



PATENT SPECIFICATION

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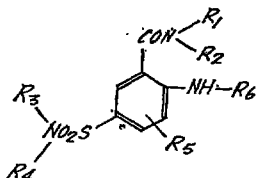
COMPLETE SPECIFICATION

New Anthranilic Acid Amides and process for preparing same

We, CIBA LIMITED, 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:—

The present invention is concerned with new anthranilic acid amides and with their manufacture and use.

The present invention provides compounds of the formula



in which R_1 and R_2 each represents a lower alkyl group which may be substituted by a hydroxyl group or by a di-(lower alkyl)-amino or together represent a lower alkylene group, a monooxa-lower alkylene group or a monoaza-lower alkylene group whose aza nitrogen atom may be substituted by a lower alkyl group or by a lower hydroxylalkyl group, R_3 and R_4 each represents a lower alkyl group, R_5 represents a hydrogen or halogen atom or a lower alkyl, lower alkoxy or trifluoromethyl group and R_6 represents a hydrogen atom or the acyl radical of an aliphatic carboxylic acid containing up to 10 carbon atoms or of an araliphatic or aromatic carboxylic acid, and the acid addition salts of these new compounds that contain basic groups.

As lower alkyl groups which may be substituents of the carbamyl group, there may be mentioned, for example, methyl, ethyl, *n*-propyl or isopropyl, or straight-chained or branched butyl, pentyl, hexyl or heptyl bound in any

position. Corresponding groups substituted by hydroxyl or di-(lower alkyl)-amino groups are, for example, dimethyl-, methylethyl- or diethyl-amino-ethyl or -propyl or 2-hydroxy-ethyl or -propyl. As examples of the bivalent radicals which R_1 and R_2 taken together may represent, there may be mentioned butylene-(1:4), pentylene-(1:5) hexylene-(1:5), hexylene-(1:6), or heptylene-(2:6); 3-oxa- or 3-aza-pentylene-(1:5) or -hexylene-(1:6); 3-methyl-, 3-ethyl- or 3-propyl-3-aza-pentylene-(1:5) or -hexylene-(1:6); 4-methyl-4-aza-heptylene-(2:6) or 3-(β -hydroxyethyl)-3-aza-pentylene-(1:5).

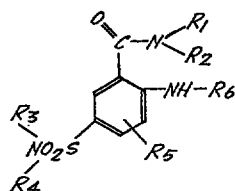
The term "lower" in qualifying alkyl, alkylene, alkanoyl and alkoxy groups is used herein to mean those groups containing up to 7 carbon atoms.

The dialkylsulphamyl group in the 5-position contains, for example, the above-mentioned lower alkyl groups. The acyl radicals which may substitute the amino group in the 2-position, are radicals of aliphatic carboxylic acids containing up to 10 carbon atoms or of araliphatic or aromatic carboxylic acids, for example lower alkoxy carbonyl radicals, such as methoxy- or ethoxy-carbonyl radicals, fatty acid radicals, for example lower alkanoyl radicals, such as acetyl, propionyl, butyryl, pivalyl, valeroyl or caproyl, or phenyl-lower alkanoyl radicals, for example phenylacetyl radicals, or benzoyl radicals which may be substituted in the aromatic nuclei, for example by lower alkyl groups, such as those mentioned above, lower alkoxy groups, for example methoxy, ethoxy, butoxy or pentyloxy groups, halogen atoms, such as fluorine, chlorine or bromine atoms, or trifluoromethyl groups.

The new compounds may be substituted in the 3-, 4- or 6-position. Substituents for these positions are halogen atoms, such as fluorine or chlorine atoms, trifluoromethyl groups, lower

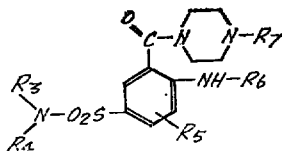
alkyl groups, for example those mentioned above, or lower alkoxy groups such as methoxy, ethoxy, propoxy or butoxy groups.

- The new compounds have valuable pharmacological properties, in particular anti-inflammatory and anti-allergic properties. Thus, for example, in rats, guinea pigs and rabbits, they suppress inflammatory processes and allergic reactions. Accordingly, they can be employed as anti-phlogistics and anti-allergics. Furthermore, they reduce blood pressure, for example in animal experiments on the rat, and may be used as hypotensives. They are also valuable intermediate products for the manufacture of other substances, for example of pharmacologically active substances. Particularly valuable are compounds of the formula



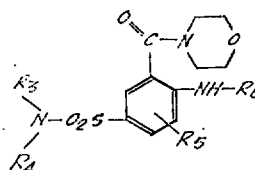
- in which R_1 and R_2 each represents a lower alkyl group or together represent a lower alkylene or a mono-oxa- or -aza-lower alkylene group, R_3 and R_4 each represents a lower alkyl group, R_5 represents in particular a hydrogen atom but may also represent a lower alkyl group, a chlorine atom or a trifluoromethyl group, and R_6 represents a hydrogen atom or the acyl radical of an aliphatic, araliphatic or aromatic carboxylic acid containing up to 10 carbon atoms.

- The compounds of the formula



- in which R_3 and R_4 each represents a lower alkyl group, R_5 represents a lower alkyl group, a chlorine atom, a trifluoromethyl group or, more especially, a hydrogen atom, R_6 represents a hydrogen atom, a lower alkanoyl group or a benzoyl group, which benzoyl group may be substituted by one or more substituents selected from lower alkyl groups, halogen atoms, trifluoromethyl groups and lower alkoxy groups, and R_7 represents a hydrogen atom, a lower alkyl group or a lower hydroxyalkyl group, and particularly 5-(dimethylsulphamyl)-anthranilic acid-(N'-methyl-piperazide) and 5-(dimethylsulphamyl)-anthranilic acid-[N'-(β -hydroxyethyl)-piperazide], are particularly outstanding on account of their antiinflammatory effect.

