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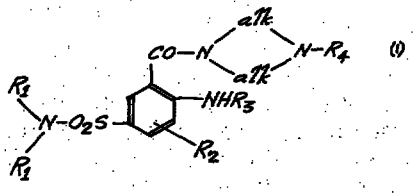
(54) SULPHAMOYLBENZOIC ACID AMIDES

(71) We, CIBA-GEIGY A.G., a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to sulphamoyl benzoic acid amides.

In British Patent Specificaiton No. 1,311,812 there are described and claimed 2 - hydroxyamino - 5 - (tert. - sulphamoyl) - benzoic acid piperazides in particular those in which the piperazine moiety is N - unsubstituted or is N - substituted by alkyl, alkenyl or hydroxyalkyl radicals.

The present invention provides 2 - amino - 5 - sulphamoyl - benzoic acid amides of the general formula I



(I)

wherein R_1 denotes a lower alkyl group, R_3 denotes a hydrogen or halogen atom, or a trifluoromethyl, lower alkyl or lower alkoxy group, R_5 denotes a hydrogen atom or a hydroxyl or lower alkyl group, R_4 denotes a group of the formula —A—Y—R_5, wherein A represents a lower alkyl or lower alkenyl radical, Y represents a hetero atom or a direct bond and R_5 represents an aryl radical, and alk denotes a lower alkylene radical which separates the nitrogen atoms by 2 or 3 C atoms.

In the preceding and following text, "lower" radicals are radicals which contain up to 7, above all up 1 to 4, C atoms.

The radicals R_1 and alk can respectively be identical or different.

Lower alkyl radicals R_1, R_2 and R_3 contain 1 to 7, above all 1 to 4, C atoms and are straight or branched chain heptyl, hexyl or pentyl radicals bonded in any desired position, or above all *n*-, *sec.*- or *tert.* - butyl, isobutyl, isopropyl, *n* - propyl or especially ethyl or methyl radicals.

A halogen atom R_3 is, in particular, a fluorine, bromine or above all chlorine atom.

A lower alkoxy radical R_3 contains 1 to 7, above all 1 to 4, C atoms and is thus a straight or branched chain heptyloxy, hexyloxy or pentyloxy radical bonded in any desired position, or, above all, an *n*-, *sec.*- or *tert.* - butoxy isobutoxy, isopropoxy, *n* - propoxy or especially ethoxy or methoxy radical.

In radicals R_4 the aryl radical is, in particular, a phenyl radical which is optionally monosubstituted or polysubstituted by one or more substituents, as appropriate, selected from lower alkyl, lower alkoxy, halogen and trifluoromethyl, or is a pyridyl or thienyl radical which may be substituted by lower alkyl and/or lower alkoxy radicals at one or more C atoms.

In radicals R_4, the aliphatic part —A— in particular contains 1 to 6, above all 1 to 4, C atoms if Y denotes a direct bond, or 1 to 5, above all 1 to 3, C-atoms, if Y denotes a hetero atom, and can be straight-chain or branched, preferably in the 1- or 2-position, and bonded in any desired position. A heteroatom is, in particular oxygen or optionally mono - oxidised or di - oxidised sulphur. Examples of preferred aryl-lower alkyl or aryl - lower alkenyl radicals R_4 are arylmethyl, 2 - aryl - 1 - methyl - ethyl, 3 - arylprop - 2 - enyl, 3 - arylpropyl, 2 - aryl - 2 - methyl - ethyl and 2 - aryl-ethyl, possible aryl radicals being in each case, in particular, phenyl, pyridyl or thienyl which are optionally substituted as above, and specifically 2 - methyl - 2 - phenyl - ethyl, 3 - phenylpropyl, 2 - (*p* - chlorophenyl) - ethyl, 2 - (*p* - methoxyphenyl) - ethyl, 3 - phenylpropyl - 2 - enyl, 2 - (2 -, 3- or 4 - pyridyl) - ethyl, 3 - (2 pyridyl) - propyl or 3 - (3 - pyridyl) - propyl, benzyl and 2 - phenylethyl radicals.

Examples of preferred arylhetero - lower alkyl and arylhetero - lower alkenyl radicals R_4 are 3 - aryloxypropyl, 3 - arylthiopropyl, 3 - arylsulphinylpropyl - and 3 - arylsulphonylpropyl as well as 2 - aryloxyethyl, 2 - arylthioethyl, 2 - arylsulphinylethyl and 2 - arylsulphonylethyl, the aryl radicals in each case being in particular, a pyridyl or thienyl radical or above all a phenyl radical, which radicals are optionally substituted as indicated above, and specifically β - phenoxyethyl, β - phenylthioethyl, β - phenylsulphinylethyl and β - phenylsulphonylethyl.

The radicals alk can be straight-chain or branched and optionally contain 1 to 7, in particular 1 to 4, C atoms in the side chain. The following may be mentioned as examples: isobutylene - 1,3 and above all isobutylene - 1,2, butylene - 2,3 and, in particular, propylene - 1,3 and especially butylene - 1,2, propylene - 1,2 and ethylene.

The 2 - amino - 5 - sulphamoyl - benzoic acid amides of the invention possess valuable pharmacological properties. Thus they display, in particular, a distinct anti-inflammatory action, such as can be shown, for example, in the turpentine pleurisy test on rats, and above all a distinct antinociceptive (analgesic) action, such as can be shown, for example, in the acetic acid and benzoquinone writhing test on mice. They are, furthermore, distinguished by a comparatively low toxicity, as can be shown, for example, on rats. The 2 - amino - 5 - sulphamoyl - benzoic acid amides of the invention therefore are useful as analgesics in conditions of slight to medium pain of the most diverse etiology.

Preferred compounds of the invention are those 2 - amino - 5 - sulphamoyl - benzoic acid amides of the formula I, wherein the radicals R_1 denote identical alkyl groups with 1 to 4 C atoms, for example, methyl or ethyl groups, R_2 denotes a hydrogen atom or a halogen atom up to atomic number 17, for example a fluorine or chlorine atom, R_3 denotes a hydrogen atom, a hydroxyl group or a alkyl group with 1 to 4 C atoms, for example, an isopropyl, *n* - propyl or above all, ethyl or methyl group, R_4 denotes a phenyl - lower alkyl or phenyl - lower alkenyl radical optionally monosubstituted or polysubstituted in the phenyl part by substituent(s) selected from lower alkyl and lower alkoxy radicals, halogen atoms and trifluoromethyl groups, or represents a pyridyl- or thienyl-lower alkyl or -lower alkenyl radical optionally substituted by lower alkyl and/or lower alkoxy groups at one or more C atoms in the pyridyl or thienyl part, all these R_4 radicals having 1 to 6 C atoms in the aliphatic part, and alk denotes an alkylene radical with 2 to 4 C atoms, for example, a butylene - 2,3, butylene - 1,2, propylene - 1,2 or propylene - 1,3 or above all ethylene radical.

