

PATENT SPECIFICATION

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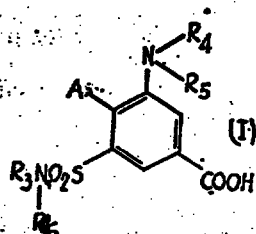
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(54) NEW SULPHAMYL-BENZOIC ACID DERIVATIVES

(71) We, LØVENS KEMISKE FABRIK PRODUKTIONSSELSKAB, a Company incorporated under the Laws of Denmark, of 2750 Ballerup, Denmark, 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:—

10 This invention relates to a series of new compounds, and to methods for the production of the compounds.

The new compounds have the general formula I:



in which A stands for

R_2-O , R_2-S , R_2-OS or R_2-O_2S , and R_1 , R_2 , R_3 and R_4 are unsubstituted or substituted, saturated or unsaturated radicals and each represents an aliphatic radical, a cyclo- 20
 aliphatic radical, or an aromatically, cyclo-
 aliphatically or heterocyclically substituted
 aliphatic radical; in addition R_2 and R_3 may
 each represent an aromatic or heterocyclic 25

radical; and when A is R_1 and R_2

can together with the nitrogen atom represent a heterocyclic ring-system with from 5 to 8 ring members, and which may have one or more nitrogen, oxygen or sulphur atoms in the ring; R_5 represents a C_1 to C_6 alkyl radical, 30

and R_6 represents a C_1 to C_8 alkyl radical or an acyl group; R_1 , R_2 , R_3 , and R_4 may each also be a hydrogen atom. The invention also comprises salts, esters and amides of the compounds of formula I.

- 5 In particular, R_1 , R_2 , R_3 , and R_4 may each represent a straight or branched, saturated or unsaturated, aliphatic radical, e.g. a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or tert-butyl radical, or one of the different isomeric pentyl, hexyl or heptyl radicals, an alkenyl or alkynyl radical, e.g. a vinyl, allyl, or propargyl radical, a cycloalkyl or cycloalkenyl radical, e.g. a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl radical, or one of the different isomeric cyclopentenyl or cyclohexenyl radicals, or an adamantyl radical. The aliphatic radicals may further contain hetero atoms, e.g. oxygen, sulphur, or nitrogen, which may interrupt the carbon chain, and may be further substituted, e.g. with C_1 to C_8 alkyl radicals. In the aromatically, cycloaliphatically or heterocyclically substituted aliphatic radicals, the aromatic part of the radical can be a mono- or bicyclic aryl radical, e.g. a phenyl or naphthyl radical, the cycloaliphatic part of the radical can be one of the cycloalkyl or cycloalkenyl radicals mentioned above, the heterocyclic part of the radical can be a mono- or bicyclic radical containing one or more oxygen, sulphur and nitrogen atoms as ring members, e.g. 2-, 3- or 4-pyridyl, 2- or 3-furyl or -thienyl, thiazolyl, imidazolyl, benzimidazolyl, and the corresponding hydrogenated ring-systems, and the aliphatic part of the radicals can contain 1 to 4 carbon atoms. Illustrative examples of such aromatically or heterocyclically substituted aliphatic radicals are benzyl, 1- or 2-phenylethyl, 1- or 2-naphthyl-methyl, furyl-methyl and the corresponding ethyl, propyl and butyl radicals. When additionally R_2 and R_3 represent aromatic or heterocyclic radicals these can be the mono- or bicyclic radicals already mentioned above.

When A represents



and R_1 and R_2

- together with the nitrogen atom represent a heterocyclic ring-system, this particularly stands for a saturated or unsaturated heterocyclic ring optionally containing one or more nitrogen, oxygen or sulphur atoms, such as piperidyl, morpholinyl, thiomorpholinyl, pyrrolidyl, imidazolyl, thiazolidyl or piperazinyl. When R_5 represents an acyl group, it is preferably a C_1 to C_8 aliphatic acyl group, e.g. an acetyl or propionyl group.

All the above mentioned radicals can be substituted in different positions with different groups, such as one or more halogen atoms,

e.g. chlorine or bromine atoms, alkyl, haloalkyl, e.g. trifluoromethyl, carboxy, carbalkoxy or carbamyl radicals, di-lower alkylamino radicals, hydroxy groups, which may be etherified or esterified, or etherified mercapto groups, or sulphonamide groups.

The salts of the compounds of the invention are pharmaceutically acceptable salts, and include, for example, alkali metal salts, alkaline earth metal salts, the ammonium salt, or amine salts formed, for instance, from mono-, di-, or trialkylamines, or mono-, di-, or trialkanolamines or cyclic amines. The esters of the compounds are preferably derived from substituted or unsubstituted C_1 to C_8 aliphatic alcohols, aryl- or aralkyl-alcohols, e.g. the methyl ester, the cyanomethyl ester, the phenyl ester, and the benzyl ester.

The compounds of the invention possess valuable therapeutic properties and have, according to animal experiments performed in connection with the present invention, a particularly strong effect as diuretics and saluretics, the ratio between the excretion of sodium ions and potassium ions being very favourable. Furthermore the compounds are not carbonhydrase inhibitors, and these facts in connection with a favourable therapeutic index and a low toxicity make the present compounds particularly valuable.

The effect of the present compounds is surprising in respect to the disclosure in the specification of our Belgian Patent No. 716,122 as it was not to be foreseen that the halogen substituent in the neighbouring position to the sulphonamide group could be replaced with the result that compounds with even stronger activity were obtained.

Illustrative examples of compounds of formula I having a particularly strong effect are compounds where A is as defined above and where R_1 , R_2 and R_3 are hydrogen, R_2 is a mononuclear aryl radical, preferably a substituted or unsubstituted phenyl group, R_1 is an aliphatic radical, preferably an alkyl radical having from 3 to 6 carbon atoms, or a mononuclear aralkyl radical, preferably a benzyl, furfuryl or thienylmethyl radical, R_4 is hydrogen, a methyl group or an acyl group, preferably a C_1 to C_8 aliphatic acyl group, and the salts or esters, especially the methyl esters, of these compounds.

The present compounds are effective after oral, enteral or parenteral administration, and are preferably prescribed in the form of tablets, pills, dragees, or capsules containing the free acid or salts thereof with atoxic bases, or the esters or amides thereof, mixed with carriers and/or auxiliary agents.

Pharmaceutical organic or inorganic, solid or liquid carriers suitable for oral, enteral or parenteral administration can be used to make up compositions containing the present compounds. Gelatine, lactose, starch, magnesium stearate, talc, vegetable and animal fats and

oils, gum, polyalkylene glycol, or other known carriers for medicaments are all suitable as carriers.

The compositions may further contain other therapeutic compounds applied in the treatment of, for example oedemas and hypertension, besides the well known auxiliary agents. Such other compounds may be, for instance, Veratrum- or Rauwolfia alkaloids, e.g. reserpine, rescinnamine or picroveratrine or synthetic hypotensive compounds, e.g. hydralazine, or other diuretics and saluretics, such as the well-known benzothiadiazines, e.g. hydroflumethiazide and bendroflumethiazide. Potassium-sparing diuretics, e.g. triamterene, may also be used in the preparation of the compositions. For some purposes it may be desirable to add small amounts of carbonhydrase inhibitors or aldosterone antagonists, e.g. spironolactone.

Salts, which are soluble in water, may with advantage be administered by injection. The pharmaceutical preparations are useful in the treatment of oedematous conditions, e.g. cardiac, hepatic, renal, lung and brain oedema, or oedematous conditions during pregnancy, and of pathological conditions which produce an abnormal retention of the electrolytes of the body, and in the treatment of hypertension.

Another object of the invention resides in the selection of a dose of one of the new compounds, and its salts which can be administered so that the desired activity is achieved without simultaneous secondary effects. It has been found that the compounds and their salts are conveniently administered in dosage units containing not less than 0.1 mg, and up to 25 mg, preferably from 0.25 to 2.5 mg, calculated as the free acid of formula I.

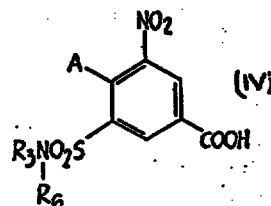
By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

If the composition is to be injected, a sealed ampoule, a vial or a similar container may be provided containing a parenterally acceptable aqueous or oily injectable solution or dispersion of the active material as the dosage unit.

The parenteral preparations are in particular useful in the treatment of conditions in which a quick dehydration is desirable, e.g. in the intensive therapy in the case of oedemas in the lung. In the continuous therapy of patients suffering from e.g. hypertension, the tablets or capsules may be the appropriate form of pharmaceutical preparation owing to the prolonged effect obtained when the drug is given orally, in particular in the form of sustained-release tablets.

In the treatment of heart failure and hypertension such tablets may advantageously contain other active components, as specified hereinbefore.

The present compounds may be provided by various methods. In one embodiment of the invention a compound of the general formula IV:



in which A, R₃ and R₆ have the meanings before defined, or a salt, ester or an amide thereof, is reduced, for example by catalytic hydrogenation using a noble metal catalyst or Raney-nickel, to the compounds of the invention, in which R₁ and R₂ are hydrogen atoms. In some cases, for instance when the substituents would be affected by catalytic hydrogenation, other reducing agents, such as sodium dithionite or iron, may be preferred. The compounds so obtained can be mono-alkylated, preferably in the form of a salt or an ester, by reaction with a compound of the formula R₁X, R₁ being as defined before and X being a halogen atom, preferably chlorine or bromine, a hydroxyl group, or a sulphonyloxy group, an alkyl- or aryl-sulphonyloxy group, the carboxylic acid group subsequently being liberated, if desired. The R₃ group can thereafter be introduced by an ordinary alkylation process utilising R₃X or by a reductive alkylation in known manner.

In another embodiment, a compound of the general formula (I) in which R₆ is an acyl group may be subjected to deacylation to prepare a compound of formula (I) in which R₆ is hydrogen.

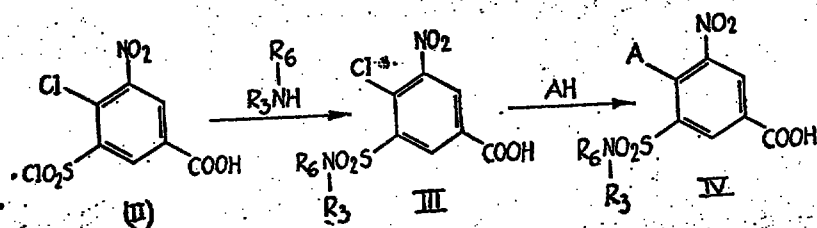
In yet another embodiment, 3-amino-4-A-5-R₃R₆-sulphamyl-benzoic acid or an ester or amide thereof is subjected to reductive alkylation, using in the reaction an aldehyde, which is capable of introducing the corresponding R₁ substituent, whereafter, if desired, R₂ is introduced as described above; on the other hand the esters and amides can be prepared as the last step from the carboxylic acid of formula I, and the R₆ substituent may be introduced as an intermediary step or as a last step.

The different steps of the process are standard procedures including reductive alkylation, hydrogenation, esterification, amidation, using a reactive derivative of the corresponding carboxylic acid or hydrolysis, and the reaction conditions may vary according to the starting products and the substituents of the reacting compounds. The compounds are obtained in free form or in form of their salts,

esters or amides depending upon the conditions under which the reaction is performed.

The starting material of formula IV is pre-

pared according to the following reaction scheme:



in which formulae A and R₃ have the meanings before defined and R₆ is a C₁ to C₈ alkyl, the compound III being used either as the free carboxylic acid or in the form of a salt, amide or an ester, in which case the compound IV is obtained as a salt or an amide or as an ester, which may, if desired, be hydrolyzed. In the case where R₆ is an acyl group, the compounds of formula IV can be provided by acylation of the corresponding compounds in which R₆ is hydrogen.

If desired, the carboxylic acid group of the compounds of formula IV can be amidated using a reactive derivative thereof, e.g. an acid halide.

The starting material of formula II and of formula III, when R₃ and R₆ are hydrogen atoms, are described in the specification of our Belgian Patent No. 716,122.

The N-substituted sulphonyl derivatives III are prepared by treating a compound of

formula II with an amine R₃NH, R₃ being different from hydrogen and R₆ being an alkyl group or hydrogen, preferably under mild conditions, i.e. at low temperature and with-

out an excess of the amine R₃NH and usually in the presence of a base which is not capable of being alkylated and which is used as an acceptor for the acid liberated by the process.