The compounds of the formula



in which R_3 and R_4 each represents a lower alkyl group, R_5 represents a lower alkyl group, a chlorine atom, a trifluoromethyl group or more particularly a hydrogen atom, and R_6 represents a hydrogen atom, a lower alkanoyl group or a benzoyl group, which benzoyl group may be substituted by one or more substituents selected from lower alkyl groups, halogen atoms, trifluoromethyl groups and lower alkoxy groups, and more especially 5-(dimethylsulphamyl)-anthranilic acid morpholide, are especially valuable on account of their hypotensive effect.

The new compounds are prepared by methods known *per se*. For example they are obtained when a pure or mixed anhydride of a 5-(dialkylsulphamyl)-anthranilic acid having a free or acylated amino group in the 2-position or an inner anhydride of an N-acyl-5-(dialkylsulphamyl)-anthranilic acid, that is to say a 6-(dialkylsulphamyl)-4-H-3:1-benzoxazine-4-one, for example an inner anhydride of an N-acetyl-5-(dialkylsulphamyl)-anthranilic acid or a 5-(dialkylsulphamyl)-isatoic anhydride or an inner anhydride of an N-(α -hydroxyalkyl)-5-(dialkylsulphamyl)-anthranilic acid, for example an N-hydroxymethyl-5-(dialkylsulphamyl)-anthranilic acid, is reacted with a secondary amine of the formula NHR_1R_2 , in which R_1 and R_2 have the meanings given above, or, in an appropriate N:N-aliphatically disubstituted 2-nitro-5-(dialkylsulphamyl)-benzoic acid amide the nitro group is converted by reduction into a free amino group and, if desired, a resulting 2-amino compound is acylated or a resulting 2-acylamino compound is hydrolysed.

Mixed anhydrides are, for example, those with carbonic acid monoalkyl esters, such as carbonic acid monoethyl or isobutyl esters.

The reaction of the said compounds with the secondary amine is effected in a manner known *per se*, in particular in the presence of a solvent or diluent, in the presence or absence of reaction accelerators, at room temperature or preferably at an elevated temperature and, if necessary, in a closed vessel under pressure and/or under an inert gas, for example nitrogen.

When inner anhydrides of N-(α -hydroxyalkyl)-5-(dimethylsulphamyl)-anthranilic acids are used as starting materials, the hydroxyalkyl group is split off during the reaction. When



inner anhydrides of N - acyl - 5 - (dialkyl-sulphamyl) - anthranilic acids are used as starting materials, the reaction conditions may, if desired, be so chosen that the acyl radical is split off simultaneously.

The reduction of the 2-nitro group is effected by known methods. It may, for example, be carried out by nascent hydrogen (for example with iron and hydrochloric acid or with aluminium amalgam) or with catalytically activated hydrogen, such as hydrogen in the presence of a platinum, nickel or palladium catalyst.

Further substituents can be introduced into the compounds obtained, or existing substituents present can be modified or split off, by known methods. Thus, 2-amino compounds obtained can be acylated, for example, by reaction with reactive functional derivatives of carboxylic acids, such as anhydrides or halides, or 2-acylamino compounds obtained can be hydrolysed, in particular by reaction with alkaline agents.

The said reactions are carried out in a conventional manner in the presence or absence of solvents or diluents, acid or basic condensing agents and/or catalysts at lowered, ordinary or elevated temperature, if required in a closed vessel under elevated pressure and/or under an inert gas atmosphere.

Depending on the conditions of the process and the starting materials, the final compounds containing basic groups are obtained in the free form or in the form of their acid addition salts, which are likewise included within the scope of the present invention. The acid addition salts of these final compounds can be converted into the free bases in a manner known *per se*, for example with alkalis or ion exchangers. From these free bases salts can be recovered by reaction with organic or inorganic acids, in particular those which are suitable for the formation of therapeutically usable salts. As such acids there may be mentioned, for example, hydrohalic acids, sulphuric acids, phosphoric acids, nitric acid, perchloric acid; aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulphonic acids, such as formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic or pyroracemic acid; phenyl-acetic, benzoic, *p*-aminobenzoic, anthranilic, *p*-hydroxybenzoic, salicylic, *p*-aminosalicylic or embonic acid, methanesulphonic, ethanesulphonic, hydroxyethanesulphonic, *ethylene*-sulphonic acid; halobenzenesulphonic, toluenesulphonic, naphthalenesulphonic acids or sulphamyl acid; or methionine, tryptophan, lysine or arginine.

These or other acid addition salts of the new compounds containing basic groups, such as for example the picrates, can also be used for purifying the bases obtained by converting the bases into salts, separating the latter and

liberating the bases from the salts again. Owing to the close relationship between the bases in the free form and in the form of their acid addition salts, there are to be understood as being correspondingly and appropriately included, under the free bases in the foregoing and hereinafter, if required, also the corresponding acid addition salts.

The invention also relates to those embodiments of the process in which the starting point is a compound obtainable as intermediate product at any stage and the missing steps of the process are carried out, or the process is discontinued at any stage at which a compound of the invention is formed, or in which a starting material is formed under the reaction conditions or is used in the form of an acid addition salt. For the reactions of the invention starting materials are preferably used which yield the above-mentioned preferred compounds.

The starting materials are known, or, if they are new, can be prepared by methods known *per se*.