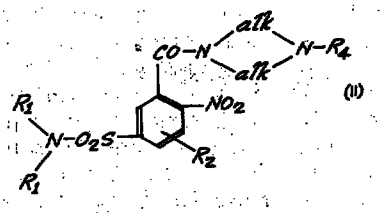
Particularly preferred are those 5 - sulphamoyl - anthranilic acid amides of the formula I wherein R_1 is a methyl group, R_2 is a chlorine atom or a methoxy or methyl group or above all a hydrogen atom, R_3 is a hydrogen atom or an alkyl group with 1 to 4 C atoms, for example an ethyl or methyl group, R_4 is a phenyl - lower alkyl or phenyl - lower alkenyl radical optionally monosubstituted or polysubstituted as described above, or represents a pyridyl- or thienyl - lower alkyl or -lower alkenyl radical optionally substituted as described above, all these R_4 radicals having 1 to 5, above all 1 to 4, C atoms in the aliphatic part, and alk denotes a 1,2 - alkylene radical with 2 to 4 C atoms, for example, a butylene - 1,2, propylene - 1,2 or, above all, ethylene radical.

Very particularly preferred are those 5 - sulphamoyl - anthranilic acid amides of the formula I wherein R_1 is a methyl group, R_2 is a hydrogen atom, R_3 is a hydrogen atom or an ethyl or methyl group, R_4 denotes an R_5 - methyl, 2 - R_5 - ethyl, 2 - methyl - 2 - R_5 - ethyl, 3 - R_5 - propyl or 3 - R_5 - prop - 2 enyl radical, wherein R_5 is a phenyl radical which is optionally monosubstituted or polysubstituted as described above or represents a pyridyl radical which is optionally substituted as described above, and alk denotes a propylene - 1,2 or, above all, ethylene radical.

Especially preferred are those 5 - sulphamoyl - anthranilic acid amides of the formula I wherein R_1 is a methyl group, R_2 is a hydrogen atom, R_3 is a hydrogen atom or an ethyl group, R_4 is a R_5' - methyl, 2 - R_5' - ethyl, 2 - methtyl - 2 - R_5' - ethyl, 3 - R_5' - propyl or 3 - R_5' - prop - 2 - radical, wherein R_5' is a phenyl radical which is unsubstituted, halogenated, for example, chlorinated or fluorinated, or lower alkoxylated, for example, methoxylated, these substituents being above all in the *m*- or *p*-position, or denotes a pyridyl radical, and alk is an ethylene radical and specifically the 2 - amino - 5 - sulphamoyl - benzoic acid amides of the general formula I which are mentioned in the examples.

The 2 - amino - 5 - sulphamoyl - benzoic acid amides of the invention can be obtained according to processes which are in themselves known for the manufacture of analogous compounds.

Thus it is possible, for example, to manufacture a 2 - amino - 5 - sulphamoyl - benzoic acid amide of the formula I, wherein R_3 is a hydrogen atom or a hydroxyl group, by reducing the nitro group in a 2 - nitro - 5 - sulphamoylbenzoic acid amide of the formula II



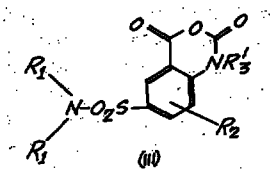
(II)

wherein R_1, R_2, R_4 and alk have the indicated meanings.

The reduction of the nitro group can be carried out in a manner which is in itself known, and has in particular been described for analogous reactions, for example, with nascent hydrogen, for example, generated by the action of a strong acid, for example, a hydrohalic acid, above all hydrochloric acid, sulphuric acid or a lower aliphatic carboxylic acid, for example, acetic acid, on a base metal, for example, iron, zinc, magnesium or aluminium, or with a suitable light metal hydride, for example, lithium borohydride or above all sulphurised sodium borohydride, or with hydrogen in the presence of a suitable hydrogenation catalyst, for example, palladium on charcoal, platinum oxide or Raney nickel or Rupe nickel, in a solvent which is inert under the hydrogenation conditions, if necessary under elevated pressure and/or at elevated temperature.

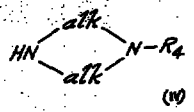
The nitro group can be reduced either to the hydroxyamino group or as far as the primary amino group, depending on the reaction conditions. Thus, the reduction with nascent hydrogen in neutral or weakly acid solution, and the reaction with hydrogen at room temperature under normal pressure in the presence of 10% strength palladium on charcoal, with discontinuation of the hydrogenation after 2 equivalents of hydrogen have been taken up, give predominantly 2 - hydroxyamino - 5 - sulphamoyl - benzoic acid amides. In contrast, 5 - sulphamoyl - anthranilic acid amides are obtained under drastic conditions, for example with nascent hydrogen in mineral acid solution or with hydrogen under elevated pressure and/or at elevated temperature or above all when using Rupe nickel as the catalyst.

Moreover 2 - amino - 5 - sulphamoyl - benzoic acid amides of formula I can also be manufactured by reacting a 5 - sulphamoyl - isatoic anhydride of the formula III



(III)

wherein R_1 and R_2 have the indicated meanings and R_3' denotes hydrogen or a lower alkyl group with an amine of the formula IV

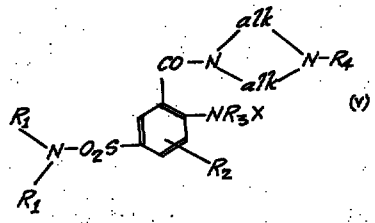


(IV)

wherein alk and R_4 have the indicated meanings.

The reaction with the amine of the formula IV can be carried out in a manner which is in itself known, if necessary in the presence of a solvent and/or of a condensation agent, especially a basic condensation agent, and advantageously at elevated temtemperature.