The reaction product of formula III, or an ester or an amide thereof, is treated with a compound of the formula A—H, A being as defined above, i.e. with an amine, an alcohol, a thioalcohol, a phenol, a thiophenol, or a sulphonic acid to form a compound of formula IV, or the corresponding ester. In the case

where A stands for , A—H is used

in the reaction in the form of the free amine, in the case where A stands for R₂—O, R₂—S,

or R₂—O₂S, reaction conditions are used in which the ionic form of A is present or in which A is an alcoholate, thioalcoholate, phenolate or thiophenolate, or a sulphinylate, respectively. Water, ethanol, aqueous alcohols, or alcohols of the formula R₂—OH, as well as other suitable solvents may, if desired, be used as reaction media in this process, and the reaction temperature depends on the reactants used.

In the case where A stands for



and is identical with R₃N, the compound of

formula II can be transformed in one step into a compound of formula IV, using not less

than two equivalents of the amine R₃NH.

The compounds of formula IV, A being R₂—S, can furthermore be converted to the corresponding sulphonyl or sulphonyl derivatives by oxidation, e.g. with hydrogen peroxide, the amount of peroxide and the reaction conditions being decisive for the degree of the oxidation, whereafter the compounds of formula I can be obtained as described above.

In another embodiment of the method for the preparation of the compounds of the invention in which A stands for R₂—OS and R₂—O₂S the compounds can also and preferably be prepared from the corresponding compounds of formula I in which A is R₂—S by oxidation with, for instance, hydrogen peroxide. Depending upon the amount of hydrogen peroxide and the reaction conditions used, the oxidation results in the sulphonyl or the sulphonyl derivatives. These oxidations can be performed on the free carboxylic acids as well as on salts or esters or amides thereof. In the case where a carboxylic acid derivative is obtained, the free carboxylic acid may be subsequently liberated by well-known processes, if desired. Compounds of the invention

in which the substituents are unsaturated may be hydrogenated or transformed by addition-reactions to other compounds of the invention, and further substituents in R_2 and R_4 may be introduced or removed on any reaction step.

A more limited aspect of the present invention relates to a pharmaceutical composition for the treatment of oedematous conditions and hypertension, to dosage units of the composition.

More particularly, this aspect of the invention relates to a pharmaceutical composition containing as an active agent 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid or a salt thereof with a pharmaceutically acceptable inorganic or organic base, together with auxiliary agents, and to a dosage unit of the composition for the treatment of oedematous conditions and hypertension.

The substance 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid is a new compound of the general formula I where R_1 is butyl, R_2 , R_3 and R_4 are each hydrogen and A is phenoxy.

3 - Butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid possesses a particularly favourable diuretic and saluretic activity. As far as the saluretic effect is concerned the compound causes, in particular, an excretion of sodium and of chlorine ions in approximately equivalent proportions, while the excretion of the potassium ion remains substantially normal, or is only slightly increased.

It has been found that among a series of 4 - substituted - 3 - R' - amino - 5 - sulfamyl - benzoic acids, in which R' represents alkyl, aralkyl, or a heterocyclic radical, the 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid is superior in activity.

From a pharmaceutical point of view, it is a further advantage that 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid is chemically stable under acid conditions. Thus, for instance, no discoloration or loss in activity has been observed in pharmaceutical preparations containing the free acid, which when given orally is readily resorbed through the upper part of the gastro-intestinal tract and distributed in the body.

Specifically, it is advantageous that 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid has proved to be outstanding in having a diuretic effect which is comparable in type and activity to that of the well known diuretic Furoscimide, belonging to the group of chlorosulfamylanthranilic acids.

In several cases it has been found that this compound can cause allergic reactions in the patients and it has been found that such patients without any risk can be treated with 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid.

The advantageous diuretic and saluretic effects of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, in the following Table I called PF 1593, have been demonstrated in animal experiments in which the test animals were female dogs. For intravenous injection, the compound was brought into solution with diluted sodium hydroxide, whereas oral application was in form of the free acid in capsules. Urine was taken by catheter with hourly intervals for a total of 6 hours after application. The following Table I contains the excretion of water, Na^+ , K^+ , and Cl^- both for the first 3 hours and for the total period of 6 hours.

TABLE I

Diuretic activity of PF 1593 in dogs.

Dose µg/kg	Water ml/kg		Na ⁺		K ⁺ mval/kg		Cl ⁻	
	3h	6h	3h	6h	3h	6h	3h	6h
Intravenously								
5	5.7	6.3	0.51	0.52	0.12	0.15	0.73	0.75
10	11	12	1.1	1.2	0.24	0.32	1.4	1.5
25	12	12	1.1	1.1	0.22	0.22	1.3	1.3
50	24	28	2.4	2.6	0.36	0.47	3.4	3.8
100	23	26	2.5	2.7	0.51	0.65	3.2	3.5
Orally								
5	4.5	5.7	0.72	0.94	0.25	0.3	0.88	1.1
10	11	15	1.2	1.4	0.32	0.39	1.5	1.8
25	19	20	2.1	2.2	0.31	0.33	2.9	3
50	29	32	3.2	3.4	0.56	0.7	4.5	4.9
100	25	33	2.9	3.7	0.44	0.65	3.8	4.9

It is apparent from the Table I that the diuretic effect is very intensive and short-lasting. It will further be seen that in most instances the effect of a given dose was more pronounced after oral than after intravenous application. This may be explained by the renal excretion of the drug being so rapid that not enough solute is available to be excreted within the short period of rather high serum concentrations after the intravenous injection. It shows further that the compound is excellently absorbed from the gastrointestinal tract.

In the animal experiment above the effect of PF 1593 was tested against the effect of the well-known diuretic Furosemide which until now has been considered one of the most active diuretics of this type. The comparison showed that 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid was 50—100 times as effective as Furosemide on a weight basis. The maximal effect obtainable with both compounds, however, seemed to be the same.

As far as the potassium excretion is concerned, Table I above illustrates a favourably low kaliuresis when compared to the very high excretion of water and of sodium.

In order to determine the acute toxicity of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, animal experiments were per-

formed. After intravenous injection an acute LD₅₀ of 330 mg/kg (290—380) was determined. This corresponds well to the value of 308 mg/kg given for Furosemide by Muschaweck and Hajdu (Arzneimittel-Forsch. 14, 44, 1964). Thus, the higher diuretic and saluretic activities of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid taken into account, its toxicity must be considered extremely low.

When given orally in the above test, doses up to 1 g/kg were given and survived by all mice.

Accordingly, it is the object of the present aspect of the invention to provide a pharmaceutical composition with diuretic and saluretic effect which is useful in the treatment of oedematous conditions, e.g. cardiac, hepatic, renal, lung, and brain oedema, of oedematous conditions during pregnancy, and of other pathological conditions disturbing the balance of the electrolyte concentration in the body, for example in the form of an abnormal retention of the sodium ion, in the treatment of congestive heart failure, and in the treatment of hypertension.

With this object in view the compositions of this aspect of the invention contain as an active component at least one member of the group consisting of 3 - butylamino - 4 - phen-

oxy - 5 - sulfamyl - benzoic acid and its pharmaceutically acceptable salts with inorganic and organic bases, together with solid or liquid pharmaceutical carriers and auxiliary agents.

In the said compositions, the percentage of the diuretically active substance can vary between 0.02 and 20%.

The compositions in question can be worked up to pharmaceutical forms of presentation, such as capsules, tablets, pills, dragees, and suppositories, or they can be filled into the usual containers for injectable medicines, such as vials or ampoules or, as far as liquid mixtures for oral use are concerned, they may be filled into bottles and similar containers.

Pharmaceutical organic or inorganic, solid or liquid carriers suitable for enteral and parenteral administration can be used to make up the compositions. For example, water, gelatine, lactose, starch, magnesium stearate, stearic acid, talc, vegetable and animal oils and fats, wax, benzyl alcohol, gum polyalkylene glycol, cetylalcohol, petroleum jelly, cocoa butter, lanolin, and other known carriers for medicaments are all suitable as carriers, while stabilizing agents, wetting or emulsifying agents, salts for varying the osmotic pressure, and buffers for securing an adequate pH-value of the composition, can be used as auxiliary agents.

Among suitable salts of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid for use in the present compositions mention may be made of the alkali metal salts, the alkaline-earth metal salts, the ammonium salt, and salts with organic bases, such as the ethanolamine salt and the diethanolamine salt. Besides, the free acid itself may also be used in a composition according to the invention which also contains 3,5 - diamino - 6 - chloropyrazinoylguanidine.

Thus, for preparations in the form of, e.g., tablets, or in injectable preparations, the sodium salt or the potassium salt may be used, being sufficiently water-soluble. For injectable preparations, however, salts with certain organic bases may advantageously be employed due to their high solubility in water.

The free acid or its salts may also be administered in capsules, or in effervescent tablets in order to obtain a quick resorption, or in sustained-release tablets in order to obtain a prolonged effect which, in particular, is desirable in the treatment of hypertension.

In addition to 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid or a salt thereof, the compositions of the invention may contain other suitable active components in the treatment of hypertension and oedematous conditions, such as hypotensors, e.g. hydrazine, methyldopa, reserpine, and other *Rauwolfia serpentina* alkaloids, veratrum alkaloids and/or tranquilizers, such as

meprobamate, or potassium-sparing substances, such as triamterene, the alkaloids especially being present in amounts between 0.05 and 0.5 mg. in a single dose.

Since hypopotassemia may sometimes occur in the course of prolonged treatment of hypertensive individuals, it has been found desirable in some cases to include a small amount of an organic potassium salt in the compositions of this invention, such as potassium acetate, potassium propionate, potassium lactate, potassium ascorbate, potassium mandelate, potassium hippurate, or potassium gluconate, or a nontoxic inorganic potassium salt, such as potassium chloride. Since hypochloremia as well as hypopotassemia sometimes occurs during treatment of hypertensive individuals, potassium chloride may be used to supply chloride ions as well as potassium ions.

The term "veratrum alkaloids", when used in this specification, is intended to cover the group of chemically related organic nitrogenous bases obtained from liliaceous plants belonging to the suborder *Melanthaceae*.

The veratrum alkaloids are useful in pure, crystalline form or in the form of mixtures obtained from the powdered root or rhizome. The preferred veratrum alkaloids for use in the composition of the present invention are Veratrum viride, and phtoveratrine A and B.

The term "rauwolfia alkaloids" comprises the group of organic nitrogenous bases which may be obtained from *Rauwolfia serpentina* Benth. This component may be used in the form of the powdered whole root or in the form of the pure crystalline alkaloids, reserpine, rescinnamine, and deserpidine, which are obtainable from the whole root. The above examples of additional active ingredients are not to be considered limitative for the compositions of the present invention.

Owing to the short-lasting effect of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, even when administered orally in the form of capsules, the compound is preferably administered in the form of sustained-release tablets. In such tablets 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, preferably in the form of a water-soluble salt, can be embedded in a tablet core consisting of a hydrophobic material, such as a wax with a melting point at or slightly above the body temperature. On administration, the compound will then gradually be extracted into the gastro-intestinal tract without disintegration of the tablet core whereby a controlled diuresis and a prolonged effect is obtained.

In this embodiment, if the composition of the invention in dosage unit form contains other active ingredients, these may be contained in the coating material for the core of the sustained-release tablet whereby a tablet is provided which is particularly advantageous in the control of hypertension.

6h

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Thus, the coating may contain ingredients such as reserpine and other alkaloids, methyl-dopa, and similar hypotensors.

On the other hand, the sustained-release tablet may advantageously contain a potassium salt in the tablet core in order to obtain a slow release of the potassium ion, thereby avoiding disturbances in the gastro-intestinal tract due to instantaneous high salt-concentrations after the intake.

Another object of the invention resides in the selection of a dose of the 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid and its salts which can be administered so that the desired activity is achieved without simultaneous secondary effects. It has been found that 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid and its salts are conveniently administered in dosage units containing not less than 0.1 mg, and up to 10 mg, preferably from 0.25 to 2.5 mg, calculated as the free acid 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid.

It is possible with the compounds of the present invention to treat patients suffering from oedematous conditions and hypertension, for example by administering to the patient from 0.1 to 25 mg per day of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid or a corresponding dose of one of its salts with a pharmaceutically acceptable base. Preferably, the compound is given in the form of the dosage unit aforesaid.

For oral administration, the dosage unit may conveniently contain from 0.1—10 mg of the 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, as such or in the form of one of its salts, the unit being in the form of a tablet, a pill, or a capsule, to be given at suitable intervals, for instance once, twice, or thrice daily, always depending, however, on the patient and his condition. Preferably, each tablet contains from 0.25 to 2.5 mg of the 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, or a corresponding amount of one of its salts. If the dosage unit is injectable, the unit may consist of from 0.1 to 5 mg of the 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and conveniently from 0.2 to 2 mg dissolved in an aqueous solvent, the said dosage unit for instance being enclosed in an ampoule containing, for example, 2 ml of a 0.025 per cent aqueous solution of the sodium salt of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid.