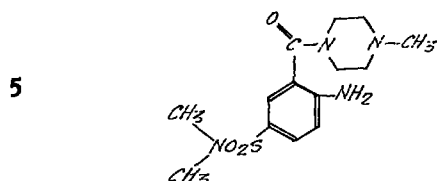
The new compounds can be employed as medicaments, for example in the form of pharmaceutical preparations, which contain them in admixture or conjunction with a pharmaceutical organic or inorganic, solid or liquid, carrier suitable for enteral, parenteral or local application. The new compounds that contain basic groups may be present in the pharmaceutical preparations in the free form or in the form of their physiologically tolerable acid addition salts. For forming these preparations there are used substances which do not react with the new compounds, such as, for example, water, gelatine, lactose, starch, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, petroleum jelly, cholesterol or other known carriers for medicaments. The pharmaceutical preparations may be in the form, for example, of tablets, dragées, ointments, creams or in liquid form as solutions, suspensions or emulsions. If desired, they are sterilised and/or contain auxiliary substances, such as preserving, stabilising, wetting or emulsifying agents, salts for altering the osmotic pressure or buffers. They may also contain other therapeutically valuable substances. The preparations, which are also to be employed in veterinary medicine, are obtained by conventional methods.

The following Examples illustrate the invention.

EXAMPLE 1

A solution of 57.3 grams of 5-(dimethylsulphamyl)-2-nitrobenzoic acid-(N'-methylpiperazide) in 2500 ml of ethanol is shaken in the presence of 30 grams of a nickel catalyst (Rupe nickel) in a hydrogen atmosphere until the theoretical quantity of hydrogen has been consumed. The catalyst is then filtered off, the filtrate is concentrated to a volume of 150

ml and petroleum ether is added to the filtrate. This precipitates 5 - (dimethylsulphamyl)-anthranilic acid-(N'-methyl-piperazide) of the formula



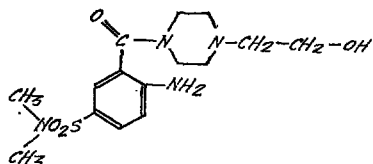
in the form of white crystals having a melting point of 151—152°C. By reacting the same with alcoholic hydrochloric acid, the monohydrochloride with a melting point of 280—282°C is obtained.

The starting material can be prepared as follows:

To a solution of 80 grams of N-methyl-piperazine in 800 ml of absolute dioxan which has been cooled to 10°C there is added drop by drop while stirring a solution of 109 grams of 5-(dimethylsulphamyl)-2-nitrobenzoic acid chloride in 300 ml of absolute dioxan. The reaction mixture is stirred further for 5 hours at room temperature, water and saturated sodium hydroxide solution are thereupon added thereto and the mixture is extracted with chloroform. The organic phase, washed with water, is dried with magnesium sulphate and evaporated *in vacuo*. The solid residue is recrystallised from ethanol-petroleum ether and 5 - (dimethylsulphamyl) - 2 - nitrobenzoic acid-(N' - methylpiperazide) having a melting point of 170—172°C is obtained.

EXAMPLE 2

A solution of 10 grams of 5-(dimethylsulphamyl) - 2 - nitrobenzoic acid - [N' - (β - hydroxyethyl) - piperazide] in 100 ml of ethanol is hydrogenated in the presence of 1 gram of a nickel catalyst (Rupe nickel). After the theoretical quantity of hydrogen has been consumed, the solution is filtered off from the catalyst and the filtrate is evaporated *in vacuo*. On recrystallisation of the residue from ethanol-petroleum ether, 5 - (dimethylsulphamyl) - anthranilic acid - [N' - (β - hydroxyethyl) - piperazide] of the formula



is obtained as colourless crystals having a melting point of 98—100°C. The monohydrochloride melts at 245—247°C.

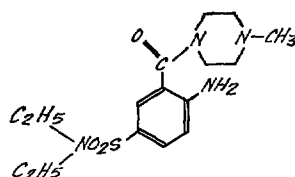
The starting material can be prepared in the following manner:

To a solution of 9 grams of N-(β-hydroxyethyl)-piperazine in 100 ml of toluene which has been cooled to 0°C there is added drop

by drop while stirring well a solution of 10 grams of 5-(dimethylsulphamyl)-2-nitrobenzoic acid chloride in 50 ml of toluene. After the mixture has been stirred for 3 hours at room temperature, the precipitated substance is filtered off, stirred with dilute sodium hydroxide solution and filtered off again. After drying, the substance is crystallised from ethanol and 5-(dimethylsulphamyl)-2-nitrobenzoic acid-[N'-(β-hydroxyethyl)-piperazide] having a melting point of 138—139°C is obtained.

EXAMPLE 3

14.7 grams of 5-(diethylsulphamyl)-2-nitrobenzoic acid-(N'-methyl-piperazide) are dissolved in 500 ml of methanol and hydrogenated in the presence of 1 gram of palladium carbon until the absorption of hydrogen ceases. The catalyst is filtered off, the filtrate evaporated under reduced pressure and the residue crystallized from a mixture of ethanol and petroleum ether. The resulting 5-(diethylsulphamyl)-anthranilic acid-(N'-methylpiperazide) of the formula



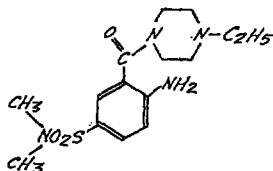
melts at 144—145°C. The hydrochloride melts at 265°C. The 5-(diethylsulphamyl)-2-nitrobenzoic acid-(N'-methylpiperazide) used as starting material may be prepared as follows:

74 grams of 5-(chlorosulphonyl)-2-nitrobenzoic acid are introduced in portions and with stirring into a solution of 280 ml of diethylamine in 700 ml of water. The batch is then stirred for 4 hours, active carbon is added, the reaction mixture is filtered and the filtrate is acidified with concentrated hydrochloric acid with ice-cooling. The precipitated substance is dried and then recrystallized from ethyl acetate or benzene and melts at 141—142°C. 35 grams of the so-obtained 5 - (diethylsulphamyl) - 2 - nitrobenzoic acid are converted into 5 - (diethylsulphamyl) - 2 - nitro - benzoyl chloride melting at 69—70°C by being boiled for 3 hours with 300 ml of thionyl chloride, evaporation and recrystallization from a mixture of benzene and petroleum ether. A solution of 15 grams of this acid chloride in 30 ml of absolute dioxan is poured, with stirring, into a solution of 8 grams of N-methyl-piperazine in 100 ml of absolute dioxan, previously cooled to 10°C. The batch is stirred for 3 hours at room temperature, and is then treated with water and sodium carbonate solution, extracted with chloroform, and the chloroform solution is washed with water, dried over magnesium sulphate and evaporated under reduced pres-

sure. The residue is recrystallized from a mixture of ethanol and petroleum ether to yield 5 - (diethylsulphamyl) - 2 - nitrobenzoic acid - (N' - methylpiperazide) melting at 95—96°C.

EXAMPLE 4

A solution of 8 grams of 5 - (dimethylsulphamyl) - 2 - nitrobenzoic acid - (N' ethyl - piperazide) in 200 ml of ethanol is hydrogenated with hydrogen in the presence of 1 gram of palladium carbon (10%). After the evolution of hydrogen has subsided, the catalyst is filtered off, the solution evaporated under reduced pressure and the residue crystallized from a mixture of ethanol, and petrolcum ether, 5 - (dimethylsulphamyl) - anthranilic acid - (N' ethyl - piperazide) of the formula

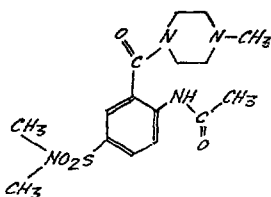


being obtained in the form of white crystals melting at 150—151°C. The hydrochloride melts at 266—267°C.

The 5 - (dimethylsulphamyl) - 2 - nitro - benzoic acid - (N' - ethyl - piperazide) melting at 150—151°C, used as starting material, may be obtained by reacting 5 - (dimethylsulphamyl) - 2 - nitro - benzoyl chloride with N - ethyl - piperazine in absolute dioxan in the presence of triethylamine.

EXAMPLE 5

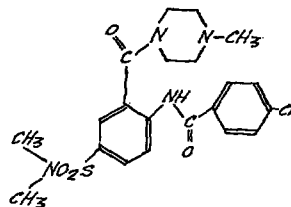
A solution of 10 grams of 5 - (dimethylsulphamyl) - anthranilic acid - (N' - methyl - piperazide) and 3 ml of absolute pyridine in 100 ml of absolute dioxan is cooled to 15°C and treated dropwise with a solution of 2.65 grams of acetyl chloride in 50 ml of absolute dioxan. The batch is stirred for 1 hour at room temperature and for 1 hour at 50°C. The reaction suspension is then evaporated under reduced pressure. The residue is dissolved in water, neutralized with sodium bicarbonate and extracted with chloroform. The chloroform residue is recrystallized from a mixture of ethanol and petroleum ether to yield 5 - (dimethylsulphamyl) - 2 - acetyl-amino - benzoic acid - (N' - methylpiperazide) of the formula



in the form of white crystals melting at 191—193°C.

EXAMPLE 6

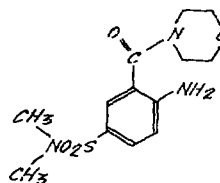
A solution of 10 grams of 5-(dimethylsulphamyl)-anthranilic acid-(N'-methyl-piperazide) and 3 ml of absolute pyridine in 100 ml of absolute dioxan is cooled to 15°C and treated dropwise with a solution of 6 grams of para-chlorobenzoyl chloride in 50 ml of absolute dioxan. The batch is stirred for 1 hour at room temperature and for 1 hour at 50°C. After cooling, the reaction mixture is filtered, and the solid substance is extracted with chloroform in the presence of 2N-sodium hydroxide solution. The chloroform solution is dried over magnesium sulphate and the solvent evaporated; the residue is recrystallized from a mixture of ethanol and methylene chloride to yield 5 - (dimethylsulphamyl) - 2 - (para - chlorobenzoylamino) - benzoic acid - (N' - methyl - piperazide) of the formula



in the form of white crystals melting at 235—237°C.

EXAMPLE 7

A solution of 7.19 grams of 5 - (dimethylsulphamyl) - 2 - nitrobenzoic acid morpholide in 300 ml of ethanol is hydrogenated in the presence of 0.5 grams of palladium carbon (10%) until the absorption of hydrogen ceases. The catalyst is filtered off, evaporated under reduced pressure and the residue crystallized from a mixture of ethanol and petroleum ether to yield 5 - (dimethylsulphamyl) - anthranilic acid morpholide of the formula



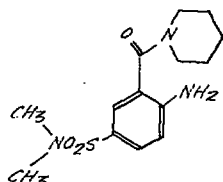
in the form of white crystals melting at 163—165°C.

The 5 - (dimethylsulphamyl) - 2 - nitrobenzoic acid morpholide melting at 204—205°C used as starting material may be prepared by reacting 5 - (dimethylsulphamyl) - 2 - nitrobenzoyl chloride with morpholine in absolute dioxan.

