z is hydrogen or, in the case of a radical Z_2, is a group R_3 which differs from hydrogen, the replacement of the radical Z by hydrogen, or reacting an acid of the formula



(III)

or a reactive functional derivative thereof, with an amine of the formula



(IV)

or a reactive derivative or salt thereof, and, if desired, converting the compound thus obtainable into another compound of the formula I and/or converting a resulting free compound into a salt and/or converting a resulting salt into the free compound or into another salt.

9. Compounds of the formula I according to any one of claims 1—6 having an analgetic, antiinflammatory and/or antiallergic action.

10. The use of compounds of the formula I according to any one of claims 1—6 for producing pharmaceutical preparations.

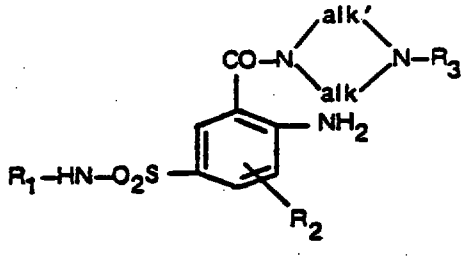
11. The use of compounds of the formula I according to any one of claims 1—6 for producing analgetic, antiinflammatory and/or antiallergic preparations.

12. Compounds of the formula I according to any of claims 1—6 for application in a process for the therapeutic treatment of warm-blooded species.

13. The compounds obtainable by the process according to claim 8.

Claims for the Contracting State: AT (as printed)

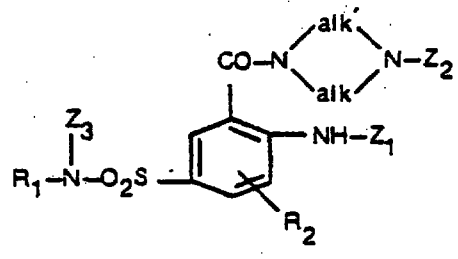
1. A process for the manufacture of a substituted anthranilamide of the formula



(I),

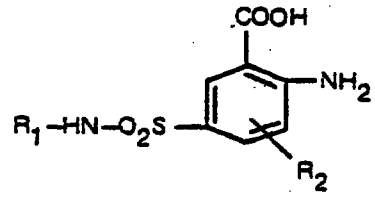
in which R_1 is hydrogen, lower alkyl having not more than 4 C atoms, lower alkenyl having not more than 4 C atoms, cycloalkyl having 5 to 8 ring members, bicyclo- or tricyclo-alkyl having 5 or 6 ring members in each ring, cycloalkyl-lower alkyl having 5 to 8 ring members and having not more than 4 C atoms in the lower alkylene moiety, or bicyclo- or tricyclo-alkyl-lower alkyl having 5 or 6 ring members in each ring and having not more than 4 C atoms in the lower alkylene moiety, R_2 is hydrogen, lower

alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35, or trifluoromethyl, alk and alk' are identical or different lower alkylene which separates the nitrogen atoms by 2 C atoms and has not more than 4 C atoms, and R_3 is hydrogen, lower alkyl having not more than 4 C atoms, lower alkenyl having not more than 4 C atoms or a phenyl-lower alkyl radical which can be substituted in the phenyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35 and/or trifluoromethyl and has not more than 4 C atoms in the lower alkylene moiety, a phenyl-lower alkenyl radical which can be substituted in the phenyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35 and/or trifluoromethyl and has not more than 4 C atoms in the lower alkenylene moiety, a pyridyl-lower alkyl radical which can be substituted in the pyridyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35 and/or trifluoromethyl, and has not more than 4 C atoms in the lower alkylene moiety, or a thienyl-lower alkyl radical, which can be substituted in the thienyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, halogen with an atomic number of not more than 35, and/or trifluoromethyl and has not more than 4 C atoms in the lower alkylene moiety, or a salt thereof, which comprises effecting, in a compound of the formula



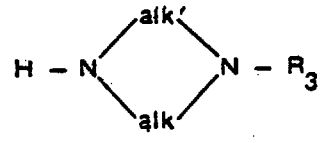
(II)

in which at least one of the radicals Z_1, Z_2 and Z_3 is a radical Z which is replaceable by hydrogen, and a radical Z_1, Z_2 or Z_3 which may differ from Z is hydrogen or, in the case of a radical Z_2, is a group R_3 which differs from hydrogen, the replacement of the radical Z by hydrogen, or reacting an acid of the formula



(III)

or a reactive functional derivative thereof, with an amine of the formula



(IV)

or a reactive derivative or salt thereof, and, if desired, converting the compound thus obtainable into another compound of the formula I and/or converting a resulting free compound into a salt and/or converting a resulting salt into the free compound or into another salt.