The parenteral preparations are in particular useful in the treatment of conditions in which a quick dehydration is desirable, e.g. in the intensive therapy in the case of oedemas in the lung. In the continuous therapy of patients suffering from e.g. hypertension, the tablets or capsules may be the appropriate form of pharmaceutical preparation owing to the prolonged effect obtained when the drug is given

orally, in particular in the form of sustained-release tablets.

In the treatment of heart failure and hypertension such tablets may advantageously contain other active components, as specified hereinafter.

Thus for instance the tablets may contain each 0.25 mg of the 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid or one of its salts in combination with hydralazine in amounts from 10 to 50 mg, or reserpine in amounts from 0.05 to 0.5 mg, or from 20 to 100 mg in the form of powdered whole root, or protoveratrine in amounts ranging from 0.05 to 0.4 mg, and if in the form of a mixture of alkaloids, e.g. *Veratrum viride*, 50 mg is preferred, or methyl-dopa in amounts from 100 to 500 mg, and furthermore the tablets may contain, as a tranquilizer, meprobamate {2:2 - di(carbamoyloxymethyl) - pentane} in amounts from 100 to 400 mg, preferably 150 mg to 250 mg.

The invention will now be described by the following examples which are only illustrative and are not to be limiting: of the examples, Examples 1 to 84 describe the preparation of various compounds of the general formula I and Examples 85 to 93 describe dosage units of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid (prepared as described in Example 41) and salts thereof:—

EXAMPLE 1

3 - Amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

A. 3 - Nitro - 4 - phenoxy - 5 - sulphamyl - benzoic acid

A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (140 g.), phenol (100 g.), sodium bicarbonate (170 g.), and water (1000 ml.) was heated to 85°C. while stirring, and kept at this temperature for 16 hours. After cooling to 4°C., the precipitated sodium salt of 3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzoic acid was filtered off and washed with ice water. The sodium salt was dissolved in boiling water (3000 ml.) and the 3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzoic acid precipitated by the addition of 4N hydrochloric acid. After cooling, the acid was isolated by suction and dried. The melting point was 255—256°C.

B. 3 - Amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

A suspension of 3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzoic acid (20 g.) in water (100 ml.) was adjusted to a pH of 8 by the addition of 1N lithium hydroxide. The resulting solution was hydrogenated at room temperature and 1.1 atmosphere hydrogen pressure after the addition of a palladium-on-carbon catalyst (0.6 g. catalyst containing 10% Pd). After the hydrogen uptake had become negligible, the catalyst was removed by filtration, and the 3 - amino - 4 - phenoxy - 5 -

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1.5 g. of the sodium salt of 3 - amino - 4 - anilino - 5 - phenylsulphamyl - benzoic acid was dissolved in hot water (50 ml.). 1N hydrochloric acid was added until pH 2 and the mixture was cooled. The precipitated 3 - amino - 4 - anilino - 5 - phenylsulphamyl

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acid was collected, recrystallized from aqueous methanol, and dried *in vacuo* at 78°C. The crystalline compound contained 1 mol of water. The melting point was 222—223°C.

EXAMPLE 5

3 - Amino - 4 - (*p* - methoxyphenoxy) - 5 - sulphamyl - benzoic acid

A. 4 - (*p* - Methoxyphenoxy) - 3 - nitro - 5 - sulphamyl - benzoic acid

10 A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (14 g.), *p*-methoxyphenol (9.3 g.), and 1N sodium bicarbonate (200 ml.) was stirred at 90°C. for 5 hours. After cooling, the 4 - (*p* - methoxyphenoxy) - 3 - nitro - 5 - sulphamyl - benzoic acid was precipitated by the addition of 4N hydrochloric acid until the pH was 1, and collected by suction. The crude acid was dissolved in hot methanol (100 ml.) and precipitated by the addition of water (100 ml.) and cooling. After collection and drying *in vacuo*, the melting point was 229—230°C.

B. 3 - Amino - 4 - (*p* - methoxyphenoxy) - 5 - sulphamyl - benzoic acid

25 By substituting 4 - (*p* - methoxyphenoxy) - 3 - nitro - 5 - sulphamyl - benzoic acid (7 g.) for 3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzoic acid in Example 1B, the compound was obtained with a melting point of 260—261°C.

EXAMPLE 6

3 - Amino - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoic acid

A. 3 - Nitro - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoic acid

35 A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (7 g.), *m* - trifluoromethylphenol (20 g.), and 1N sodium bicarbonate (100 ml.) was stirred at 95°C. for 6 hours. Then the reaction mixture was acidified by the addition of 4N hydrochloric acid and the excess of trifluoromethylphenol was removed by steam distillation. After cooling, the precipitated 3 - nitro - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoic acid was collected by suction and recrystallized several times from methanol-water. The melting point of the pure compound was 205—206°C.

50 B. 3 - Amino - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoic acid

By substituting 3 - nitro - 5 - sulphamyl - 4 - (*m* - trifluoromethyl - phenoxy) - benzoic acid for 3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzoic acid in Example 1B, the compound was obtained with a melting point of 270°C.

EXAMPLE 7

3 - Amino - 4 - (*m* - chlorophenoxy) - 5 - sulphamyl - benzoic acid

A. 4 - (*m* - Chlorophenoxy) - 3 - nitro - 5 - sulphamyl - benzoic acid

65 A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (28 g.), *m* - chlorophenol (26 g.), sodium bicarbonate (34 g.), and

water (200 ml.) was stirred at 85°C. for 10 hours. After cooling, excess *m*-chlorophenol was removed by extraction with diethyl ether, and the 4 - (*m* - chlorophenoxy) - 3 - nitro - 5 - sulphamyl - benzoic acid was precipitated from the aqueous layer by the addition of 4N hydrochloric acid. After recrystallization from aqueous methanol, the melting point was 230—232°C.

B. 3 - Amino - 4 - (*m* - chlorophenoxy) - 5 - sulphamyl - benzoic acid

A mixture of ammonium chloride (1.2 g.), metallic iron powder (11 g.), concentrated hydrochloric acid (0.05 ml.), and water (30 ml.) was heated on a steam bath. 4 - (*m* - chlorophenoxy) - 3 - nitro - 5 - sulphamyl - benzoic acid (3 g.) was added while stirring, and the heating continued for 6 hours. Then 1N sodium hydroxide (50 ml.) was added and the reaction mixture was filtered. The filter cake was washed twice with 1N sodium hydroxide (50 ml. each time). The combined filtrates were adjusted to a pH of 2.5 by the addition of 4N hydrochloric acid. After cooling, the precipitated 3 - amino - 4 - (*m* - chlorophenoxy) - 5 - sulphamyl - benzoic acid was collected by suction, and recrystallized from aqueous ethanol. The melting point was 239—240°C.

EXAMPLE 8

3 - Amino - 4 - methoxy - 5 - sulphamyl - benzoic acid

A. 4 - Methoxy - 3 - nitro - 5 - sulphamyl - benzoic acid

4 - Chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (14 g.) was added to a solution of sodium methanolate—prepared from sodium (6.9 g.)—in methanol (200 ml.). The reaction mixture was refluxed for 5 hours and evaporated *in vacuo*. The residue was dissolved in water (100 ml.) and conc. hydrochloric acid was added (50 ml.). The precipitated 4 - methoxy - 3 - nitro - 5 - sulphamyl - benzoic acid was recrystallized from water. The melting point was 200—201°C.

B. 3 - Amino - 4 - methoxy - 5 - sulphamyl - benzoic acid.

4 - Methoxy - 3 - nitro - 5 - sulphamyl - benzoic acid (2.8 g.) was dissolved in 1N sodium bicarbonate solution (12 ml.), hydrogenated using Pd-on-carbon as a catalyst, and the 3 - amino - 4 - methoxy - 5 - sulphamyl - benzoic acid was isolated as described in Example 1B. After several recrystallizations from water and drying at 78°C. *in vacuo*, the melting point was 210°C. under decomposition.

EXAMPLE 9

3 - Amino - 4 - anilino - 5 - sulphamyl - benzoic acid

A. 4 - Anilino - 3 - nitro - 5 - sulphamyl - benzoic acid

A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (8.4 g.), aniline (8.4 g.) and water (40 ml.) was stirred at 80°C. for 2 hours. After the addition of 1N hydro-

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chloric acid (50 ml.) and cooling, the precipitated 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid was collected by suction, washed with water and recrystallized from aqueous ethanol; the melting point was 261—262°C.

B. 3 - Amino - 4 - anilino - 5 - sulphamyl - benzoic acid

A suspension of 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid (7 g.) in water (80 ml.) was adjusted to a pH of 9 by the addition of 2N sodium hydroxide or lithium hydroxide and the resulting solution was hydrogenated at room temperature and 1.1 atmosphere hydrogen pressure after the addition of a palladium-on-carbon catalyst (0.3 g. catalyst containing 10% Pd). After the hydrogen uptake had become negligible, the catalyst was removed by filtration and the 3 - amino - 4 - anilino - 5 - sulphamyl - benzoic acid precipitated from the filtrate by the addition of 4N hydrochloric acid until the pH was 2.5. After recrystallization from aqueous ethanol and drying *in vacuo*, the melting point was 251°C.

EXAMPLE 10

3 - Amino - 5 - sulphamyl - 4 - (m - toluidino) - benzoic acid

A. 3 - Nitro - 5 - sulphamyl - 4 - (m - toluidino) - benzoic acid

A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (28 g.), m - toluidine (32.2 g.) and water (500 ml.) was refluxed for 3 hours. After cooling and acidification with 2N hydrochloric acid, the precipitated 3 - nitro - 5 - sulphamyl - 4 - (m - toluidino) - benzoic acid was collected by suction, washed with water and recrystallized from isopropanol. After drying at 115°C. *in vacuo*, the melting point was 256—259°C.

B. 3 - Amino - 5 - sulphamyl - 4 - (m - toluidino) - benzoic acid

By substituting 3 - nitro - 5 - sulphamyl - 4 - (m - toluidino) - benzoic acid for 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 9B, the title compound was obtained with a melting point of 280—282°C. after recrystallization from ethanol.

EXAMPLE 11

3 - Amino - 5 - sulphamyl - 4 - (p - toluidino) - benzoic acid

A. 3 - Nitro - 5 - sulphamyl - 4 - (p - toluidino) - benzoic acid

By substituting p - toluidine for m - toluidine in Example 10A, the compound was obtained with a melting point of 252—253°C., after recrystallization from ethanol and drying.

B. 3 - Amino - 5 - sulphamyl - 4 - (p - toluidino) - benzoic acid

By substituting 3 - nitro - 5 - sulphamyl - 4 - (p - toluidino) - benzoic acid for 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 9B, the compound was obtained with a melting point of 249—252°C.

EXAMPLE 12

3 - Amino - 5 - sulphamyl - 4 - (o - toluidino) - benzoic acid

A. 3 - Nitro - 5 - sulphamyl - 4 - (o - toluidino) - benzoic acid

By substituting o - toluidine for m - toluidine in Example 10A, the compound was obtained with a melting point of 251—252°C.

B. 3 - Amino - 5 - sulphamyl - 4 - (o - toluidino) - benzoic acid

By substituting 3 - nitro - 5 - sulphamyl - 4 - (o - toluidino) - benzoic acid for 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 9B, the compound was obtained.

EXAMPLE 13

3 - Amino - 4 - (o - methoxyanilino) - 5 - sulphamyl - benzoic acid

A. 4 - (o - Methoxyanilino) - 3 - nitro - 5 - sulphamyl - benzoic acid

By substituting o - anisidine (37 g.) for m - toluidine in Example 10A, the compound was obtained with a melting point of 207—208°C. after recrystallization from ethanol and drying *in vacuo*.

B. 3 - Amino - 4 - (o - methoxyanilino) - 5 - sulphamyl - benzoic acid

By substituting 4 - (o - methoxyanilino) - 3 - nitro - 5 - sulphamyl - benzoic acid for 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 9B, the compound was obtained after recrystallization from aqueous ethanol.

EXAMPLE 14

3 - Amino - 4 - (m - methoxyanilino) - 5 - sulphamyl - benzoic acid

A. 4 - (m - Methoxyanilino) - 3 - nitro - 5 - sulphamyl - benzoic acid

By substituting m - anisidine (37 g.) for m - toluidine in Example 10A, the compound was obtained with a melting point of 253—254°C.