Further, a 5 - sulphamoyl - anthranilic acid amide of formula I can be manufactured by solvolytically splitting off X from a 5 - sulphamoyl - anthranilic acid amide of the formula V



(V)

wherein R_1, R_2, R_3 and R_4 and alk have the indicated meanings and X denotes an acyl radical, for example, an optionally functionally modified carboxyl group, for example an oxycarbonyl radical, for example, an alkoxycarbonyl radical, for example the tert. - butoxycarbonyl radical, an arylsulphonylethoxycarbonyl radical, for example, the benzene sulphonylethoxycarbonyl radical, an arylthioethoxycarbonyl radical, for example, the phenylthioethoxycarbonyl radical, or the ethoxycarbonyl radical, an aralkoxycarbonyl radical, for example, a phenyl - lower alkoxycarbonyl radical, for example a carbobenzoxy radical, a halogenocarbonyl radical, for example the chlorocarbonyl radical, or an arylsulphonyl radical, for example, a toluenesulphonyl or bromobenzenesulphonyl radical, or an optionally halogenated, for example, fluorinated, lower alkanyl radical, for example the formyl, acetyl or trifluoroacetyl radical, or an aroyl radical, for example, a benzoyl radical, or the nitrile group, a sulphinyl radical or a silyl radical, for example, the trimethylsilyl radical.

The solvolysis is carried out in the usual manner, for example in the presence of a hydrolysing agent, for example in the presence of an acid agent, for example, of an aqueous mineral acid, for example, sulphuhic acid or a hydrogen halide acid, or of an organic acid, for example a suitable carboxylic acid, for example, α - halogenoalkanecarboxylic acid, for example trifluoroacetic

acid or chloroacetic acid, or an organic sulphonic acid, for example benzenesulphonic acid or toluenesulphonic acid, or of an acid ion exchange, or in the presence of a basic agent, for example an alkali metal hydroxide, for example, sodium hydroxide. An oxycarbonyl radical, arylsulphonyl radical or nitrile group is advantageously split off by an acid agent, for example, a hydrohalic acid. For example, splitting off by means of aqueous hydrochloric acid, optionally mixed with acetic acid, is particularly suitable for this purpose. Furthermore it is possible to split off, for example, a tert. - butoxycarbonyl radical under anhydrous conditions by treatment with a suitable acid, for example trifluoroacetic acid.

In the resulting 2 - amino - 5 - sulphamoyl - benzoic acid amide substituents can be introduced, modified and split off, within the scope of the definition of formula I.

Thus, for example, it is possible to introduce a halogen atom in the usual manner into a resulting 2 - amino - 5 -sulphamoyl - benzoic acid amide which contains an aromatically bonded hydrogen atom, for example by reaction with chlorine or bromine, preferably in the presence of a catalyst, for example, iron-(III) chloride, or by reaction with N - chlorosuccinimide. Further, a trifluoromethyl group can be introduced in the usual manner, for example by reaction with trifluoroiodomethane in the presence of a metal, for example, copper powder. In addition, a lower alkyl group can be introduced in the usual manner, for example by reaction with a lower alkyl halide, advantageously in the presence of a catalyst, for example, a metal halide, for example aluminium chloride or aluminium bromide.

In a resulting 5 - sulphamoyl - anthranilic acid amide of the formula I wherein R_8 is a hydrogen atom, it is furthermore possible to introduce a lower alkyl group R_8 in the usual manner, for example by reaction with a customary alkylating agent, for example, a reactive ester of an alcohol of the formula R_8—OH, for example with an organic sulphonic acid, for example, benzenesulphonic acid, p - bromobenzenesulphonic acid, toluenesulphonic acid or methanesulphonic acid, or with an inorganic sulphonic acid, for example with fluorosulphonic acid, or with a strong inorganic acid, for example, hydrochloric acid, hydrobromic acid, hydroiodic acid or sulphuric acid, or by reaction with a corresponding onium salt, for example with a tri-lower alkyloxonium tetrafluoborate or with a di-lower alkyl- iodonium iodide.

The reaction with such a reactive ester is preferably carried out in the presence of an acid-binding agent, for example, a tertiary organic base, for example ethyldiisopropylamine, pyridine or quinoline, or of an inorganic base, for example, 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. Preferably, the alkylation measures described above are carried out in an inert organic solvent, for example, a hydrocarbon, for example in benzene, toluene or xylene, or, in the case of the reaction with a reactive ester, for example, in an ether, for example, diethyl ether, tetrahydrofuran or dioxane, or, in the case of the reaction with an onium salt, in a chlorinated or nitrated hydrocarbon, for example in methylene chloride, carbon tetrachloride, nitrobenzene or nitromethane.

However, the alkylation can also be effected 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, suitably 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, elevated pressure, or in the presence of a hydrogen donor, such as one of those mentioned, for example lithium aluminium hydride, sodium cyanoborohydride, of sodium borohydride, in each case advantageously in a solvent which is inert under the reduction conditions. For example, it is particularly advantageous to introduce a methyl group by heating the compound which is to be methylated with a mixture of formaldehyde and formic acid, for example for 1 to 24 hours to temperatures between approx. 60° and 120°C, and preferably to the reflux temperature of the reaction mixture. The formaldehyde can also be employed in the form of a formaldehyde donor, for example as paraformaldehyde or as an aqueous solution. In a preferred embodiment, for example, paraformaldehyde in 90% strength formic acid, or approx. 30% strength aqueous formaldehyde solution/80% strength formic acid is used.

A resulting 2 - hydroxyamino - 5 - sulphamoyl - benzoic acid can furthermore be reduced in the customary manner to the corresponding 5 - sulphamoyl - anthranilic acid amide, for example by treatment with sufficiently strong reducing agent, for example, nascent hydrogen, generated, for example, by the action of a strong acid, for example, a hydrohalic acid, above all hydrochloric acid, sulphuric acid or a lower aliphatic carboxylic acid, for example, acetic acid, on a base metal, for example, iron, zinc, magnesium or aluminium, or by means of a suitable light metal hydride, for example, lithium borohydride or above all sulphurised sodium borohydride, or by means of hydrogen in the

presence of a suitable hydrogenation catalyst, for example Rupe nickel or Raney nickel or platinum oxide, preferably under elevated pressure.

In the above reductions care must be taken, where relevant, that further reducible groups are not attacked. Thus care must be taken in particular in the case of the reduction with Raney nickel and hydrogen that any α - aryl - lower alkyl or alkenyl radical R_4 and/or halogen atom bonded to aromatic rings is or are not replaced by hydrogen atoms. If necessary, the hydrogen uptake should be followed volumetrically and the hydrogenation discontinued when the calculated amount has been taken up. Furthermore, the 5 - (di - lower alkylsulphamyl) group requires consideration in the case of all the reductions, but especially with a complex hydride.

The reactions mentioned can optionally be carried out simultaneously or successively and in optional sequence.