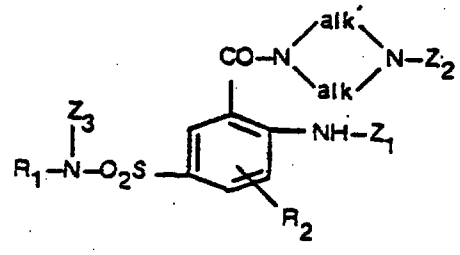
2. A process according to claim 1 for the manufacture of a compound of the general formula I, in which R_1 is lower alkyl having not more than 4 C atoms, R_2 is hydrogen, alk and alk' are methylene, and R_3 is hydrogen, lower alkyl having not more than 4 C atoms, or a phenyl-lower-alkyl radical which can be substituted in the phenyl moiety by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms and/or halogen, and which has not more than 10 C atoms, or of a salt thereof.

3. A process according to claim 1, wherein 5-(N-methylsulfamoyl)-anthanilic acid-(4-methyl)-piperazide or a salt thereof is produced.

4. A process according to claim 1, wherein 5-(N-ethylsulfamoyl)-anthranilic acid-(4-methyl)-piperazide or a salt thereof is produced.

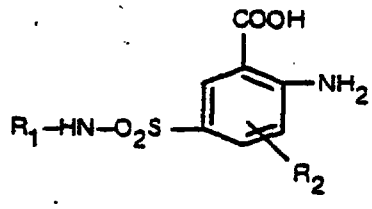
5. A process according to claim 1, wherein 5-(N-methylsulfamoyl)-anthranilic acid-4-[2-(p-chlorophenyl)-ethyl]-piperazide or a salt thereof is produced.

dans laquelle R_1 représente l'hydrogène, un groupe alkyle inférieur contenant jusqu'à 4 atomes de carbone, alcényle inférieur contenant jusqu'à 4 atomes de carbone, cycloalkyle contenant 5 à 8 chaînons cycliques, bicyclo- ou tricyclo-alkyle contenant chacun 5 ou 6 chaînons cycliques, cycloalkyl-alkyle inférieur contenant 5 à 8 chaînons cycliques et jusqu'à 4 atomes de carbone dans la partie alkylène inférieur, ou bicyclo- ou tricyclo-alkyl-alkyle inférieur contenant chacun 5 ou 6 chaînons cycliques et jusqu'à 4 atomes de carbone dans la partie alkylène inférieur, R_2 représente l'hydrogène, un groupe alkyle inférieur contenant jusqu'à 4 atomes de carbone, alkoxy inférieur contenant jusqu'à 4 atomes de carbone, un halogène de numéro atomique allant jusqu'à 35 ou un groupe trifluorométhyle, alk et alk', ayant des significations identiques ou différentes, représentent chacun un groupe alkylène inférieur contenant jusqu'à 4 atomes de carbone et séparant les atomes d'azote par deux atomes de carbone, et R_3 représente l'hydrogène, un groupe alkyle inférieur contenant jusqu'à 4 atomes de carbone, alcényle inférieur contenant jusqu'à 4 atomes de carbone, ou un groupe phényl-alkyle inférieur, phényl-alcényle inférieur, pyridyl-alkyle inférieur ou thiénylalkyle inférieur éventuellement substitué dans la partie respective phényle, pyridyle ou thiényle par un groupe alkyle inférieur contenant jusqu'à 4 atomes de carbone, alcoxy inférieur contenant jusqu'à 4 atomes, un halogène de numéro atomique allant jusqu'à 35 et/ou un groupe trifluorométhyle, et contenant jusqu'à 4 atomes de carbone dans la partie alc-(én)-ylène inférieur, et de leurs sels, caractérisé en ce que, dans un composé de formule