B. 3 - Amino - 4 - (m - methoxyanilino) - 5 - sulphamyl - benzoic acid

By substituting 4 - (methoxyanilino) - 3 - nitro - 5 - sulphamyl - benzoic acid for 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 9B, the compound was obtained with a melting point of 232—234°C. after recrystallization from aqueous methanol.

EXAMPLE 15

3 - Amino - 4 - (p - methoxyanilino) - 5 - sulphamyl - benzoic acid

A. 4 - (p - Methoxyanilino) - 3 - nitro - 5 - sulphamyl - benzoic acid

By substituting p - anisidine (37 g.) for m - toluidine in Example 10A, the compound was obtained with a melting point of 246°C. (decomp.).

B. 3 - Amino - 4 - (p - methoxyanilino) - 5 - sulphamyl - benzoic acid

By substituting 4 - (p - methoxyanilino) - 3 - nitro - 5 - sulphamyl - benzoic acid for 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 9B, the compound was obtained with a melting point of 214°C.

EXAMPLE 16

3 - Amino - 5 - sulphamyl - 4 - (*m* - trifluoromethylanilino) - benzoic acid

A. 3 - Nitro - 5 - sulphamyl - 4 - (*m* - trifluoromethylanilino) - benzoic acid

By substituting *m*-trifluoromethylaniline (49.5 g.) for *m*-toluidine in Example 10A and extending the reaction time to 7 hours, the compound was obtained after the cooled reaction mixture had been acidified and diluted with ethanol (150 ml.). After recrystallization from aqueous ethanol, the melting point was 213—215°C.

B. 3 - Amino - 5 - sulphamyl - 4 - (*m* - trifluoromethylanilino) - benzoic acid

By substituting 3 - nitro - 5 - sulphamyl - 4 - (*m* - trifluoromethylanilino) - benzoic acid for 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 9B, the compound was obtained with a melting point of 273—274°C.

EXAMPLE 17

3 - Amino - 4 - (2,4 - dimethylanilino) - 5 - sulphamyl - benzoic acid

A. 4 - (2,4 - Dimethylanilino) - 3 - nitro - 5 - sulphamyl - benzoic acid

By substituting 2,4-dimethylaniline (36.5 g.) for *m*-toluidine in Example 10A, the compound was obtained with a melting point of 224—226°C. after recrystallization from ethanol and drying. The compound crystallized with one mol of ethanol.

B. 3 - Amino - 4 - (2,4 - dimethylanilino) - 5 - sulphamyl - benzoic acid

By substituting 3 - nitro - 5 - sulphamyl - 4 - (2,4 - dimethylanilino) - benzoic acid for 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 9B, the compound was obtained with a melting point of 241—241.5°C. after recrystallization from ethanol.

EXAMPLE 18

3 - Amino - 4 - (*p* - chloroanilino) - 5 - sulphamyl - benzoic acid

A. 4 - (*p* - Chloroanilino) - 3 - nitro - 5 - sulphamyl - benzoic acid

By substituting *p*-chloroaniline (39 g.) for *m*-toluidine in Example 10A, the compound was obtained with a melting point of 241—243°C. after recrystallization from ethanol and drying *in vacuo*.

B. 3 - Amino - 4 - (*p* - chloroanilino) - 5 - sulphamyl - benzoic acid

A mixture of 4 - (*p* - chloroanilino) - 3 - nitro - 5 - sulphamyl - benzoic acid (7.43 g.), water (50 ml.), and concentrated aqueous ammonia (15 ml.) was stirred at 25°C. and a solution of sodium dithionite (13.5 g.) in water (50 ml.) was added dropwise. After 1 hour, the pH of the reaction mixture was adjusted to 2.5 and the precipitated reaction product was filtered off. After repeated recrystallizations from aqueous ethanol, and after drying for 4 hours *in vacuo*, the 3 - amino - 4 - (*p* -

chloroanilino) - 5 - sulphamyl - benzoic acid was obtained with a melting point of 273—274°C.

EXAMPLE 19

3 - Amino - 4 - (*p* - hydroxyanilino) - 5 - sulphamyl - benzoic acid

A. 4 - (*p* - Hydroxyanilino) - 3 - nitro - 5 - sulphamyl - benzoic acid

By substituting *p*-aminophenol (24.5 g.) for *m*-toluidine in Example 10A, the compound was obtained with a melting point of 262°C. (decomp.) after recrystallization from aqueous ethanol and water.

B. 3 - Amino - 4 - (*p* - hydroxyanilino) - 5 - sulphamyl - benzoic acid

By substituting 4 - (*p* - hydroxyanilino) - 3 - nitro - 5 - sulphamyl - benzoic acid (10 g.) for 3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzoic acid in Example 1B, the compound was obtained with a melting point of 296°C. (decomp.).

EXAMPLE 20

3 - Amino - 4 - cyclohexylamino - 5 - sulphamyl - benzoic acid

A. 4 - Cyclohexylamino - 3 - nitro - 5 - sulphamyl - benzoic acid

By substituting cyclohexylamine (30 g.) for *m*-toluidine in Example 10A, the compound was obtained with a melting point of 185—186°C. after recrystallization from aqueous ethanol and drying *in vacuo*.

B. 3 - Amino - 4 - cyclohexylamino - 5 - sulphamyl - benzoic acid

By substituting 4 - cyclohexylamino - 3 - nitro - 5 - sulphamyl - benzoic acid (15 g.) for 3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzoic acid in Example 1B, the compound was obtained with a melting point of 233°C. (decomp.).

EXAMPLE 21

3 - Amino - 4 - benzylamino - 5 - sulphamyl - benzoic acid

A. 4 - Benzylamino - 3 - nitro - 5 - sulphamyl - benzoic acid

A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (8.4 g.), benzylamine (12.84 g.), and water (40 ml.) was stirred at room temperature for 3 hours. After standing for 30 minutes, the liquor was decanted off, water (100 ml.) was added, and the 4 - benzylamino - 3 - nitro - 5 - sulphamyl - benzoic acid was precipitated by the addition of 4N hydrochloric acid. After collection and recrystallization from aqueous methanol, the melting point was 188°C. (decomp.).

B. 3 - Amino - 4 - benzylamino - 5 - sulphamyl - benzoic acid

By substituting 4 - benzylamino - 3 - nitro - 5 - sulphamyl - benzoic acid for 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 9B, the compound was obtained with a melting point of 218—219°C. after recrystallization from aqueous methanol.

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EXAMPLE 22

3 - Amino - 4 - (β - phenylethylamino) - 5 -
sulphamyl - benzoic acidA. 3 - Nitro - 4 - (β - phenylethylamino) -
5 - sulphamyl - benzoic acidA mixture of 4 - chloro - 3 - nitro - 5 -
sulphamyl - benzoic acid (22.4 g.), β - phenyl-
ethylamine (29 g.), and water (200 ml.) was
refluxed for 2.5 hours. After cooling, the re-
action mixture was adjusted to a pH of 9.5
and extracted with diethyl ether. The aqueous
layer was then acidified by the addition of 4N
hydrochloric acid and the precipitated 3 -
nitro - 4(β - phenylethylamino) - 5 - sulph-
amyl - benzoic acid collected by suction. After
recrystallization from aqueous ethanol, the
melting point was 208—208.5°C.B. 3 - Amino - 4 - (β - phenylethylamino) -
5 - sulphamyl - benzoic acidBy substituting 3 - nitro - 4 - (β - phenyl-
ethylamino) - 5 - sulphamyl - benzoic acid for
4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic
acid in Example 9B, the compound was ob-
tained with a melting point of 194—195°C.

EXAMPLE 23

3 - Amino - 4 - (*p* - carboxyanilino) - 5 -
sulphamyl - benzoic acidA. 4 - (*p* - carboxyanilino) - 3 - nitro - 5 -
sulphamyl - benzoic acidA suspension of 4 - chloro - 3 - nitro - 5 -
sulphamyl - benzoic acid (22.4 g.) and *p*-
aminobenzoic acid (10.95 g.) in water was
adjusted to a pH of 7 by the addition of
sodium bicarbonate. The resulting solution
was refluxed for 10 hours. After acidifying
with 4N hydrochloric acid and cooling, the
precipitated 4 - (*p* - carboxyanilino) - 3 -
nitro - 5 - sulphamyl - benzoic acid was col-
lected by suction and recrystallized from
aqueous ethanol. The melting point was 297°C.
(decomp.). The compound contained one mol
of water of crystallization.B. 3 - Amino - 4 - (*p* - carboxyanilino) - 5 -
sulphamyl - benzoic acidBy substituting 4 - (*p* - carboxyanilino) - 3 -
nitro - 5 - sulphamyl - benzoic acid for 4 -
anilino - 3 - nitro - 5 - sulphamyl - benzoic
acid in Example 9B, the compound was ob-
tained with a melting point of 262°C. (de-
comp.) after drying *in vacuo* at 115°C.

EXAMPLE 24

3 - Amino - 4 - (2 - methoxyethylamino) - 5 -
sulphamyl - benzoic acidA. 4 - (2 - Methoxyethylamino) - 3 - nitro -
5 - sulphamyl - benzoic acid.A mixture of 4 - chloro - 3 - nitro - 5 -
sulphamyl - benzoic acid (4.2 g.), 2 - methoxy-
ethylamine (5.6 g.) and 50% ethanol (10 ml.)
was heated to 60°C. for 1 hour. The ethanol
was distilled off under reduced pressure and
the 4 - (2 - methoxyethylamino) - 3 - nitro -
5 - sulphamyl - benzoic acid precipitated by
addition of 4N hydrochloric acid until pH 2.
After recrystallization from water the meltingpoint was 192—194°C. The compound crystal-
lized with 1 mol of water.B. 3 - Amino - 4 - (2 - methoxyethylamino) -
5 - sulphamyl - benzoic acid4 - (2 - Methoxyethylamino) - 3 - nitro -
5 - sulphamyl - benzoic acid (3.2 g.) was dis-
solved in 1N sodium hydroxide (10 ml.) and
hydrogenated after addition of moist Raney-
Nickel (1 g.). When the hydrogen uptake had
become negligible, the catalyst was removed
by filtration and the 3 - amino - 4 - (2 - meth-
oxyethylamino) - 5 - sulphamyl - benzoic acid
precipitated from the filtrate by addition of
4N hydrochloric acid until pH 3. After re-
crystallization from water the melting point
was 209—211°C.

EXAMPLE 25

3 - Amino - 4 - isopropylamino - 5 - sulph-
amyl - benzoic acidA. 4 - Isopropylamino - 3 - nitro - 5 - sulph-
amyl - benzoic acidIsopropylamine (120 ml.) and water (8 ml.)
were added to 4 - chloro - 3 - nitro - 5 -
sulphamyl - benzoic acid (22.4 g.), while cool-
ing. Then the reaction mixture was stirred
for 5 days at room temperature. After evapora-
tion *in vacuo*, the residue was triturated with
4N hydrochloric acid, whereafter the 4 - iso-
propylamino - 3 - nitro - 5 - sulphamyl -
benzoic acid was collected by suction. After
recrystallization from aqueous ethanol, the acid
was obtained with a melting point of 206°C.
(decomp.).B. 3 - Amino - 4 - isopropylamino - 5 - sulph-
amyl - benzoic acidBy substituting 4 - isopropylamino - 3 -
nitro - 5 - sulphamyl - benzoic acid for 4 -
anilino - 3 - nitro - 5 - sulphamyl - benzoic
acid in Example 9B, the compound was ob-
tained with a melting point of 226°C. (de-
comp.).

EXAMPLE 26

3 - Amino - 4 - (N - methyl - ethanolamino) -
5 - sulphamyl - benzoic acidA. 4 - (N - Methyl - ethanolamino) - 3 -
nitro - 5 - sulphamyl - benzoic acidA mixture of 4 - chloro - 3 - nitro - 5 -
sulphamyl - benzoic acid (14 g.), 2 - methyl-
amino - ethanol (19 g.) and 50% ethanol (30
ml.) in water was stirred at 50°C. for 2 hours.
After addition of water (100 ml.), 1N hydro-
chloric acid was added until pH 2 causing
precipitation of 4 - (N - methyl - ethanol-
amino) - 3 - nitro - 5 - sulphamyl - benzoic
acid. After recrystallization from water the
melting point was 125—127°C.B. 3 - Amino - 4 - (N - methyl - ethanol-
amino) - 5 - sulphamyl - benzoic acid4 - (N - methyl - ethanolamino) - 3 - nitro -
5 - sulphamyl - benzoic acid (9 g.) was dis-
solved in water by adjusting the pH to 8 by
means of 1N sodium hydroxide. Raney-Nickel
catalyst (1 g.) was added and the solution
hydrogenated until the hydrogen uptake had

become negligible. The catalyst was removed by filtration and the 3 - amino - 4 - (N - methyl - ethanolamino) - 5 - sulphamyl - benzoic acid was collected and recrystallized addition of 4N hydrochloric acid until pH 2.5. After recrystallization from water the melting point was 209—211°C.