The reactions mentioned are carried out in the usual manner in the presence or absence of a diluent, condensation agent and/or catalytic agent, at lowered, ordinary or elevated temperature, and if necessary in a closed vessel.

Depending on the process conditions and starting materials, the end products are obtained in the free form or in the form of their acid addition salts which are also included in the invention. Thus, for example, basic, neutral or mixed salts and, where relevant, also hemihydrates, monohydrates, sesquihydrates or polyhydrates thereof can be obtained. The acid addition salts of the compounds of the invention can be converted into the free compound in a manner which is in itself known, for example by means of a basic agent, for example, an alkali or an ion exchanger. On the other hand, a resulting free base obtained can form salts with organic or inorganic acids. In particular, acids which are suitable for forming physiologically tolerable salts are employed to manufacture acid addition salts. As examples of such acids there may be mentioned: hydrohalic acids, sulphuric acids, phosphoric acids, nitric acid, fumaric acid, aliphatic, alicyclic aromatic or heterocyclic carboxylic acids or sulphonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycollic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid or pyruvic acid, benzoic acid, anthranilic acid, *p* - hydroxybenzoic acid, salicylic acid or embonic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid, ethylene sulphonic acid, halogenobenzene sulphonic acids, toluenesulphonic acid, cyclohexylaminesulphonic acid or sulphanilic acid.

These or other salts of the compounds of the invention, for example, the picrates can also serve for purification of the free bases obtained, by converting the free base into a salt, isolating this and again liberating the base from the salt. Because of the close relationships between the compounds of the invention in the free form and in the form of their salts, the free compounds are, in the preceding and following text, where appropriate also to be understood to include the corresponding salts, in respect of general sense and intended use.

The invention also relates to those embodiments of the process in which a starting material is formed *in situ* under the reaction conditions or in which a reactant is employed in the form of a salt, if appropriate.

Depending on the choice of the starting materials and procedures, the compounds of the invention can be in the form of optical antipodes or racemates, or, if they contain at least two asymmetric carbon atoms, also as isomer mixtures (racemate mixtures).

Resulting isomer mixtures (racemate mixtures) can be separated into the two stereoisomeric (diastereomeric) pure racemates in a known manner on the basis of the physiochemical differences of the constituents, for example by chromatography and/or fractional crystallisation.

Resulting racemates can be resolved into the diastereomers according to known methods, for example by recrystallisation from an optically active solvent, by means of micro-organisms or by reaction with an optically active acid which forms salts with the racemic compound and separation of the salts obtained in this manner, for example on the basis of their different solubilities, and the antipodes can then be liberated by treatment with suitable agents. Particularly customary optically active acids are, for example, the D- and L-forms of tartaric acid, di - o - toluytartaric acid, malic acid, mandelic acid, camphor - sulphonic acid or quinic acid. Advantageously, the more active of the two antipodes is isolated.

Suitably, those starting materials are used for carrying out the reactions according to the invention which lead to the groups of end product which initially were mentioned particularly and especially to the end products which have been specially described or singled out.

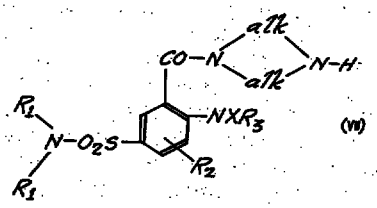
The starting compounds are known or can, if they are new, be obtained according to methods which are in themselves known. (The term "known" is used herein to mean in actual use in the art or described in the literature of the art).

Thus, for example, the *o* - nitrobenzoic acid amides of the formula II mentioned as starting materials can be manufactured by first reacting a 5 - (halogenosulphonyl) - 2 -

nitro - benzoic acid with a di - lower alkylamine of the formula $(R_1)_2NH$ and then with a halogenating agent, for example, a halide of phosphorous acid or sulphurous acid, of sulphuric acid or of phosphoric acid, for example with thionyl chloride and condensing the resulting 5 - (di - lower alkylsulphamoyl) - 2 - nitrobenzoyl halide with an amine of the formula IV in the usual manner, for example as described for the reaction of an amine of the formula IV with a functional derivative of a compound of the formula III.

The isatoic anhydrides of the formula III mentioned as starting materials can be manufactured, for example, by reacting a 5 - sulphamoyl - anthranilic acid with a difunctional carbonic acid derivative, for example with a dihalide, diester or, in particular, ester-halide thereof, for example with chloroformic acid ethyl ester.

The starting compounds of the formula V, wherein R_6 is hydrogen can be manufactured, for example, by condensing a corresponding 5 - sulphamoyl - anthranilic acid with a functional acetic acid derivative, for example with acetic anhydride, and reacting the resulting 6 - sulphamoyl - 2 - methyl - 4H - 3,1 - benzoxazin - 4 - one with an amine of the formula IV in the usual manner, for example as described above for the reaction with a functional derivative of an isatoic anhydride of the formula III, or by introducing R_4 into a 2 - (X - amino - 5 - sulphamoyl - benzoic acid amide of the formula VII



(VII)

in the usual manner.

The compounds of the invention can be used as medicaments, for example in the form of pharmaceutical preparations in which they or their physiologically tolerable salts are present in admixture or conjunction with a phamaceutical, organic or inorganic, solid or liquid carrier, which is suitable, for example, for enteral or parenteral administration. Suitable carriers are those which do not react with the compounds of the invention, for example, water, gelatine, lactose, starch, magnesium stearate, talc, vegetable oils, benzyl alcohols, rubber, polyalkylene glycols, white petroleum jelly, and cholesterol. The pharmaceutical preparations can be, for example, in the form of tablets, dragées, capsules, suppositories, ointments or creams or in the form of a liquid, as solutions for example as an elixir or syrup, suspensions or emulsions. Optionally, they are sterilised and/or contain auxiliaries, for example preservatives, stabilisers, wetting agents or emulsifiers, salts for regulating the osmotic pressure or buffers. They can also contain further therapeutically valuable materials. The preparations, which can also be used in veterinary medicine, are formulated in accordance with customary methods, preferably in unit dosage form. The recommended daily dose given orally to a warm-blooded animal weighing about 75 kg is about 15—350 mg and a unit dose preferably contains this amount of the compound or salt.

The Examples which follow illustrate the invention.