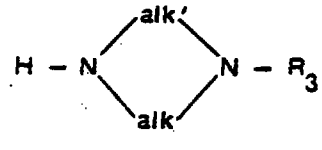
(II)

dans laquelle l'un au moins des restes Z_1, Z_2 et Z_3 est un reste Z remplacable par l'hydrogène et un reste Z_1, Z_2 ou Z_3 éventuellement différent de Z représente l'hydrogène ou, dans le cas d'un reste Z_2, un groupe R_3 différent de l'hydrogène, on remplace le reste Z par l'hydrogène, ou bien on fait réagir un acide de formule



(III)

ou un dérivé fonctionnel réactif d'un tel acide, avec une amine de formule



(IV)

ou un dérivé réactif ou un sel de cette amine, et si on le désire, on convertit le composé obtenu en un autre composé de formule I et/ou on convertit un composé libre obtenu en un sel ou un sel obtenu en le composé libre ou en un autre sel.

9. Composés de formule I selon l'une des revendications 1 à 6, possédant une activité analgésique, anti-inflammatoire et ou anti-allergique.

10. Utilisation des composés de formule I selon l'une des revendications 1 à 6 pour la préparation de médicaments.

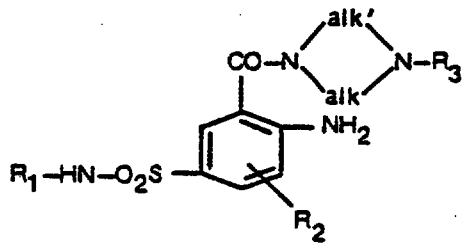
11. Utilisation des composés de formule I selon l'une quelconque des revendications 1 à 6, pour la préparation d'analgésiques, d'anti-inflammatoires et/ou d'anti-allergiques.

12. Composés de formule I selon l'une des revendications 1 à 6 et 9 pour l'utilisation dans un procédé pour le traitement thérapeutique de l'homme ou des espèces à sang chaud.

13. Les composés susceptibles d'être obtenus par le procédé selon la revendication 8.

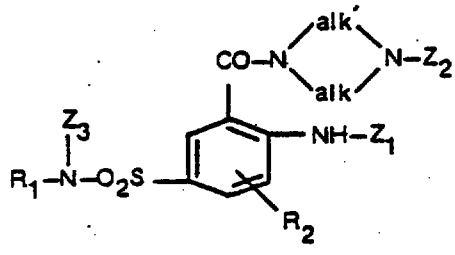
Revendications pour l'Etat contractant: AT (as printed)