EXAMPLE 27

3 - Amino - 4 - piperidino - 5 - sulphamyl - benzoic acid

A. 3 - Nitro - 4 - piperidino - 5 - sulphamyl - benzoic acid

A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (2.8 g.), piperidine (3.4 g.) and water (13 ml.) was stirred at 95°C. for 2 hours. Then the reaction mixture was adjusted to a pH of 2.5 by the addition of 4N hydrochloric acid, and the precipitated 3 - nitro - 4 - piperidino - 5 - sulphamyl - benzoic acid was collected and recrystallized from aqueous methanol. The melting point was 237—238°C. (decomp.).

B. 3 - Amino - 4 - piperidino - 5 - sulphamyl - benzoic acid

By substituting 3 - nitro - 4 - piperidino - 5 - sulphamyl - benzoic acid for 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 9B, the compound was obtained with a melting point of 279°C. (decomp.) after recrystallization from aqueous methanol.

EXAMPLE 28

3 - Amino - 4 - morpholino - 5 - sulphamyl - benzoic acid

A. 4 - Morpholino - 3 - nitro - 5 - sulphamyl - benzoic acid

By substituting morpholine (3.48 g.) for piperidine in Example 27A, the compound was obtained with a melting point of 273°C. (decomp.).

B. 3 - Amino - 4 - morpholino - 5 - sulphamyl - benzoic acid

By substituting 4 - morpholino - 3 - nitro - 5 - sulphamyl - benzoic acid for 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 9B, the compound was obtained with a melting point of 297°C. (decomp.) after recrystallization from aqueous methanol.

EXAMPLE 29

3 - Amino - 4 - (3 - dimethylaminopropylamino) - 5 - sulphamyl - benzoic acid

A. 4 - (3 - Dimethylaminopropylamino) - 3 - nitro - 5 - sulphamyl - benzoic acid

To a suspension of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (22.4 g.) in water (24 ml.), 3-dimethylaminopropylamine (120 ml.) was added, while cooling. Then the reaction mixture was heated to 100°C. and kept at this temperature for 2 hours. After cooling and evaporating *in vacuo* to dryness, the residue was dissolved in water (80 ml.) and adjusted to a pH of 7.5 by the addition of 4N hydrochloric acid. The precipitated 4 - (3 - dimethylaminopropylamino) - 3 - nitro - 5 - sulphamyl - benzoic acid was collected by

suction and recrystallized from water. The melting point was 262°C. (decomp.).

B. 3 - Amino - 4 - (3 - dimethylaminopropylamino) - 5 - sulphamyl - benzoic acid

4 - (3 - Dimethylaminopropylamino) - 3 - nitro - 5 - sulphamyl - benzoic acid (6.92 g.) was dissolved in 2N sodium hydroxide (25 ml.), and the solution was hydrogenated at room temperature and 1.1 atmosphere hydrogen pressure after the addition of a palladium-on-carbon catalyst (0.35 g. catalyst containing 10% Pd.) After hydrogen uptake had become negligible, the catalyst was removed by filtration, and the filtrate was adjusted to a pH of 8 by the addition of 4N hydrochloric acid. The precipitated 3 - amino - 4 - (3 - dimethylaminopropylamino) - 5 - sulphamyl - benzoic acid was collected by suction and recrystallized from water. After drying *in vacuo* at 115°C. for 2 hours, the melting point was 264°C. (decomp.).

EXAMPLE 30

3 - Amino - 4 - (β - naphthylamino) - 5 - sulphamyl - benzoic acid

A. 4 - (β - Naphthylamino) - 3 - nitro - 5 - sulphamyl - benzoic acid

A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (28 g.), β - naphthylamine (43.2 g.), dry ethanol (250 ml.), and dry sodium acetate (8.2 g.) was refluxed for 5 hours. Then the reaction mixture was evaporated *in vacuo* and the residue triturated with warm 1N hydrochloric acid (350 ml.). The precipitated 4 - (β - naphthylamino) - 3 - nitro - 5 - sulphamyl - benzoic acid was filtered off and recrystallized from aqueous ethanol. The compound was obtained as a monohydrate and had a melting point of 262°C. (decomp.).

B. 3 - Amino - 4 - (β - naphthylamino) - 5 - sulphamyl - benzoic acid

By substituting 4 - (β - naphthylamino) - 3 - nitro - 5 - sulphamyl - benzoic acid for 4 - anilino - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 9B, the compound was obtained with a melting point of 245°C.

EXAMPLE 31

3 - Amino - 4 - phenylthio - 5 - sulphamyl - benzoic acid

A. 3 - Nitro - 4 - phenylthio - 5 - sulphamyl - benzoic acid

A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (28 g.), thiophenol (10.25 ml.) and 1N sodium bicarbonate (300 ml.) was refluxed for 3 hours. After cooling, the precipitated sodium salt of 3 - nitro - 4 - phenylthio - 5 - sulphamyl - benzoic acid was filtered off. The sodium salt was dissolved in hot water (200 ml.) and the 3 - nitro - 4 - phenylthio - 5 - sulphamyl - benzoic acid was precipitated by the addition of 4N hydrochloric acid until the pH was 1. After isolation and recrystallization from aqueous ethanol, the acid was obtained with a melting point of 245—247°C.

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B. 3 - Amino - 4 - phenylthio - 5 - sulphamyl - benzoic acid

- A mixture of ammonium chloride (2.4 g.), metallic iron powder (24 g.), concentrated hydrochloric acid (0.1 ml.) and water (60 ml.) was heated to 90°C. with stirring and 3 - nitro - 4 - phenylthio - 5 - sulphamyl - benzoic acid (10 g.) was added in small portions during 2 hours. The reaction mixture was stirred on a steam bath for an additional 2 hours. After the addition of dilute sodium hydroxide until the pH was 8, the hot reaction mixture was filtered and the filter-cake was washed with warm dilute sodium hydroxide. After the addition of 4N hydrochloric acid to the filtrate until its pH was 2 and cooling, the thereby precipitated 3 - amino - 4 - phenylthio - 5 - sulphamyl - benzoic acid was filtered off and dried at 78°C. *in vacuo*. The melting point was 285°C.

EXAMPLE 32

3 - Amino - 4 - n - butylthio - 5 - sulphamyl - benzoic acid

- A. 4 - n - Butylthio - 3 - nitro - 5 - sulphamyl - benzoic acid and sodium salt.
 A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (28 g.), butylmercaptan (11 ml.), and 1N sodium bicarbonate (300 ml.) was stirred at 90°C. for 22 hours. After cooling, the precipitated sodium salt of 4 - n - butylthio - 3 - nitro - 5 - sulphamyl - benzoic acid was filtered off. The salt was dissolved in hot water and the acid precipitated by the addition of 4N hydrochloric acid. After cooling, the acid was isolated and recrystallized from aqueous ethanol. The melting point was 173—174°C.

B. 3 - Amino - 4 - butylthio - 5 - sulphamyl - benzoic acid

- To a solution of sodium dithionite (15.9 g.) in aqueous ammonia (13 g. NH_3 in 150 ml. water) 4 - n - butylthio - 3 - nitro - 5 - sulphamyl - benzoic acid (8.35 g.) was added in portions during 1 hour, while stirring. The reaction mixture was then heated on a steam bath for 30 minutes. Hydrochloric acid was added until the pH was 1 and heating was continued for 1 hour. After cooling, the pH was adjusted to 3 by the addition of 2N sodium hydroxide, and isopropanol (25 ml.) was added. The precipitated 3 - amino - 4 - n - butylthio - 5 - sulphamyl - benzoic acid was filtered off and recrystallized from aqueous ethanol. The melting point was 223—224°C.

EXAMPLE 33

3 - Amino - 5 - sulphamyl - 4 - (o - tolylthio) - benzoic acid

- A. 3 - Nitro - 5 - sulphamyl - 4 - (o - tolylthio) - benzoic acid
 A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (28 g.), o-thiocresol (12.4 g.), and 1N sodium bicarbonate (300 ml.) was refluxed for 3 hours. After cooling, the precipitated sodium salt of 3 - nitro - 5 - sulphamyl - 4 - o - tolylthio - benzoic acid was

filtered off and washed with 1N sodium bicarbonate solution. The sodium salt was dissolved in hot water (250 ml.) and the acid was precipitated by the addition of 4N hydrochloric acid (17 ml.). After isolation, recrystallization from aqueous ethanol and drying at 115°C. and 10 mm. Hg for 3 hours, the acid was obtained with a melting point of 165—166°C.

B. 3 - Amino - 5 - sulphamyl - 4 - (o - tolylthio) - benzoic acid

By substituting 3 - nitro - 5 - sulphamyl - 4 - (o - tolylthio) - benzoic acid (7.7 g.) for 4 - butylthio - 3 - nitro - 5 - sulphamyl - benzoic acid in Example 32B, 3 - amino - 5 - sulphamyl - 4 - (o - tolylthio) - benzoic acid was obtained with a melting point of 277°C.

EXAMPLE 34

3 - Amino - 4 - phenylsulphonyl - 5 - sulphamyl - benzoic acid

A. 3 - Nitro - 4 - phenylsulphonyl - 5 - sulphamyl - benzoic acid

A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (24 g.) benzene-sulphonic acid (13 g.), sodium acetate (16 g.) and anhydrous ethanol (65 ml.) was stirred at 78°C. for 20 hours. After cooling, the precipitated sodium salt of 3 - nitro - 4 - phenylsulphonyl - 5 - sulphamyl - benzoic acid was collected by suction. The sodium salt was dissolved in aqueous ethanol and the acid precipitated by acidification with 4N hydrochloric acid. After collection by suction and recrystallization from aqueous ethanol, the 3 - nitro - 4 - phenylsulphonyl - 5 - sulphamyl - benzoic acid had a melting point of 291°C. (decomp.)

B. 3 - Amino - 4 - phenylsulphonyl - 5 - sulphamyl - benzoic acid

A suspension of 3 - nitro - 4 - phenylsulphonyl - 5 - sulphamyl - benzoic acid (6 g.) in water (300 ml.) was hydrogenated at room temperature and 1.1 atmosphere hydrogen pressure after addition of Pd-on-carbon catalyst (0.3 g. catalyst containing 10 per cent Pd). After the hydrogen uptake had become negligible, the reaction mixture was neutralized by addition of 2N sodium hydroxide and from the resulting suspension the catalyst was removed by filtration. The filtrate was adjusted to a pH of 2.5 by addition of 4N hydrochloric acid and the precipitated 3 - amino - 4 - phenylsulphonyl - 5 - sulphamyl - benzoic acid was collected by suction. After recrystallization from aqueous ethanol, the acid had a melting point of 278°C. (decomp.).

EXAMPLE 35

3 - Amino - 4 - n - butylsulphonyl - 5 - sulphamyl - benzoic acid

A. 4 - n - Butylsulphonyl - 3 - nitro - 5 - sulphamyl - benzoic acid
 To a solution of 4 - n - butylthio - 3 - nitro - 5 - sulphamyl - benzoic acid (10 g.) in acetic acid (150 ml.) perhydrol (30 ml. of 30 per cent hydrogen peroxide in water) was added, while stirring. After additional stirring for 24 hours

at room temperature, the reaction mixture was diluted with water (150 ml.) and left standing for 8 hours. The precipitated 4 - n - butylsulphinyl - 3 - nitro - 5 - sulphamyl - benzoic acid was collected by suction, recrystallized from aqueous ethanol and dried *in vacuo*. The acid was obtained as a semi-hydrate with a melting point of 165°C. (decomp.).

5. B. 3 - Amino - 4 - n - butylsulphinyl - 5 - sulphamyl - benzoic acid

10 To a solution of sodium dithionite (7.3 g.) in water (50 ml.) conc. aqueous ammonia (25 ml.) was added, whereafter 4 - n - butylsulphinyl - 3 - nitro - 5 - sulphamyl - benzoic acid (4 g.) was added in portions at 25°C., while stirring. The reaction mixture was heated on a steam bath for 30 minutes. Thereafter 4N hydrochloric acid was added until a pH of 1, while the heating was continued. After the evolution of sulphur dioxide had ceased, the reaction mixture was adjusted to a pH of 2.5 by addition of 2N sodium hydroxide and cooled. The precipitated 3 - amino - 4 - n - butylsulphinyl - 5 - sulphamyl - benzoic acid was collected by suction, recrystallized from aqueous ethanol and dried *in vacuo* at 115°C. The acid was obtained with a melting point of 237°C. (decomp.).