Example 1

A suspension of 32.4 g of 5 - (dimethylsulphamoyl) - isatoic anhydride in 150 ml of absolute toluene is warmed gently. As soon as the reaction mixture has reached 40°C, a solution of 22.2 g of 1 - benzylpiperazine is added dropwise and the mixture is then warmed further, with complete solution occurring at about 75°C. The mixture is additionally heated for 1 hour to the refluxing temperature and evaporated to dryness under reduced pressure. The oily residue is dissolved in ethanol and an equivalent amount of ethanolic hydrochloric acid is added. 23.4 g of 1 - [5 - (dimethyl - sulphamoyl) - anthraniloyl] - 4 - benzylpiperazine hydrochloride of melting point 196—198°C are thus obtained.

Example 2

23.7 g of 5 - (dimethylsulphamoyl) - isatoic anhydride in 180 ml of absolute dioxane are warmed to 80°C. A solution of 16.7 g of 1 - (β - phenyl) - ethyl - piperazine in 70 ml of absolute dioxane is then added dropwise, the whole is additionally heated for 1 hour to the reflux temperature and the reaction solution is evaporated to dryness under reduced pressure. The evaporation residue is recrystallised from isopropanol. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl) - 4 - (β - phenylethyl) - piperazine of melting point 144—5°C is thus obtained.

Example 3

25.6 g of 1 - [(5 - dimethylsulphamoyl - 2 - acetamido) - benzoyl] - 4 - (2 - phenylpropyl) - piperazine in 250 ml of methanol, 100 ml of chloroform and 200 ml of 2 N sodium hydroxide solution are warmed to 70°C, whereupon solution occurs. The two-phase system formed is concentrated in vacuo to remove the chloroform. The resulting suspension is next left for some time at room temperature and is then warmed to

50—60°C for 1 hour. It is concentrated to about one-third in vacuo and the suspension is allowed to cool. The precipitate which separates out is filtered off and dissolved in ethylene chloride. The solution is dried over sodium sulphate, filtered and evaporated. The resulting material, in 1,000 ml of methanol, is additionally left to stand with 60 ml of 15% strength sodium hydroxide solution over the weekend and the mixture is then warmed to 60°C for 2 hours. The methanol is removed in vacuo. The aqueous phase is diluted with water and twice extracted with methylene chloride. The combined dried extracts give 15.7 g of a viscous yellow oil which is chomatographed on 300 g of silica gel. The eluate is recrystallised from isopropanol/petroleum ether. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - (2 - phenylpropyl) - piperazine of melting point 100—103°C is obtained.

The starting material can be manufactured as follows: 42.2 g of 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - benzyl - piperazine are suspended in 420 ml of acetic anhydride and left to stand over the weekend at room temperature. The suspension is evaporated to dryness in vacuo, the residue is dissolved in methylene chloride and the solution in successively washed with water, sodium carbonate solution and water. The dried methylene chloride solution is evaporated and the residue is recrystallised from chloroform-alcohol. 1 - [5 - (Dimethylsulphamoyl) - N - acetyl - anthraniloyl] - 4 - benzyl - piperazine of melting point 174—78°C is obtained. 34.7 g of this material in 350 ml of glacial acetic acid are subjected to hydrogenating debenzylation with hydrogen in the presence of palladium/charcoal at 20—35°C. The reaction mixture is freed from the catalyst by filtration and is evaporated in vacuo. The residue is dissolved in water and the solution is rendered alkaline with sodium hydroxide solution and extracted with chloroform. The chloroform extracts are combined, dried and evaporated. The resulting crude 1 - [5 - (dimethylsulphamoyl) - N - acetyl - anthraniloyl] - piperazine is then reacted with 8.1 g of hydratropaldehyde and 3.4 g of 98—100% strength formic acid, an exothermic reaction taking place. The mixture is slowly heated, whereupon a homogeneous solution is formed. At about 100°C, evolution of gas commences; this has practically ceased after 5 minutes at 120°C. The mixture is heated at 120°C for a further 25 minutes and allowed to cool. The cool reaction mixture is dissolved in methylene chloride and the resulting solution is washed with water. The organic phase is separated off, dried and evaporated. 1 - [5 - Dimethylsulphamoyl - 2 - acetamido - benzoyl)] - 4 - (2 - phenylpropyl) - piperazine is thus obtained in the form of tacky crystals and is further processed without additional purification.

Example 4

7 g of 5 - (dimethylsulphamoyl) - 2 - nitro - benzoic acid in 70 ml of thionyl chloride are heated to the boil for 3 hours. The excess thionyl chloride is removed in vacuo and the residue is recrystallised from ether-petroleum ether. 5 - (Dimethylsulphamoyl) - 2 - nitro - benzyl chloride of melting point 69—70°C is obtained. This acid chloride is dissolved in 30 ml of absolute dioxane. A solution of 6 g of N - phenylethylpiperazine in 80 ml of absolute dioxane is then added dropwise thereto at about 10°C, whilst stirring, and the mixture is stirred overnight at room temperature. Water and sodium carbonate solution are successively added to the dioxane solution and the mixture is extracted with chloroform. The chloroform solution is dried and evaporated. The product is hydrogenated directly in 150 ml of ethanol in the presence of palladium on charcoal. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - (β - phenylethyl) - piperazine of melting point 144—5°C is thus obtained.

Example 5

The following compounds can also be prepared analogously to the description in Examples 1 and 2: 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (*m* - chlorophenyl) - ethyl] - piperazine; 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - (3 - phenylpropyl) - piperazine, melting point 130—137°C; 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (*p* - chlorophenyl) - ethyl] - piperazine, melting point 80—82°C; 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (*p* - methoxyphenyl) - ethyl] - piperazine, melting point 138°C; 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - (3 - phenyl - propen - 2 - yl) - piperazine, melting point 173—6°C; 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (2 - pyridyl) - ethyl] - piperazine, melting point 176°C (with decomposition); 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [3 - (2 - pyridyl) - propyl] - piperazine, 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (4 - pyridyl) - ethyl] - piperazine, melting point 95—100°C; 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [3 - (3 - pyridyl) - propyl] - piperazine and 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (*p* - fluorophenyl) - ethyl - piperazine.