1. Procédé de préparation d'anthranilamides substitués de formule



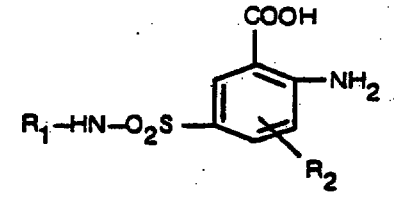
(I),

dans laquelle R_1 représente l'hydrogène, un groupe alkyle inférieur contenant jusqu'à 4 atomes de carbone alcényle inférieur contenant jusqu'à 4 atomes de carbone, cycloalkyle contenant 5 à 8 chaînons cycliques, bicyclo- ou tricyclo-alkyle contenant chacun 5 ou 6 chaînons cycliques, cycloalkyl-alkyle inférieur contenant 5 à 8 chaînons cycliques et jusqu'à 4 atomes de carbone dans la partie alkylène inférieur, ou bicyclo ou tricyclo-alkyl-alkyle inférieur contenant chacun 5 ou 6 chaînons cycliques et jusqu'à 4 atomes de carbone dans la partie alkylène inférieur, R_2 représente l'hydrogène, un groupe alkyle inférieur contenant jusqu'à 4 atomes de carbone, alcoxy inférieur contenant jusqu' 4 atomes de carbone, un halogène de numéro atomique allant jusqu'à 35 ou un groupe trifluorométhyle, alk et alk', ayant des significations identiques ou différentes, représentent chacun un groupe alkylène inférieur contenant jusqu'à 4 atomes de carbone et séparant les atomes d'azote par deux atomes de carbone, et R_3 représente l'hydrogène, un groupe alkyle inférieur contenant jusqu'à 4 atomes de carbone, alcényle inférieur contenant jusqu'à 4 atomes de carbone, ou un groupe phényl-alkyle inférieur, phényl-alcényle inférieur, pyridyl-alkyle inférieur ou thiénylalkyle inférieur éventuellement substitué dans la partie respective phényle, pyridyle ou thiényle par un groupe alkyle inférieur contenant jusqu'à 4 atomes de carbone, alcoxy inférieur contenant jusqu'à 4 atomes, un halogène de numéro atomique allant jusqu'à 35 et/ou un groupe trifluorométhyle, et contenant jusqu'à 4 atomes de carbone dans la partie alc-(én)-ylène inférieur, et de leurs sels, caractérisé en ce que, dans un composé de formule



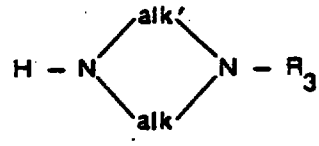
(II)

dans laquelle l'un au moins des restes Z_1, Z_2 et Z_3 est un reste Z remplaçable par l'hydrogène et un reste Z_1, Z_2 ou Z_3 éventuellement différent de Z représente l'hydrogène ou, dans le cas d'un reste Z_2, un groupe R_3 différent de l'hydrogène, on remplace le reste Z par l'hydrogène, ou bien on fait réagir un acide de formule



(III)

ou un dérivé fonctionnel réactif d'un tel acide, avec une amine de formule



(IV)

ou un dérivé réactif ou un sel de cette amine, et si on le désire, on convertit le composé obtenu en un autre composé de formule I et/ou on convertit un composé libre obtenu en un sel ou un sel obtenu en le composé libre ou en un autre sel.

2. Procédé selon la revendication 1 caractérisé en ce que l'on prépare un composé de formule générale I dans laquelle R_1 représente un groupe alkyle inférieur contenant jusqu'à 4 atomes de carbone, R_2 représente l'hydrogène, alk et alk' représentent des groupes éthylène et R_3 représente l'hydrogène, un groupe alkyle inférieur contenant jusqu'à 4 atomes de carbone ou un groupe phénylalkyle inférieur éventuellement substitué dans la partie phényle par un groupe alkyle inférieur contenant jusqu'à 4 atomes de carbone, alcoxy inférieur contenant jusqu'à 4 atomes de carbone et/ou un halogène, et contenant jusqu'à 10 atomes de carbone, et leurs sels.

3. Procédé selon la revendication 1 caractérisé en ce que l'on prépare le 4-méthyl-pipérazide de l'acide 5-(N-méthylsulfamoyl)-anthranilique ou un sel de ce composé.

4. Procédé selon la revendication 1, caractérisé en ce que l'on prépare le 4-méthyl-pipérazide de l'acide 5-(N-éthylsulfamoyl)-anthranilique ou un sel de ce composé.

5. Procédé selon la revendication 1, caractérisé en ce que l'on prépare le 4-[2-(p-chlorophényl)-éthyl]-pipérazide de l'acide 5-(N-méthyl-sulfamoyl)-anthranilique ou un sel de ce composé.

6. Procédé selon la revendication 1, caractérisé en ce que l'on prépare le 4-benzyl-pipérazide de l'acide 5-(N-méthylsulfamoyl)-anthranilique ou un sel de ce composé.

7. Procédé selon la revendication 1, caractérisé en ce que l'on prépare le pipérazide de l'acide 5-(N-méthylsulfamoyl)-anthranilique ou un sel de ce composé.

8. Procédé de préparation d'une composition pharmaceutique contenant un composé selon l'une des revendications 1 à 7, caractérisé en ce que l'on met ce composé en oeuvre avec des produits auxiliaires et/ou véhicules pharmaceutiques usuels.