EXAMPLE 36

- 30 3 - Amino - 5 - sulphamyl - 4 - (β,β,β - trifluoroethoxy) - benzoic acid

A. 3 - Nitro - 5 - sulphamyl - 4 - (β,β,β - trifluoroethoxy) - benzoic acid

35 To a solution of sodium β,β,β -trifluoroethanolate in β,β,β - trifluoro - ethanol (prepared by dissolving 2.1 g. of sodium in 45 ml. of β,β,β - trifluoroethanol) 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (4.2 g.) was added and the resulting solution was refluxed for 5 days. After evaporation of the reaction mixture *in vacuo*, water (50 ml.) was added and the aqueous solution was acidified with 4N hydrochloric acid. After standing in a refrigerator, the precipitate was collected by suction. After several recrystallizations from aqueous ethanol the 3 - nitro - 5 - sulphamyl - 4 - (β,β,β - trifluoroethoxy) - benzoic acid was obtained with a melting point of 195—197°C.

- 40 B. 3 - Amino - 5 - sulphamyl - 4 - (β,β,β - trifluoroethoxy) - benzoic acid

50 3 - Nitro - 5 - sulphamyl - 4 - (β,β,β - trifluoroethoxy) - benzoic acid (2 g.) in water (30 ml.) was adjusted to a pH of 9 by addition of lithium hydroxide and the resulting solution was hydrogenated at room temperature and at a hydrogen pressure of 1.1 atmosphere after addition of Pd-on-Carbon catalyst (0.2 g. catalyst containing 10 per cent Pd). After the hydrogen uptake had become negligible, the catalyst was removed by filtration and the 3 - amino - 5 - sulphamyl - 4 - (β,β,β - trifluoroethoxy) - benzoic acid was precipitated from the filtrate by addition of 4N hydrochloric acid until a pH of 2.5. After recrystallization from

aqueous ethanol and drying, the melting point of the compound was 253—254°C.

EXAMPLE 37

- 3 - Amino - 4 - (2 - methyl - 6 - pyridylamino) - 5 - sulphamyl - benzoic acid

A. Ethyl 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoate

A solution of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (28 g.) in dry ethanol (250 ml.) was saturated with gaseous hydrochloric acid. The reaction mixture was allowed to warm during the inlet of the hydrochloric acid. After standing for 3 hours, the solvent was removed by evaporation *in vacuo*. The residue was dissolved in a mixture of diethyl ether and dilute sodium hydrogen carbonate. The organic layer was separated, washed with water and dried. The diethyl ether was distilled off and the residue was recrystallized from dry ethanol yielding the ethyl 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoate with a melting point of 154°C.

- B. Ethyl 4 - (2 - methyl - 6 - pyridylamino) - 3 - nitro - 5 - sulphamyl - benzoate

A mixture of ethyl 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoate (3.08 g.) and 6 - amino - 2 - methyl - pyridine (3.24 g.) was melted in an oil bath at 140°C. and kept at this temperature for 2 hours, while stirring. The still warm reaction mixture was triturated with ethanol (35 ml.) and after cooling, the ethyl 4 - (2 - methyl - 6 - pyridylamino) - 3 - nitro - 5 - sulphamyl - benzoate was collected by suction and washed with ethanol. After recrystallization from acetonitrile the compound had a melting compound of 203—204°C.

- C. 4 - (2 - Methyl - 6 - pyridylamino) - 3 - nitro - 4 - sulphonyl - benzoic acid

Ethyl 4 - (2 - methyl - 6 - pyridylamino) - 3 - nitro - 5 - sulphamyl - benzoate (2 g.) was dissolved in 1N sodium hydroxide (30 ml.) and heated on a steam bath for 1 hour. After cooling, water (50 ml.) was added and the pH of the reaction mixture was adjusted to 4.5 by addition of 1N hydrochloric acid. The precipitated 4 - (2 - methyl - 6 - pyridylamino) - 3 - nitro - 5 - sulphamyl - benzoic acid was collected by suction, washed with water and dried. The compound had a melting point of 305°C. (decomp.).

- D. 3 - Amino - 4 - (2 - methyl - 6 - pyridylamino) - 5 - sulphamyl - benzoic acid

A suspension of 4 - (2 - methyl - 6 - pyridylamino) - 5 - sulphamyl - benzoic acid (4 g.) in water (20 ml.) was adjusted to pH 8 by addition of 1N lithium hydroxide and the resulting solution was hydrogenated at room temperature and at a hydrogen pressure of 1.1 atmosphere after addition of a Pd-on-Carbon catalyst (0.2 g. catalyst containing 10 per cent Pd). After the hydrogen uptake had become negligible, the catalyst was removed by filtration and the 3 - amino - 4 - (2 - methyl - 6 - pyridylamino) - 5 - sulphamyl - benzoic

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acid was precipitated from the filtrate by addition of 4N hydrochloric acid until a pH of 5. After recrystallization from aqueous ethanol and drying *in vacuo*, the melting point of the compound was 256°C. (decomp.).

EXAMPLE 38

3 - Amino - 4 - (4 - benzyloxyphenoxy) - 5 - sulphamyl - benzoic acid

A. *n* - Butyl 4 - chloro - 3 - nitro - 5 - sulphamyl benzoate

A mixture of 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoic acid (10 g.), *n*-butanol (100 ml.), and conc. sulphuric acid (2 ml.) was refluxed for 4 hours, during which 50 ml. of the solvent were distilled off slowly. After cooling, the *n* - butyl 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoate was isolated by filtration and recrystallized from *n*-butanol. The compound was obtained with a melting point of 140—141°C.

B. *n* - Butyl 4 - (4 - benzyloxyphenoxy) - 3 - nitro - 4 - sulphamyl - benzoate

To a solution of sodium *n*-butylate in *n*-butanol (prepared from 0.074 g. of sodium and 16 ml. of dry *n*-butanol) 4-benzyloxyphenol (0.64 g.) and *n* - butyl 4 - chloro - 3 - nitro - 5 - sulphamyl - benzoate were added. The reaction mixture was refluxed for 4 hours and cooled, whereafter the precipitated *n* - butyl 4 - (4 - benzyloxyphenoxy) - 3 - nitro - 5 - sulphamyl - benzoate was isolated and recrystallized from *n*-butanol. After drying, the compound was obtained with a melting point of 138—144°C.

C. 4 - (4 - benzyloxyphenoxy) - 3 - nitro - 5 - sulphamyl - benzoic acid

A solution of *n* - butyl 4 - (4 - benzyloxyphenoxy) - 3 - nitro - 5 - sulphamyl - benzoate (7.3 g.) in 1N sodium hydroxide (120 ml.) was heated on a steam bath for 45 minutes. After cooling and acidification by addition of 4N hydrochloric acid, the precipitated 4 - (4 - benzyloxyphenoxy) - 3 - nitro - 5 - sulphamyl - benzoic acid was isolated by filtration and recrystallized from aqueous ethanol. After drying, the compound was obtained with a melting point of 247°C.

D. 3 - Amino - 4 - (4 - benzyloxyphenoxy) - 5 - sulphamyl - benzoic acid

A suspension of 4 - (4 - benzyloxyphenoxy) - 3 - nitro - 5 - sulphamyl - benzoic acid (10 g.) in water (250 ml.) was adjusted to pH 11 by addition of 1N sodium hydroxide. The resulting solution was hydrogenated at room temperature and at 1.1 atmosphere hydrogen pressure after addition of a platinum oxide catalyst (0.4 g.). After the hydrogen uptake had become negligible, the catalyst was removed by filtration and the 3 - amino - 4 - (4 - benzyloxyphenoxy) - 5 - sulphamyl - benzoic acid was precipitated by adjusting the filtrate to pH 2.5 by addition of 4N hydrochloric acid. After recrystallization from aqueous ethanol and drying, the compound was obtained with a melting point of 264—265°C.

EXAMPLE 39

3 - Amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

A. 3 - Nitro - 4 - phenoxy - 5 - sulphamyl - benzoyl chloride

A mixture of 3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzoic acid (5 g.) and thionyl chloride (50 ml.) was heated on a steam bath for 5 hours. After evaporation *in vacuo* to dryness the compound was obtained as a crude product, which was used in the next step without further purification.

B. 3 - Nitro - 4 - phenoxy - 5 - sulphamyl - benzamide

3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzoyl chloride (4 g.) was added in portions to liquid ammonia (40 ml.). Then excess of ammonia was distilled off and the residue was triturated with water (50 ml.). The precipitated 3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzamide was isolated by filtration and recrystallized twice from aqueous ethanol. After drying *in vacuo*, the compound was obtained with a melting point of 255—256°C.

C. 3 - Amino - 4 - phenoxy - 5 - sulphamyl - benzamide

To a suspension of 3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzamide (2.4 g.) in water (25 ml.) 1N lithium hydroxide (10 ml.) was added. The resulting solution was hydrogenated at room temperature and at 1.1 atmosphere hydrogen pressure after addition of Pd-on-carbon catalyst (0.2 g. catalyst containing 10% Pd). After the hydrogen uptake had become negligible, the catalyst was removed by filtration, and the filtrate was then adjusted to pH 7.5 by addition of 4N hydrochloric acid. The precipitated 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzamide was isolated and dried *in vacuo*. The compound was obtained with a melting point of 291—292°C.

D. 3 - Amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

A mixture of 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzamide (1 g.) and 1N sodium hydroxide (20 ml.) was refluxed for 1 hour. After cooling, the 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid was precipitated from the reaction mixture by addition of 4N hydrochloric acid until pH 2.5. After several recrystallizations from aqueous ethanol and drying, the compound was obtained with a melting point of 252—253°C.

EXAMPLE 40

3 - Amino - 5 - acetylsulphamyl - 4 - phenoxy - benzoic acid

A. 5 - Acetylsulphamyl - 3 - nitro - 4 - phenoxy - benzoic acid

3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzoic acid (10 g.) was dissolved in water (250 ml.) by adjusting the pH to 8 by addition of 1N lithium hydroxide. Then acetic anhydride (12 g.) was added dropwise, while stirring and keeping the pH constant at pH 9 by means of 1N lithium hydroxide, using an

automatic titrator. After the acetic anhydride was consumed, the reaction mixture was acidified by addition of 4N hydrochloric acid. The precipitated 5 - acetylsulphamyl - 3 - nitro - 4 - phenoxy - benzoic acid was isolated by filtration and recrystallized from aqueous ethanol. The compound was obtained with a melting point of 270—271°C.

10 B. 3 - Amino - 5 - acetylsulphamyl - 4 - phenoxy - benzoic acid

By substituting 5 - acetylsulphamyl - 3 - nitro - 4 - phenoxy - benzoic acid for 3 - nitro - 4 - phenoxy - 5 - sulphamyl - benzoic acid in Example 1B the compound was obtained as a monohydrate with a melting point of 290—293°C.

EXAMPLE 41

3 - *n* - Butylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid and its sodium salt

20 To a suspension of 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (10 g.) in *n*-butanol (200 ml.) concentrated sulphuric acid (2 ml.) was added, while stirring. The reaction mixture was heated under reflux under such conditions that the water formed during the reaction was separated. When the NMR-spectrum of a sample of the reaction mixture diluted with *n*-butanol showed at the two doublets of the aromatic protons of the ring carrying the sulphamyl group that more than 90% of the butyl 3 - amino - 4 - phenoxy - 5 - sulphamyl benzoate intermediate formed, was converted to the corresponding 3 - *n* - butylamino - benzoate, which caused a frequency shift to higher field, 2N sodium hydroxide (200 ml.) was added and the boiling was continued for 45 minutes. After this saponification, the reaction mixture was neutralized to a pH of 8 by the addition of concentrated hydrochloric acid. After cooling, the sodium salt precipitated. It was filtered off and recrystallized from water (100 ml.). The sodium salt which crystallized with 3 mol. of water was then dissolved in boiling water (200 ml.). 1N Hydrochloric acid was added until the pH was 2.5, and, after cooling, the precipitated 3 - *n* - butylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid was collected by filtration. After recrystallization from aqueous ethanol and drying, the pure compound was obtained with a melting point of 230—231°C.