EXAMPLE 8

10.5 grams of 5 - (dimethylsulphamyl) - 2 - nitrobenzoic acid piperidide are dissolved in 100 ml of dimethylformamide and hydrogenated with hydrogen in the presence of 0.5 gram of palladium carbon (10%). After the absorption of hydrogen has ceased, the catalyst

is filtered off, the filtrate evaporated under reduced pressure and the residue crystallized from a mixture of alcohol and petroleum ether to yield 5 - (dimethylsulphamyl) - anthranilic acid piperidide of the formula

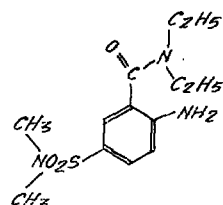


in the form of white crystals melting at 153—154°C.

The 5 - (dimethylsulphamyl) - 2 - nitrobenzoic acid piperidide melting at 177—179°C used as starting material may be obtained by reacting 2 - nitro - 5 - (dimethylsulphamyl) - benzoyl chloride with piperidine in absolute dioxan.

EXAMPLE 9

A solution of 10.2 grams of 5 - (dimethylsulphamyl) - 2 - nitrobenzoic acid diethylamide in 300 ml of absolute ethanol is hydrogenated in the presence of 1 gram of palladium carbon (10%) until the absorption of hydrogen ceases. The catalyst is filtered off, the solution evaporated under reduced pressure and the residue crystallized from a mixture of ethanol and petroleum ether to yield 5 - (dimethylsulphamyl) - anthranilic acid diethylamide of the formula



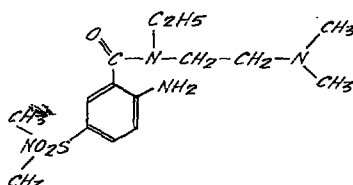
in the form of white crystals melting at 125—127°C.

The 5 - (dimethylsulphamyl) - 2 - nitrobenzoic acid diethylamide melting at 138—140°C used as starting material may be obtained by reacting 5 - (dimethylsulphamyl) - 2 - nitrobenzoyl chloride with diethylamine in absolute dioxan.

EXAMPLE 10

A solution of 11.5 grams of 2 - nitro - 5 - (dimethylsulphamyl) - benzoic acid - [N - ethyl - N - (β - dimethylaminoethyl) - amide] hydrochloride in 100 ml of ethanol and 50 ml of water is hydrogenated with hydrogen in the presence of 0.5 gram of palladium carbon (10%). After the absorption of hydrogen ceases, the solution is filtered, evaporated and the residue dissolved in water. The solution is rendered alkaline with ammonia, extracted with methylene chloride and evaporated under reduced pressure. The oily residue

becomes solid on being allowed to stand and is recrystallized from a mixture of alcohol and petroleum ether to yield 5 - (dimethylsulphamyl) - anthranilic acid - [N - ethyl - N - (β - dimethylamino - ethyl) - amide] of the formula



in the form of crystals melting at 137—138°C.

The 2 - nitro - 5 - (dimethylsulphamyl) - benzoic acid - [N - ethyl - N - (β - dimethylamino - ethyl) - amide] hydrochloride melting at 198—200°C used as starting material may be prepared by reacting 5 - (dimethylsulphamyl) - 2 - nitrobenzoyl chloride with N - ethyl(β - dimethylamino - ethyl) - amine in absolute dioxan and treating the resulting basic oil with alcoholic hydrochloric acid.

EXAMPLE 11

3.2 grams of anhydro - [N - acetyl - 5 - (dimethylsulphamyl) - anthranilic acid](6 - (dimethylsulphamyl) - 2 - methyl - 4H - 3:1 - benzoxazine - 4 - one) are boiled under reflux in the presence of 10 ml of N-methyl-piperazine for 16 hours. The reaction mixture is evaporated under reduced pressure and the residue taken up in 2N hydrochloric acid. After about 30 minutes the hydrochloric acid layer is rendered alkaline with ammonia and extracted with methylene chloride. The residue is recrystallized from a mixture of ethanol and petroleum ether to yield 5 - (dimethylsulphamyl) - anthranilic acid - (N' - methyl - piperazide) melting at 151—152°C which is identical with the product obtained according to Example 1.

The anhydro - [N - acetyl - 5 - (dimethylsulphamyl) - anthranilic acid] used as starting material may be prepared as follows:

4.5 grams of 5 - (dimethylsulphamyl) - anthranilic acid are heated in the presence of 20 ml of acetic anhydride for 2 hours at 100—105°C. The reaction mixture is cooled to room temperature and the precipitated crystals are filtered off; m.p. 186—188°C. The resulting crude product may be used directly for the above-mentioned reaction.

EXAMPLE 12

2 grams of 5 - (dimethylsulphamyl) - isatoic anhydride are boiled under reflux in the presence of 20 ml of N-methylpiperazine for 16 hours. The reaction mixture is then evaporated under reduced pressure, and the residue is taken up in 2N hydrochloric acid and extracted with ethyl acetate. The hydrochloric acid aqueous layer is rendered alkaline with ammonia and extracted with methylene

chloride. The solid residue is recrystallized from a mixture of ethanol and petroleum ether to yield 5 - (dimethylsulphamyl) - anthranilic acid - (N' - methylpiperazide) melting at 151—152°C which is identical with the products described in Examples 1 and 11.