Example 6

Tablets containing 250 mg of active compound and having the following composition were prepared:

Composition per tablet

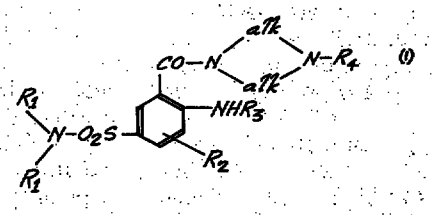
1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - [β - phenylethyl) - piperazine	250.0 mg
Mannitol	60.0 mg
Wheat starch	91.0 mg
Gelatine	4.0 mg
Talc	13.0 mg
Magnesium stearate	2.0 mg
	420.0 mg

Manufacture

The 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - (β - phenylethyl) - piperazine or a salt, for example the hydrochloride, thereof, is mixed with the mannitol and a part of the wheat starch and the mixture is forced through a sieve. The gelatine is dissolved in a 5-fold amount of water on a water bath and the powder mixture is kneaded with the solution until a plastic mass has been produced. The mass is forced through a sieve of approx. 3 mm mesh width and dried and the dried granules are again forced through a sieve. The remaining wheat starch, talc and magnesium stearate are then admixed. The resulting mixture is pressed to give tablets weighing 420 mg (and having a breaking groove)

WHAT WE CLAIM IS:—

1. 2 - Amino - 5 - sulphamoyl - benzoic acid amides of the general formula



(I)

wherein R_1 denotes a lower alkyl group, R_2 denotes a hydrogen or halogen atom or a trifluoromethyl, lower alkyl or lower alkoxy group, R_3 denotes a hydrogen atom or a hydroxyl or lower alkyl group, R_4 denotes a group of the formula

$$—A—Y—R_5,$$

wherein A represents a lower alkyl or lower alkenyl radical, Y represents a hetero atom or a direct bond and R_5 represents an aryl radical, and alk denotes a lower alkylene radical which separates the nitrogen atoms by 2 or 3 C atoms

2. 2 - Amino - 5 - sulphamoyl - benzoic acid amides of the formula I, as claimed in Claim 1, wherein R_1 denote identical alkyl groups with 1 to 4 C atoms, R_2 denotes a hydrogen atom or a halogen atom up to atomic number 17, R_3 denotes a hydrogen atom, a hydroxyl group or an alkyl group with 1 to 4 C atoms, R_4 denotes a phenyl-lower alkyl or phenyl-lower alkenyl radical optionally monosubstituted or polysubstituted in the phenyl part by substituent(s) selected from lower alkyl and lower alkoxy groups, halogen atoms and trifluoromethyl groups, or represents a pyridyl- or thienyl-lower alkyl or -lower alkenyl radical optionally substituted by lower alkyl and/or lower alkoxy radicals at one or more C atoms in the pyridyl or thienyl part, all these R_4 radicals having 1 to 6 C atoms in the aliphatic part, and alk denotes an alkylene radical with 2 to 4 C atoms.

3. 5 - Sulphamoyl - anthranilic acid amides of the formula I, as claimed in Claim 1, wherein R_1 is a methyl group, R_2 is a chlorine atom, a methoxy or methyl group or a hydrogen atom, R_3 is a hydrogen atom or an alkyl group with 1 to 4 C atoms, R_4 is a phenyl-lower alkyl or phenyl-lower alkenyl radical optionally substituted as defined in Claim 2, or represents a pyridyl- or thienyl- lower alkyl or -lower alkenyl radical optionally substituted as defined in Claim 2, all these R_4 radicals having 1 to 5 C atoms in the aliphatic part, and alk denotes 1,2 - alkylene with 2 to 4 C atoms.

4. 5 - Sulphamoyl - anthranilic acid amides of the formula I as claimed in Claim 1, wherein R_1 is a methyl group, R_2 is a hydrogen atom, R_3 is a hydrogen atom or an ethyl or methyl group, R_4 denotes an R_5-methyl, 3 - R_5 - propyl, 2 - R_5 - ethyl, 2 - methyl - 2 - R_5 - ethyl or 3 - R_5 - prop - 2 - enyl radical wherein R_5 is a phenyl radical which is optionally substituted as defined in claim 2 or represents a pyridyl radical which is optionally substituted as defined in Claim 2, and alk is a propylene - 1,2 or ethylene radical.

5. 5 - Sulphamoyl anthranilic acid amides of the Formula I, as claimed in Claim 1, wherein R_1 is a methyl group, R_2 is a hydrogen atom, R_3 is a hydrogen atom, or an ethyl or methyl group, R_4 denotes a 2 - R_5 - ethyl, 2 - methyl - 2 - R_5 - ethyl or 3 - R_5 - prop - 2 - enyl radical wherein R_5 is a phenyl radical which is optionally substituted as defined in claim 2 or represents a pyridyl radical which is optionally substituted as defined in Claim 2, and alk denotes a propylene - 1,2 or ethylene radical.

6. 5 - Sulphamoyl anthranilic acid amides of the Formula I, as claimed in Claim 1, wherein R_1 is a methyl group, R_2 is a hydrogen atom, R_3 is a hydrogen atom or an ethyl group, R_4 denotes an R_5' - methyl, 3 - R_5' - propyl, 2 - R_5' - ethyl, 2 - methyl - 2 - R_5' - ethyl or 3 - R_5' - prop - 2 - enyl radical, wherein R_5' denotes an optionally lower - alkoxylated or halogenated phenyl radical or denotes a pyridyl radical and alk is an ethylene radical.

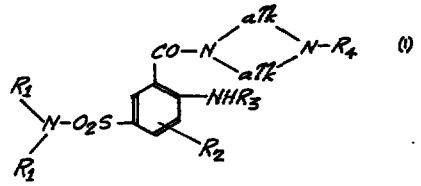
Composition per tablet	
1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - [β - phenylethyl) - piperazine	250.0 mg
Mannitol	60.0 mg
Wheat starch	91.0 mg
Gelatine	4.0 mg
Talc	13.0 mg
Magnesium stearate	2.0 mg
	420.0 mg

Manufacture

The 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - (β - phenylethyl) - piperazine or a salt, for example the hydrochloride, thereof, is mixed with the mannitol and a part of the wheat starch and the mixture is forced through a sieve. The gelatine is dissolved in a 5-fold amount of water on a water bath and the powder mixture is kneaded with the solution until a plastic mass has been produced. The mass is forced through a sieve of approx. 3 mm mesh width and dried and the dried granules are again forced through a sieve. The remaining wheat starch, talc and magnesium stearate are then admixed. The resulting mixture is pressed to give tablets weighing 420 mg (and having a breaking groove)

WHAT WE CLAIM IS:—

1. 2 - Amino - 5 - sulphamoyl - benzoic acid amides of the general formula



(I)

wherein R_1 denotes a lower alkyl group, R_2 denotes a hydrogen or halogen atom or a trifluoromethyl, lower alkyl or lower alkoxy group, R_3 denotes a hydrogen atom or a hydroxyl or lower alkyl group, R_4 denotes a group of the formula

$$—A—Y—R_5,$$

wherein A represents a lower alkyl or lower alkenyl radical, Y represents a hetero atom or a direct bond and R_5 represents an aryl radical, and alk denotes a lower alkylene radical which separates the nitrogen atoms by 2 or 3 C atoms