EXAMPLE 42

55 Ethanolamine salt of 3 - *n* - butylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

3 - *n* - Butylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (1.82 g.) was dissolved in boiling ethanol (20 ml.) and a solution of ethanolamine (0.3 g.) in ethanol (15 ml.) was added. After cooling, the precipitated ethanolamine salt was collected by filtration and recrystallized from ethanol. The melting point was 194—195°C.

EXAMPLE 43

65 Potassium salt of 3 - *n* - butylamino - 4 -

phenoxy - 5 - sulphamyl - benzoic acid

The ethanolamine salt of 3 - *n* - butylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (10 g.) was dissolved in boiling water (50 ml.) and aqueous saturated potassium chloride (5 ml.) was added. After cooling, the precipitated potassium salt was collected by filtration and recrystallized from water. The salt was obtained as a hydrate.

EXAMPLE 44

Neutral calcium salt of 3 - *n* - butylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

The ethanolamine salt of 3 - *n* - butylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (4.25 g.) was dissolved in water (150 ml.), and an aqueous solution of calcium chloride (2 ml. containing 40% CaCl₂) was added, while stirring. The precipitated calcium salt was collected by suction and dried. The salt contained 3.5 mol of water of crystallization.

EXAMPLE 45

Methyl 3 - *n* - butylamino - 4 - phenoxy - 5 - sulphamyl - benzoate

A mixture of 3 - *n* - butylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (3 g.) and methanol (60 ml.) was saturated with gaseous hydrochloric acid. The reaction mixture was allowed to warm during the saturation. After cooling and standing for 5 hours, the reaction mixture was evaporated *in vacuo* and the residue was recrystallized from methanol (12 ml.), whereby the methyl 3 - *n* - butylamino - 4 - phenoxy - 5 - sulphamyl - benzoate was obtained with a melting point of 148°C.

EXAMPLE 46

Cyanomethyl 3 - *n* - butylamino - 4 - phenoxy - 5 - sulphamyl - benzoate

A mixture of 3 - *n* - butylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (1 g.), chloroacetonitrile (0.625 g.), triethylamine (0.28 g.), and dry acetone (10 ml.) was refluxed for 19 hours. After cooling, the triethylamine hydrochloride formed was removed by filtration, and the filtrate was evaporated *in vacuo*. To the residue water (20 ml.) and ethylacetate (50 ml.) were added, and the pH of the aqueous layer was adjusted to pH 7.5. The organic layer was then separated, washed with dilute sodium bicarbonate, dried, and evaporated *in vacuo*. The residue was recrystallized several times from chloroform/petroleum ether. Thereby the cyanomethyl 3 - *n* - butylamino - 4 - phenoxy - 5 - sulphamyl - benzoate was obtained with a melting point of 159—161°C.

EXAMPLE 47

3 - Butylamino - 4 - (4 - sulphamylphenoxy) - 5 - sulphamyl - benzoic acid

To chlorosulphonic acid (5 ml.) 3 - butylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (1 g.) was added in portions, while stirring and keeping the temperature below 45°C. The reaction mixture was stirred for 10 minutes and then poured into ice water (10 g. of ice and 20 ml. of water). The precipitated

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oxy) -

butyl-
benzoic
stir-
15°C.

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r 10
10 g.
tated

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3 - butylamino - 4 - (4 - chlorosulphonyl-
phenoxy) - 5 - sulphamyl - benzoic acid was
isolated by filtration and without further puri-
fication added to aqueous ammonia (10 ml.
containing 2.5 g. of ammonia). Excess of am-
monia was removed by evaporation, and the
resulting solution adjusted to pH 2.5 by addi-
tion of 4N hydrochloric acid. The precipitated
3 - butylamino - 4(4 - sulphamylphenoxy) - 5-
sulphamyl - benzoic acid was isolated by
filtration, recrystallized from aqueous ethanol
and dried. The compound obtained had a
melting point of 265°C.

EXAMPLE 48

15 3 - n - Butylmethylanino - 4 - phenoxy - 5 -
sulphamyl - benzoic acid

A suspension of 3 - n - butylamino - 4 -
phenoxy - 5 - sulphamyl - benzoic acid (1 g.)
in aqueous ethanol (20 ml. of ethanol and 20
ml. of water) containing formaldehyde (0.35 g.)
was hydrogenated at room temperature and
at 1.1 atmosphere hydrogen pressure after
addition of Pd-on-carbon powder (0.1 g. cata-
lyst containing 10% of Pd). When the hydro-
gen uptake had become negligible, the reaction
mixture was warmed to 60°C. and the catalyst
was filtered off. After addition of water (15
ml.) to the filtrate and cooling, the precipitated
3 - n - butylmethylanino - 4 - phenoxy - 5 -
sulphamyl - benzoic acid was collected by
filtration and recrystallized from aqueous
ethanol. After drying in vacuo at 115°C., the
compound was obtained with a melting point
of 159—162°C.

EXAMPLE 49

35 3 - n - Butylamino - 4 - phenoxy - 5 - sulph-
amyl - benzamide

To a solution of 3 - butylamino - 4 - phen-
oxy - 5 - sulphamyl - benzoic acid (1 g.) in
dry acetone (10 ml.) triethylamine (0.278 g.)
was added. Methanesulphonyl chloride (0.315
g.) in dry acetone (5 ml.) was added to the
reaction mixture, while stirring. The agitation
was continued for 1.5 hours at 20°C. The re-
sulting solution of the mixed anhydride was
added dropwise to aqueous ammonia (30 ml.
containing 7 g. of ammonia), while stirring.
Then excess of ammonia and acetone were
removed by evaporation under reduced pres-
sure. The pH of the reaction mixture was
adjusted to 7.5 by means of 4N hydrochloric
acid and the precipitated 3 - butylamino - 4 -
phenoxy - 5 - sulphamyl - benzamide was
isolated by filtration and recrystallized several
times from aqueous ethanol. After drying in
vacuo at 115°C., the compound was obtained
with a melting point of 223—224°C.

EXAMPLE 50

60 3 - Benzylamino - 4 - phenylthio - 5 - sulph-
amyl - benzoic acid

A suspension of 3 - amino - 4 - phenylthio -
5 - sulphamyl - benzoic acid (4.05 g.) in water
(100 ml.) was adjusted to pH 7.5 by addition
of 1N lithium hydroxide. Benzylbromide (2.2
g.) was added and under stirring the pH was

kept at pH 7.5 by automatic titration with
lithium hydroxide. After the base consumption
had become negligible, the pH was adjusted to
2.5 by addition of dilute hydrochloric acid.
The precipitated 3 - benzylamino - 4 - phenyl-
thio - 5 - sulphamyl - benzoic acid was col-
lected and recrystallized from ethanol, where-
after the compound was obtained with a melt-
ing point of 224—225°C.

3 - Benzylamino - 4 - phenoxy - 5 - sulph-
amyl - benzoic acid

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By replacing 3 - amino - 4 - phenoxy - 5 -
sulphamyl - benzoic acid (3.8 g.) for 3 -
amino - 4 - phenylthio - 5 - sulphamyl - benzoic
acid, 3 - benzylamino - 4 - phenoxy - 5 -
sulphamyl - benzoic acid was obtained after
recrystallization from dilute ethanol with a
melting point of 264—265°C.

EXAMPLE 51

3 - n - Butylamino - 4 - phenylsulphinyl - 5 -
sulphamyl - benzoic acid

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A. 3 - n - Butylamino - 4 - phenylthio - 5 -
sulphamyl - benzoic acid and its sodium
salt

To a suspension of 3 - amino - 4 - phenyl-
thio - 5 - sulphamyl - benzoic acid (10 g.) in
n-butanol (200 ml.) concentrated sulphuric
acid (2 ml.) was added, while stirring. The
reaction mixture was heated under reflux under
such conditions that the water formed during
the reaction was separated. When the NMR-
spectrum of a sample of the reaction mixture
diluted with n-butanol, showed at the two
doublets of the aromatic protons of the ring
carrying the sulphamyl group that more than
90 per cent of the butyl 3 - amino - 4 -
phenylthio - 5 - sulphamyl benzoate inter-
mediate formed was converted to the corres-
ponding 3 - n - butylamino - benzoate, which
caused a frequency shift to higher field, 2N
sodium hydroxide (200 ml.) was added and the
boiling was continued for 45 minutes. After
this saponification, the reaction mixture was
neutralized to a pH of 8 by the addition of
concentrated hydrochloric acid. After cooling,
the sodium salt of 3 - n - butylamino - 4 -
phenylthio - 5 - sulphamyl - benzoic acid pre-
cipitated. It was filtered off and recrystallized
from water (100 ml.). The sodium salt which
dissolved in boiling water (200 ml.) 1N
Hydrochloric acid was added until the pH was
2.5, and, after cooling, the precipitated 3 - n -
butylamino - 4 - phenylthio - 5 - sulphamyl -
benzoic acid was collected by filtration. After
recrystallization from aqueous ethanol and
drying, the pure compound was obtained with
a melting point of 203—204°C.

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B. 3 - n - Butylamino - 4 - phenylsulphinyl -
5 - sulphamyl - benzoic acid

To a suspension of 3 - n - butylamino - 4 -
phenylthio - 5 - sulphamyl - benzoic acid (0.5
g.) in acetic acid (5 ml.) perhydrol (2.5 ml.
of 30 per cent hydrogen peroxide in water)
was added, while stirring. The reaction mix-

ture was stirred for an additional 24 hours at 30°C., whereafter the 3 - *n* - butylamino - 4 - phenylsulphinyl - 5 - sulphamyl - benzoic acid was collected by suction and washed with aqueous acetic acid. After recrystallization from aqueous ethanol, the compound was obtained with a melting point of 203—204°C. (decomp.).

EXAMPLE 52

10 4 - Anilino - 3 - benzylamino - 5 - sulphamyl - benzoic acid

A. Ethyl 4 - anilino - 3 - benzylamino - 5 - sulphamyl - benzoate

A mixture of 3 - amino - 4 - anilino - 5 - sulphamyl - benzoic acid (2 g.), benzylbromide (3 g.) and ethanol (50 ml. 99.9%) was refluxed for 8 hours. After cooling, the ethyl 4 - anilino - 3 - benzylamino - 5 - sulphamyl - benzoate crystallized and was collected by suction. After recrystallization from ethanol the melting point was 160—161°C.

20 B. 4 - Anilino - 3 - benzylamino - 5 - sulphamyl - benzoic acid

A solution of ethyl 4 - anilino - 3 - benzylamino - 5 - sulphamyl - benzoate (1 g.) in 1N sodium hydroxide (15 ml.) was heated on the steam bath for 1 hour. After cooling, the 4 - anilino - 3 - benzylamino - 5 - sulphamyl - benzoic acid was precipitated by addition of acetic acid, collected and recrystallized from 60% ethanol in water. The melting point was 248—249°C.

EXAMPLE 53

35 4 - Anilino - 3 - benzylamino - 5 - phenylsulphamyl - benzoic acid

A. Ethyl 4 - anilino - 3 - benzylamino - 5 - phenylsulphamyl - benzoate

By replacing in Example 52A 3 - amino - 4 - anilino - 5 - sulphamyl - benzoic acid (2 g.) with 3 - amino - 4 - anilino - 5 - phenylsulphamyl - benzoic acid (4.4 g.) and increasing the amount of benzylbromide to 3.9 g., ethyl 4 - anilino - 3 - benzylamino - 5 - phenylsulphamyl - benzoate was obtained with a melting point of 166—167°C.

45 B. 4 - Anilino - 3 - benzylamino - 5 - phenylsulphamyl - benzoic acid

A solution of ethyl 4 - anilino - 3 - benzylamino - 5 - phenylsulphamyl - benzoate (3 g.) in 1N sodium hydroxide (30 ml.) was heated on the steam bath for 1 hour. The 4 - anilino - 3 - benzylamino - 5 - phenylsulphamyl - benzoic acid was precipitated by addition of 4N hydrochloric acid until pH 2 and recrystallized from acetone-water and 80% ethanol in water; the melting point was 243°C.

EXAMPLE 54

3 - Benzylamino - 4 - phenylsulphinyl - 5 - sulphamyl - benzoic acid

60 To a suspension of 3 - benzylamino - 4 - phenylthio - 5 - sulphamyl - benzoic acid (0.8 g.) in acetic acid (20 ml.) perhydrol (1.5 ml. of 30 per cent hydrogen peroxide in water) was added while stirring. The reaction mixture

was stirred for an additional 75 hours at room temperature whereafter the 3 - benzylamino - 4 - phenylsulphinyl - 5 - sulphamyl - benzoic acid was collected by filtration and washed with acetic acid. After recrystallization from aqueous methanol and drying, the acid had a melting point of 234°C.