EXAMPLE 13

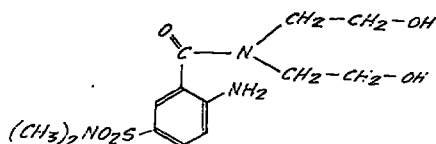
2 grams of 5 - (dimethylsulphamyl) - isatoic anhydride are boiled under reflux in the presence of 20 ml of morpholine for 16 hours. The reaction mixture is then evaporated under reduced pressure, water and glacial acetic acid are added until the reaction mixture is acidic, and the latter is neutralized with sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate residue is recrystallized from a mixture of ethanol and petroleum ether to yield 5 - (dimethylsulphamyl) - anthranilic acid morpholide melting at 163—165°C which is identical with the product described in Example 7.

The 5 - (dimethylsulphamyl) - isatoic anhydride used as starting material may be prepared as follows:

15 grams of 2 - amino - 5 - (dimethylsulphamyl) - benzoic acid are boiled under reflux in the presence of 90 ml of chloroformic acid ethyl ester for 40 hours. The reaction mixture is cooled and the precipitated crystals melting at 215—216°C are filtered off and immediately worked up as described above.

EXAMPLE 14

A solution of 6.5 g of 5 - (dimethylsulphamyl) - 2 - nitrobenzoic acid - [N - di - (β - hydroxyethyl) - amide] in 80 ml of dimethylformamide is hydrogenated in the presence of 0.5 g of palladium carbon (10%) at 40°C under atmospheric pressure until the uptake of hydrogen ceases. The catalyst is filtered off and the filtrate evaporated under reduced pressure. The residue is recrystallized from ethanol + petroleum ether and 5 - (dimethylsulphamyl) - anthranilic acid - [N - di - (β - hydroxyethyl) - amide] of the formula



is obtained in the form of colourless crystals melting at 126—127°C.

The 5 - (dimethylsulphamyl) - 2 - nitro - benzoic acid - [N - di - (β - hydroxyethyl) - amide] used as starting material is obtained by reacting 5 - (dimethylsulphamyl) - 2 - nitro - benzoylchloride with diethanolamine in dioxan. After recrystallization from a mixture of alcohol and petroleum ether it melts at 140—141°C.

EXAMPLE 15

5 - (Dimethylsulphamyl) - anthranilic acid - (N' - methyl - piperazide)	300 mg	60
Wheat starch	95 mg	
Colloidal silicic acid with hydrolysed starch	22 mg	
Arrowroot	19 mg	
Magnesium stearate	2 mg	65
Talcum	12 mg	
	450 mg	

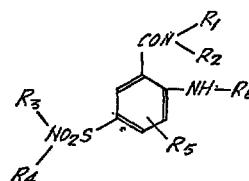
Alcohol 70% q.s.

The active substance, the wheat starch, and the colloidal silicic acid with hydrolysed starch are thoroughly mixed and moistened with sufficient 70% alcohol to produce a slightly plastic mass ready for granulation.

The mixture is passed through a 2 mm mesh sieve and dried at 45°C (Residual moisture 1%). The resulting granulate is given an average grain size of about 0.5 mm, then mixed with arrowroot, magnesium stearate and talcum. This mixture is compressed into tablets of 450 mg in the usual manner.

WHAT WE CLAIM IS:—

1. A compound of the formula



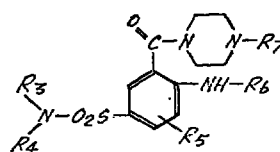
in which R₁ and R₂ each represents a lower alkyl group which may be substituted by a hydroxyl group or by a di-(lower alkyl)-amino group or together represent a lower alkylene group, a monooxa-lower alkylene group or a monoaza-lower alkylene group whose aza nitrogen atom may be substituted by a lower alkyl group or by a lower hydroxyalkyl group, R₃ and R₄ each represents a lower alkyl group, R₅ represents a hydrogen or halogen atom or a lower alkyl, lower alkoxy or trifluoromethyl group and R₆ represents a hydrogen atom or the acyl radical of an aliphatic carboxylic acid containing up to 10 carbon atoms or of an araliphatic or aromatic carboxylic acid.

2. A compound as claimed in claim 1, in which R₅ represents a hydrogen atom.

3. An acid addition salt of a compound as claimed in claim 1 or 2, containing a basic group.

4. A physiologically tolerable acid addition salt of a compound as claimed in claim 1 or 2, containing a basic group.

5. A compound of the formula



in which R₃ and R₄ each represents a lower



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chloride. The solid residue is recrystallized from a mixture of ethanol and petroleum ether to yield 5 - (dimethylsulphamyl) - anthranilic acid - (N' - methylpiperazide) melting at 151—152°C which is identical with the products described in Examples 1 and 11.

EXAMPLE 13

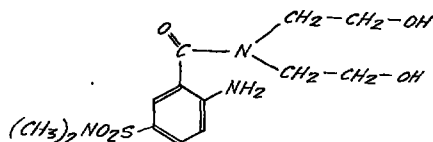
2 grams of 5 - (dimethylsulphamyl) - isatoic anhydride are boiled under reflux in the presence of 20 ml of morpholine for 16 hours. The reaction mixture is then evaporated under reduced pressure, water and glacial acetic acid are added until the reaction mixture is acidic, and the latter is neutralized with sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate residue is recrystallized from a mixture of ethanol and petroleum ether to yield 5 - (dimethylsulphamyl) - anthranilic acid morpholide melting at 163—165°C which is identical with the product described in Example 7.

The 5 - (dimethylsulphamyl) - isatoic anhydride used as starting material may be prepared as follows:

15 grams of 2 - amino - 5 - (dimethylsulphamyl) - benzoic acid are boiled under reflux in the presence of 90 ml of chloroformic acid ethyl ester for 40 hours. The reaction mixture is cooled and the precipitated crystals melting at 215—216°C are filtered off and immediately worked up as described above.