2. 2 - Amino - 5 - sulphamoyl - benzoic acid amides of the formula I, as claimed in Claim 1, wherein R_1 denote identical alkyl groups with 1 to 4 C atoms, R_2 denotes a hydrogen atom or a halogen atom up to atomic number 17, R_3 denotes a hydrogen atom, a hydroxyl group or an alkyl group with 1 to 4 C atoms, R_4 denotes a phenyl-lower alkyl or phenyl-lower alkenyl radical optionally monosubstituted or polysubstituted in the phenyl part by substituent(s) selected from lower alkyl and lower alkoxy groups, halogen atoms and trifluoromethyl groups, or represents a pyridyl- or thienyl-lower alkyl or -lower alkenyl radical optionally substituted by lower alkyl and/or lower alkoxy radicals at one or more C atoms in the pyridyl or thienyl part, all these R_4 radicals having 1 to 6 C atoms in the aliphatic part, and alk denotes an alkylene radical with 2 to 4 C atoms.

3. 5 - Sulphamoyl - anthranilic acid amides of the formula I, as claimed in Claim 1, wherein R_1 is a methyl group, R_2 is a chlorine atom, a methoxy or methyl group or a hydrogen atom, R_3 is a hydrogen atom or an alkyl group with 1 to 4 C atoms, R_4 is a phenyl-lower alkyl or phenyl-lower alkenyl radical optionally substituted as defined in Claim 2, or represents a pyridyl- or thienyl- lower alkyl or -lower alkenyl radical optionally substituted as defined in Claim 2, all these R_4 radicals having 1 to 5 C atoms in the aliphatic part, and alk denotes 1,2 - alkylene with 2 to 4 C atoms.

4. 5 - Sulphamoyl - anthranilic acid amides of the formula I as claimed in Claim 1, wherein R_1 is a methyl group, R_2 is a hydrogen atom, R_3 is a hydrogen atom or an ethyl or methyl group, R_4 denotes an R_5-methyl, 3 - R_5 - propyl, 2 - R_5 - ethyl, 2 - methyl - 2 - R_5 - ethyl or 3 - R_5 - prop - 2 - enyl radical wherein R_5 is a phenyl radical which is optionally substituted as defined in claim 2 or represents a pyridyl radical which is optionally substituted as defined in Claim 2, and alk is a propylene - 1,2 or ethylene radical.

5. 5 - Sulphamoyl anthranilic acid amides of the Formula I, as claimed in Claim 1, wherein R_1 is a methyl group, R_2 is a hydrogen atom, R_3 is a hydrogen atom, or an ethyl or methyl group, R_4 denotes a 2 - R_5 - ethyl, 2 - methyl - 2 - R_5 - ethyl or 3 - R_5 - prop - 2 - enyl radical wherein R_5 is a phenyl radical which is optionally substituted as defined in claim 2 or represents a pyridyl radical which is optionally substituted as defined in Claim 2, and alk denotes a propylene - 1,2 or ethylene radical.

6. 5 - Sulphamoyl anthranilic acid amides of the Formula I, as claimed in Claim 1, wherein R_1 is a methyl group, R_2 is a hydrogen atom, R_3 is a hydrogen atom or an ethyl group, R_4 denotes an R_5' - methyl, 3 - R_5' - propyl, 2 - R_5' - ethyl, 2 - methyl - 2 - R_5' - ethyl or 3 - R_5' - prop - 2 - enyl radical, wherein R_5' denotes an optionally lower - alkoxylated or halogenated phenyl radical or denotes a pyridyl radical and alk is an ethylene radical.

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7. 5 - Sulphamoyl anthranilic acid amides of the Formula I as claimed in Claim 1, wherein R_1 is a methyl group, R_2 is a hydrogen atom, R_3 is a hydrogen atom or an ethyl group, R_4 denotes a 2 - R_5' - ethyl, 2 - methyl - 2 - R_5' - ethyl or 3 - R_5' - prop - 2 - enyl radical, wherein R_5' denotes an optionally lower-alkoxylated phenyl radical or denotes a pyridyl radical and alk is an ethylene radical.

8. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - benzyl - piperazine.

9. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - (β - phenyl - ethyl) - piperazine.

10. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - (2 - phenyl - propyl) - piperazine.

11. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - (3 - phenyl - propyl)- piperazine.

12. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (p - chlorophenyl) ethyl] - piperazine.

13. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (p - methoxyphenyl-ethyl] - piperazine.

14. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - [3 - (phenyl - propen - 2 - yl) - piperazine.

15. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (2 - pyridyl) - ethyl] - piperazine.

16. 1 - [5 - (Dimethylsulphamoyl) -anthranilolyl] - 4 - [3 - (2 - pyridyl) - propyl] - piperazine.

17. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - [3 -(3 - pyridyl) - propyl] - piperazine.

18. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (4 - pyridyl) - ethyl] - piperazine.

19. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (m - chlorophenyl) - ethyl] - piperazine.

20. 1 - [5 - (Dimethylsulphamoyl) - anthraniloyl] - 4 - [β - p - fluorophenyl) - ethyl] - piperazine.

21. A compound as claimed in any one of Claims 1—3, in the form of a racemate mixture.

22. A compound as claimed in any one of Claims 1—3, 5, 7 and 10, in the form of the racemate.

23. A compound as claimed in any one of Claims 1—3, 5, 7 and 10, in the form of an optical antipode.

24. A compound as claimed in any one of Claims 1 to 23 in the form of a salt.

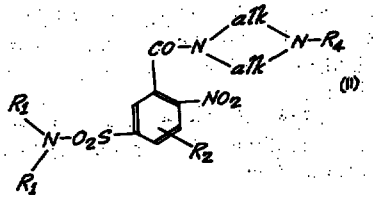
25. A compound as claimed in any one of Claims 1—3, 7—17 and 21—23, in the form of a salt.