EXAMPLE 14

A solution of 6.5 g of 5 - (dimethylsulphamyl) - 2 - nitrobenzoic acid - [N - di - (β - hydroxyethyl) - amide] in 80 ml of dimethylformamide is hydrogenated in the presence of 0.5 g of palladium carbon (10%) at 40°C under atmospheric pressure until the uptake of hydrogen ceases. The catalyst is filtered off and the filtrate evaporated under reduced pressure. The residue is recrystallized from ethanol + petroleum ether and 5 - (dimethylsulphamyl) - anthranilic acid - [N - di - (β - hydroxyethyl) - amide] of the formula



is obtained in the form of colourless crystals melting at 126—127°C.

The 5 - (dimethylsulphamyl) - 2 - nitro - benzoic acid - [N - di - (β - hydroxyethyl) - amide] used as starting material is obtained by reacting 5 - (dimethylsulphamyl) - 2 - nitro - benzoylchloride with diethanolamine in dioxan. After recrystallization from a mixture of alcohol and petroleum ether it melts at 140—141°C.

EXAMPLE 15

5 - (Dimethylsulphamyl) - anthranilic acid - (N' - methyl - piperazide)	300 mg	60
Wheat starch	95 mg	
Colloidal silicic acid with hydrolysed starch	22 mg	
Arrowroot	19 mg	
Magnesium stearate	2 mg	65
Talcum	12 mg	
	450 mg	

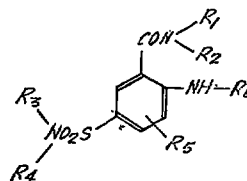
Alcohol 70% q.s.

The active substance, the wheat starch, and the colloidal silicic acid with hydrolysed starch are thoroughly mixed and moistened with sufficient 70% alcohol to produce a slightly plastic mass ready for granulation.

The mixture is passed through a 2 mm mesh sieve and dried at 45°C (Residual moisture 1%). The resulting granulate is given an average grain size of about 0.5 mm, then mixed with arrowroot, magnesium stearate and talcum. This mixture is compressed into tablets of 450 mg in the usual manner.

WHAT WE CLAIM IS:—

1. A compound of the formula



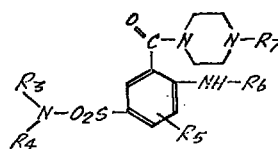
in which R_1 and R_2 each represents a lower alkyl group which may be substituted by a hydroxyl group or by a di-(lower alkyl)-amino group or together represent a lower alkylene group, a monooxa-lower alkylene group or a monoaza-lower alkylene group whose aza nitrogen atom may be substituted by a lower alkyl group or by a lower hydroxyalkyl group, R_3 and R_4 each represents a lower alkyl group, R_5 represents a hydrogen or halogen atom or a lower alkyl, lower alkoxy or trifluoromethyl group and R_6 represents a hydrogen atom or the acyl radical of an aliphatic carboxylic acid containing up to 10 carbon atoms or of an araliphatic or aromatic carboxylic acid.

2. A compound as claimed in claim 1, in which R_5 represents a hydrogen atom.

3. An acid addition salt of a compound as claimed in claim 1 or 2, containing a basic group.

4. A physiologically tolerable acid addition salt of a compound as claimed in claim 1 or 2, containing a basic group.

5. A compound of the formula



in which R_3 and R_4 each represents a lower



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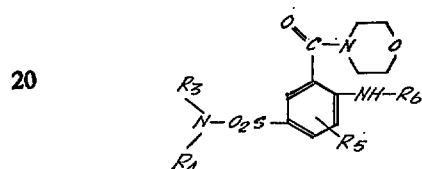
alkyl group, R_5 represents a lower alkyl group, a chlorine atom, a trifluoromethyl group or a hydrogen atom, R_6 represents a hydrogen atom, a lower alkanoyl group or a benzoyl group, which benzoyl group may be substituted by one or more substituents selected from lower alkyl groups, halogen atoms, trifluoromethyl groups and lower alkoxy groups, and R_7 represents a hydrogen atom, a lower alkyl group or a lower hydroxyalkyl group.

6. A compound as claimed in claim 5, in which R_5 represents a hydrogen atom.

7. An acid addition salt of a compound as claimed in claim 5 or 6 containing a basic group.

8. A physiologically tolerable acid addition salt of a compound as claimed in claim 5 or 6 containing a basic group.

9. A compound of the formula



in which R_3 and R_4 each represents a lower alkyl group, R_5 represents a lower alkyl group, a chlorine atom, a trifluoromethyl group or a hydrogen atom and R_6 represents a hydrogen atom, a lower alkanoyl group or a benzoyl group, which benzoyl group may be substituted by one or more substituents selected from lower alkyl groups, halogen atoms, trifluoromethyl groups and lower alkoxy groups.

10. A compound as claimed in claim 9, in which R_5 represents a hydrogen atom.

11. An acid addition salt of a compound as claimed in claim 9 or 10.

12. A physiologically tolerable acid addition salt of a compound as claimed in claim 9 or 10.

13. 5 - (Dimethylsulphamyl) - anthranilic acid - (N' - methylpiperazide).

14. 5 - (Dimethylsulphamyl) - anthranilic acid - [N' - (β - hydroxyethyl) - piperazide].

15. An acid addition salt of the compound claimed in claim 13 or 14.

16. A physiologically tolerable acid addition salt of the compound claimed in claim 13 or 14.

17. The monohydrochloride of the compound claimed in claim 13 or 14.

18. 5 - (Diethylsulphamyl) - anthranilic acid - (N' - methyl - piperazide).

19. 5 - (Dimethylsulphamyl) - anthranilic acid - (N' - ethyl - piperazide).

20. 5 - (Dimethylsulphamyl) - 2 - acetylaminobenzoic acid - (N' - methyl - piperazide).

21. 5 - (Dimethylsulphamyl) - 2 - (para - chlorobenzoyl - amino) - benzoic acid - (N' - methyl - piperazide).

22. 5 - (Dimethylsulphamyl) - anthranilic acid - morpholide.

23. 5 - (Dimethylsulphamyl) - anthranilic acid - piperidide.

24. 5 - (Dimethylsulphamyl) - anthranilic acid diethyl - amide.

25. 5 - (Dimethylsulphamyl) - anthranilic acid [N - ethyl - N - (β - dimethylamino - ethyl) - amide].

26. An acid addition salt of the compound claimed in any one of claims 18, 19 and 22 to 25.

27. A physiologically tolerable acid addition salt of the compound claimed in any one of claims 18, 19 and 22 to 25.

28. The hydrochloride of the compound claimed in claim 18 or 19.

29. 5 - (Dimethylsulphamyl) - anthranilic acid - [N - di - (β - hydroxyethyl) - amide].

30. An acid addition salt of the compound claimed in claim 29.

31. A physiologically tolerable acid addition salt of the compound claimed in claim 29.

32. A pharmaceutical preparation which comprises a compound as claimed in claim 1 or 2 in admixture or conjunction with a pharmaceutically suitable carrier.

33. A pharmaceutical preparation which comprises a physiologically tolerable acid addition salt as claimed in claim 4 in admixture or conjunction with a pharmaceutically suitable carrier.

34. A pharmaceutical preparation which comprises a compound as claimed in claim 5 or 6 in admixture or conjunction with a pharmaceutically suitable carrier.

35. A pharmaceutical preparation which comprises a physiologically tolerable acid addition salt as claimed in claim 8 in admixture or conjunction with a pharmaceutically suitable carrier.

36. A pharmaceutical preparation which comprises a compound as claimed in claim 9 or 10 in admixture or conjunction with a pharmaceutically suitable carrier.

37. A pharmaceutical preparation which comprises a physiologically tolerable acid addition salt as claimed in claim 12 in admixture or conjunction with a pharmaceutically suitable carrier.

38. A pharmaceutical preparation which comprises the compound claimed in claim 13 or 14 in admixture or conjunction with a pharmaceutically suitable carrier.

39. A pharmaceutical preparation which comprises a physiologically tolerable acid addition salt as claimed in claim 16 or 17 in admixture or conjunction with a pharmaceutically suitable carrier.

40. A pharmaceutical preparation which comprises the compound claimed in any one of claims 18 to 25 in admixture or conjunction with a pharmaceutically suitable carrier.

41. A pharmaceutical preparation which comprises a physiologically tolerable acid addition salt as claimed in claim 27 or 28 in admixture or conjunction with a pharmaceutically suitable carrier.

42. A pharmaceutical preparation which comprises the compound claimed in claim 29 in admixture or conjunction with a pharmaceutically suitable carrier.
- 5 43. A pharmaceutical preparation which comprises a physiologically tolerable acid addition salt as claimed in claim 31 in admixture or conjunction with a pharmaceutically suitable carrier.
- 10 44. A pharmaceutical preparation having the composition substantially as described in Example 15 herein.
- 15 45. A veterinary preparation which comprises a compound as claimed in any one of claims 1, 2, 4 to 6, 8 to 10, 12 to 14, 16 to 25, 27 to 29 and 31, in admixture or conjunction with a carrier suitable for veterinary use.
- 20 46. A process for the manufacture of an N:N-aliphatic disubstituted 5-(dialkylsulphamyl)-anthranilic acid amide as claimed in claim 1 or an acid addition salt thereof, wherein a pure or mixed anhydride of a 5-(dialkylsulphamyl)-anthranilic acid having a
- 25 free or acylated amino group in the 2-position is reacted with a secondary amine of the formula NHR_1R_2 , in which R_1 and R_2 have the meanings given in claim 1, or the nitro group in an appropriate N:N-aliphatic disubstituted 2-nitro-5-(dialkylsulphamyl)-benzoic acid amide is converted by reduction into a
- 30 free amino group, and, if desired, a resulting 2-free amino compound is acylated or a resulting 2-acylamino compound is hydrolysed and/or a resulting acid addition salt is converted into the corresponding free compound or a resulting free compound is converted into an acid addition salt thereof.
- 40 47. A process for the manufacture of an N:N-aliphatic disubstituted 5-(dialkylsulphamyl)-anthranilic acid amide as claimed in claim 1 or an acid addition salt thereof, wherein an inner anhydride of an N-acetyl-5-(dialkylsulphamyl)-anthranilic acid, a 5-(dialkylsulphamyl)-isatoic anhydride or an inner anhydride of an N-(α -hydroxyalkyl)-5-(dialkylsulphamyl)-anthranilic acid is reacted with a secondary amine of the formula NHR_1R_2 , in which
- 50 R_1 and R_2 have the meanings given in claim 1, and, if desired, a resulting 2-free amino compound is acylated or a resulting 2-acylamino compound is hydrolysed and/or a resulting acid addition salt is converted into the corresponding free compound or a resulting
- 55 free compound is converted into an acid addition salt thereof.
48. A process as claimed in claim 46, and conducted substantially as described in Example 1 or 2 herein.
- 60 49. A process as claimed in claim 46 or 47, and conducted substantially as described in any one of Examples 3 to 13 herein.
50. A process as claimed in claim 46, and conducted substantially as described in Example 14.
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