26. A compound as claimed in any one of Claims 1 to 23, in the form of a physiologically tolerable salt.

27. A compound as claimed in any one of Claims 1—3, 5, 7—17 and 21—23, in the form of a physiologically tolerable salt.

28. Process for the manufacture of a 2 - amino - 5 - sulphamoyl - benzoic acid amide of the general formula I as claimed in claim 1, wherein

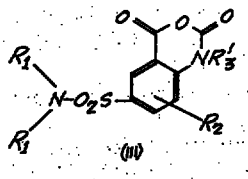
a) the nitro group in a 2 - nitro - 5 - sulphamoylbenzoic acid amide of the formula II



(II)

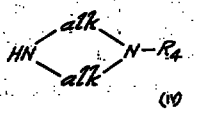
wherein R_1, R_2, R_4 and alk have the meanings given in claim 1, is reduced, or

b) a functional derivative of a 2 - amino - 5 - sulphamoylbenzoic acid of the formula III



(III)

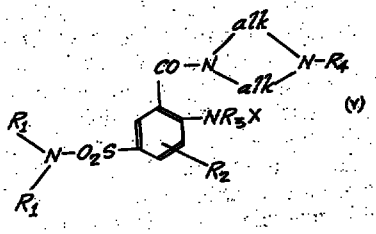
wherein R_1 and R_2 have the meanings given in Claim 1 and R_3' represents a hydrogen atom or a lower alkyl group, is reacted with an amine of the formula IV



(IV)

wherein alk and R_4 have the meanings given in Claim 1, or

c) X is split off from a 5 - sulphamoyl - anthranilic acid amide of the formula V



(V)

wherein R_1, R_2, R_3 R_4 and alk have the meanings given in Claim 1 and X denotes an acyl radical and, if desired, in resulting 2 - amino - 5 - sulphamoyl - benzoic acid amides substituents are introduced, modified and split off within the scope of the definition of formula I and/or a resulting

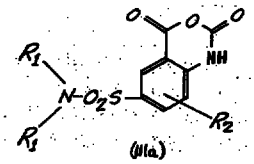
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racemate mixture is separated into the pure racemates and/or a resulting racemate is resolved into the optical antipodes and/or a resulting free compound is converted into a salt or a resulting salt is converted into the free compound.

29. A process according to Claim 28, wherein the reduction of the nitro group in a 2 - nitro - 5 - sulphamoyl - benzoic acid amide of the formula II is effected by catalytic hydrogenation.

30. Process according to Claim 28 or Claim 29, wherein the reaction is carried out with hydrogen in the presence of palladium on charcoal.

31. Process according to Claim 28, wherein a 5 - sulphamoyl - isatoic anhydride of the formula IIIa



(IIIa)

wherein R_1 and R_2 have the indicated meanings, is employed as the functional derivative of 2 - amino - 5 - sulphamoyl - benzoic acid of the formula III.

32. Process according to Claim 28, wherein a 5 - sulphamoyl - anthranilic acid amide of the formula V, wherein X is a lower alkanoyl radical, is hydrolysed in the presence of a basic agent.

33. Process according to Claim 28, wherein a starting material is formed *in situ* under the reaction conditions or a reactant is employed in the form of a salt, if appropriate.

34. Process according to any one of Claims 28 to 33, wherein there is manufactured a 2 - amino - 5 - sulphamoyl - benzoic acid amides of the formula I as claimed in Claim 2.

35. Process according to any one of Claims 28 to 33, wherein there is manufactured a 5 - sulphamoyl - anthranilic acid amide of the formula I as claimed in Claim 3.

36. Process according to any one of Claims 28 to 33, wherein there is manufactured a 5 - sulphamoyl - anthranilic acid amide of the formula I as claimed in Claim 4.

37. Process according to any one of Claims 28 to 33, wherein there is manufactured a 5 - sulphamoyl - anthranilic acid amide of the formula I as claimed in Claim 5.

38. Process according to any one of Claims 28 to 33, wherein there is manufactured a 5 - sulphamoyl - anthranilic acid amide of the formula I as claimed in Claim 6.

39. Process according to any one of Claims 28 to 33, wherein there is manufactured a 5 - sulphamoyl - anthranilic acid amide of the formula I as claimed in Claim 7.

40. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - benzyl - piperazine is manufactured.

41. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - (β - phenylethyl) - piperazine is manufactured.

42. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - (2 - phenylpropyl) - piperazine is manufactured.

43. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - (3 - phenylpropyl) - piperazine is manufactured.

44. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (p - chlorophenyl) - ethyl] - piperazine is manufactured.

45. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - (β - (p - methoxyphenyl) - ethyl] - piperazine is manufactured.

46. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [3 - phenylprop - 2 - enyl) - piperazine is manufactured.

47. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (2 - pyridyl) - ethyl] - piperazine is manufactured.

48. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [3 - (2 - pyridyl) - propyl] - piperazine is manufactured.

49. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (4 - pyridyl) - ethyl - piperazine is manufactured.

50. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [3 - (3 - pyridyl) - propyl] - piperazine is manufactured.

51. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (m - chlorophenyl) - ethyl] - piperazine is manufactured.

52. Process according to any one of Claims 28 to 33, wherein 1 - [5 - (dimethylsulphamoyl) - anthraniloyl] - 4 - [β - (p - fluorophenyl) - ethyl] - piperazine is manufactured.

53. Process according to any one of Claims 28 to 35, wherein the compounds of formula I is manufactured in the form of a racemate mixture.

54. Process according to any one of Claims 28—35, 37, 39 and 42 wherein the compound of formula I is manufactured in the form of a racemate.

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55. Process according to any one of Claims 28—35, 37, 39 and 42, wherein the compound of formula I is manufactured in the form of the optical antipodes.

56. Process according to any one of Claims 28 to 55, wherein the compound of formula I is manufactured in the form of a salt.

57. Process according to any one of Claims 28—35, 37, 39—50 and 53—55, wherein the compound of formula I is manufactured in the form of a salt.

58. Process according to any one of Claims 28 to 55, wherein the compound of formula I is manufactured in the form of a physiologically tolerable salt.

59. Process according to any one of Claims 28—35, 37, 39—50 and 53—55, wherein the compound of formula I is manufactured in the form of a physiologically tolerable salt.

60. A pharmaceutical preparation which comprises a compound of the general formula I as claimed in any one of Claims 1—24, or a physiologically tolerable salt of such a compound, together in admixture or conjunction with a pharmaceutically suitable carrier.

61. A pharmaceutical preparation which comprises a compound of the general formula I as claimed in any one of claims 1—3, 5, 7—17, 21—23 and 25, or a physiologically tolerable salt of such a compound, in admixture or conjunction with a pharmaceutically suitable carrier.

62. A pharmaceutical preparation as claimed in Claim 60 or Claim 61 in unit dosage form.

63. A pharmaceutical preparation as claimed in Claim 62, which comprises from 15 to 350 mg of the compound or salt per unit dose for oral administration.

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