EXAMPLE 55

3 - Benzylamino - 4 - *n* - butylsulphinyl - 5 - sulphamyl - benzoic acid

A mixture of 3 - amino - 4 - *n* - butylsulphinyl - 5 - sulphamyl - benzoic acid (2 g.), benzyl bromide (3.5 g.), and dry ethanol (20 ml.) was refluxed for 16 hours. The reaction mixture was evaporated *in vacuo*. The residue containing the ethyl 3 - benzylamino - 4 - *n* - butylsulphinyl - 5 - sulphamyl - benzoate was saponified by addition of 1N sodium hydroxide (30 ml.) and standing for 16 hours at room temperature. After extraction with diethyl ether, the aqueous layer was adjusted to a pH of 7.4 by addition of 4N hydrochloric acid and the sodium salt of 3 - benzylamino - 4 - *n* - butylsulphinyl - 5 - sulphamyl - benzoic acid was precipitated by addition of sodium chloride (5 g.). The sodium salt was isolated and recrystallized from a little amount of water. The salt was dissolved in aqueous ethanol (25 per cent ethanol in water) and the 3 - benzylamino - 4 - *n* - butylsulphinyl - 5 - sulphamyl - benzoic acid was precipitated by addition of 4N hydrochloric acid until a pH of 3. After recrystallization from aqueous ethanol and drying *in vacuo*, the compound was obtained as a monohydrate with a melting point of 182°C. (decomp.).

EXAMPLE 56

3 - (3,4 - Methylenedioxybenzylamino) - 4 - phenoxy - 5 - sulphamyl - benzoic acid

To a suspension of 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (1.54 g.) in acetic acid (30 ml.) piperonal (0.75 g.) was added. After the addition of platinum oxide (25 mg.) and a catalytic amount of *p*-toluenesulphonic acid, the reaction mixture was hydrogenated at room temperature and 1.1 atmosphere hydrogen pressure until the hydrogen uptake had become negligible. Then the reaction mixture was filtered by suction. The filter cake was suspended in water (100 ml.) and the pH was adjusted to 8.5 by the addition of lithium hydroxide. After the catalyst had been removed from the resulting solution, the 3 - (3,4 - methylenedioxybenzylamino) - 4 - phenoxy - 5 - sulphamyl - benzoic acid was precipitated from the filtrate by the addition of 4N hydrochloric acid until the pH was 3. After recrystallization from methanol, the melting point was 229—230°C.

3 - (Methoxy-, methyl-, or chloro - benzylamino) - 4 - phenoxy - 5 - sulphamyl - benzoic acids

By substituting methyl-, or methoxy-, or chloro-benzaldehyde (0.005 mol.) for the

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piperonal in Example 56 and recrystallization from aqueous ethanol, the corresponding benzoic acids were obtained.

EXAMPLE 57

- 5 3 - n - Hexylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid, and its sodium salt
A. n - Hexyl 3 - n - hexylamino - 4 - phenoxy - 5 - sulphamyl - benzoate

A mixture of 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (4.62 g.), 1 - bromo - n - hexane (5 g.), methanesulphonic acid (0.05 ml.), and n-hexanol (40 ml.) was refluxed for 60 hours. After cooling, the precipitated n-hexyl 3 - n - hexylamino - 4 - phenoxy - 5 - sulphamyl - benzoate was collected and recrystallized from hexanol. The melting point was 137—138°C.

- B. 3 - n - Hexylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid, and its sodium salt

20 n - Hexyl 3 - n - hexylamino - 4 - phenoxy - 5 - sulphamyl - benzoate (2 g.) was dissolved in 1N sodium hydroxide (30 ml.) and heated on a steam bath for 1 hour. Then the reaction mixture was adjusted to a pH of 8 by the addition of 4N hydrochloric acid. After cooling, the sodium salt of 3 - n - hexylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid was collected by suction and dried. The sodium salt was dissolved in hot water (100 ml.) and the acid was precipitated by the addition of 4N hydrochloric acid until the pH was 2.5. After cooling, the acid was collected and recrystallized from aqueous ethanol. The melting point was 221—223°C.

EXAMPLE 58

- 3 - Allylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

- A. Ethyl 3 - allylamino - 4 - phenoxy - 5 - sulphamyl - benzoate

A mixture of 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (3.08 g.), allylbromide (7.25 g.) and dry ethanol was refluxed for 24 hours. After cooling, the precipitated ethyl 3 - allylamino - 4 - phenoxy - 5 - sulphamyl - benzoate was filtered off and recrystallized from ethanol. The melting point of the ester was 153—154°C.

- B. 3 - Allylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

50 Ethyl 3 - allylamino - 4 - phenoxy - 5 - sulphamyl - benzoate (1 g.) was dissolved in 1N sodium hydroxide (15 ml.) and left standing at room temperature for 24 hours. Then water (5 ml.) was added and the pH was adjusted to 3 by the addition of 4N hydrochloric acid. The precipitated 3 - allylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid was collected and dried. The melting point was 223—225°C.

EXAMPLE 59

- 4 - Phenoxy - 3 - propargylamino - 5 - sulphamyl - benzoic acid

- A. Ethyl 4 - phenoxy - 3 - propargylamino - 5 - sulphamyl - benzoate

By substituting propargylbromide (4.8 g.) for the allylbromide in Example 58A and extending the reaction time to 48 hours, ethyl 4 - phenoxy - 3 - propargylamino - 5 - sulphamyl - benzoate was obtained with a melting point of 189—190°C.

- B. 4 - Phenoxy - 3 - propargylamino - 5 - sulphamyl - benzoic acid

By substituting ethyl 4 - phenoxy - 3 - propargylamino - 5 - sulphamyl - benzoate for ethyl 3 - allylamino - 4 - phenoxy - 5 - sulphamyl - benzoate in Example 58B and by recrystallizing from dilute ethanol, 4 - phenoxy - 3 - propargylamino - 5 - sulphamyl - benzoic acid was obtained with a melting point of 222—223°C.

EXAMPLE 60

- 4 - Phenoxy - 3 - n - propylamino - 5 - sulphamyl - benzoic acid

- A. Ethyl 4 - phenoxy - 3 - n - propylamino - 5 - sulphamyl - benzoate

A solution of ethyl 3 - allylamino - 4 - phenoxy - 5 - sulphamyl - benzoate (1.65 g.) in ethanol (150 ml.) was hydrogenated at room temperature, and 1.1 atmosphere hydrogen pressure after the addition of a palladium-on-carbon catalyst (0.6 g. catalyst containing 10% Pd). After the hydrogen uptake had become negligible, the catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was recrystallized twice from aqueous ethanol, resulting in ethyl 4 - phenoxy - 3 - n - propylamino - 5 - sulphamyl - benzoate with a melting point of 150—151°C.

- B. 4 - Phenoxy - 3 - n - propylamino - 5 - sulphamyl - benzoic acid

Ethyl 4 - phenoxy - 3 - n - propylamino - 5 - sulphamyl - benzoate (1 g.) was dissolved in 1N sodium hydroxide (15 ml.), and heated on a steam bath for 1 hour. After cooling, the 4 - phenoxy - 3 - n - propylamino - 5 - sulphamyl - benzoic acid was precipitated by the addition of 4N hydrochloric acid until the pH was 2.5; the melting point was 223—224°C.

EXAMPLE 61

- 3 - Ethylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

A mixture of 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (3.08 g.), ethyl iodide (20 ml.), and ethanol (20 ml.) was refluxed for 6 days. After cooling, the reaction mixture was evaporated to dryness and the residue was washed with a little ethanol followed by diethyl ether. The ethyl 3 - ethylamino - 4 - phenoxy - 5 - sulphamyl - benzoate obtained was dissolved in 1N sodium hydroxide (35 ml.) and heated on a steam bath for 30 minutes. After cooling, the reaction mixture was adjusted to pH 2.5 by addition of 4N hydrochloric acid and the precipitated 3 - ethylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid was isolated by filtration. After recrystallization from ethanol and drying *in vacuo* at 115°C., the compound was obtained with a melting point of 236—237°C.

EXAMPLE 62

3 - *n* - Pentylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

A. *n* - Pentyl 3 - *n* - pentylamino - 4 - phenoxy - 5 - sulphamyl - benzoate

A mixture of 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (6 g.), *n*-pentanol (60 ml.) and conc. sulphuric acid (0.5 ml.) was refluxed for 24 hours. After cooling, the precipitated *n* - pentyl 3 - *n* - pentylamino - 4 - phenoxy - 5 - sulphamyl - benzoate was isolated by filtration and recrystallized from *n*-pentanol. After drying *in vacuo*, the compound was obtained with a melting point of 138—139°C.

B. 3 - *n* - Pentylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

A mixture of *n* - pentyl 3 - *n* - pentylamino - 4 - phenoxy - 5 - sulphamyl - benzoate (4.5 g.) and 1N sodium hydroxide (70 ml.) was heated on a steam bath for 1 hour. After cooling, the reaction mixture was adjusted to a pH at 2.5 by addition of 4N hydrochloric acid. The precipitated 3 - *n* - pentyl - 4 phenoxy - 5 - sulphamyl - benzoic acid was isolated by filtration and recrystallized from aqueous ethanol. After drying *in vacuo*, the compound was obtained with a melting point of 223—224°C.

EXAMPLE 63

3 - Benzylamino - 4 - (4 - benzyloxyphenoxy) - 5 - sulphamyl - benzoic acid

A. Ethyl 3 - benzylamino - 4 - (4 - benzyloxyphenoxy) - 5 - sulphamyl - benzoate

A mixture of 3 - amino - 4 - (4 - benzyloxyphenoxy) - 5 - sulphamyl - benzoic acid (4 g.), benzyl bromide (4.1 g.), and ethanol (60 ml.) was refluxed for 4 hours. After cooling, the precipitated ethyl 3 - benzylamino - 4 - (4 - benzyloxyphenoxy) - 5 - sulphamyl - benzoate was isolated by filtration and recrystallized from ethanol. The compound was obtained with a melting point of 166°C.

B. 3 - Benzylamino - 4 - (4 - benzyloxyphenoxy) - 5 - sulphamyl - benzoic acid

A solution of ethyl 3 - benzylamino - 4 - (4 - benzyloxyphenoxy) - 5 - sulphamyl - benzoate (2 g.) in 1N sodium hydroxide (45 ml.) was left standing at room temperature for 40 hours. Then the reaction mixture was adjusted to a pH of 2.5 by addition of 4N hydrochloric acid. The precipitated 3 - benzylamino - 4 - (4 - benzyloxyphenoxy) - 5 - sulphamyl - benzoic acid was isolated by filtration and recrystallized from aqueous ethanol. After drying, the compound was obtained with a melting point of 249—251°C.

EXAMPLE 64

3 - Benzylamino - 4 - (4 - hydroxyphenoxy) - 5 - sulphamyl - benzoic acid

A suspension of 3 - benzylamino - 4 - (4 - benzyloxyphenoxy) - 5 - sulphamyl - benzoic acid (0.5 g.) in water (5 ml.) was adjusted to a pH of 11 by addition of 1N sodium hydroxide. The resulting solution was hydro-

genated at room temperature and 1.1 atmosphere hydrogen pressure after addition of Pd-on-carbon powder catalyst (0.025 g. catalyst containing 10% of Pd). After the hydrogen uptake had become negligible, the catalyst was removed by filtration, and from the filtrate the 3 - benzylamino - 4 - (4 - hydroxyphenoxy) - 5 - sulphamyl - benzoic acid was precipitated by addition of 4N hydrochloric acid until a pH of 2. After isolation by filtration and recrystallization from aqueous ethanol, the compound was obtained with a melting point of 276—277°C. (decomp.).

EXAMPLE 65

3 - Furfurylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid and its sodium salt

A. Sodium salt of 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

A suspension of 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (10 g.) in water (25 ml.) was adjusted to a pH of 8 by the addition of 1N sodium hydroxide at 80°C. After cooling, the precipitated sodium salt was collected by suction and dried *in vacuo* at 115°C.

B. Sodium salt of 3 - furfurylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

A mixture of the sodium salt of 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (5 g.), furfural (2.2 g.), and methanol (75 ml.) was refluxed for 5 hours. Then the reaction mixture was cooled to 0°C. and sodium borohydride, NaBH₄, (2.2 g.) was added in portions during 1 hour, while stirring and keeping the temperature at 0—5°C. After standing for 16 hours, the solvent was distilled off *in vacuo* and the residue dissolved in water (45 ml.). The solution was adjusted to a pH of 7.5 by the addition of 4N hydrochloric acid and cooled. The precipitated sodium salt of 3 - furfurylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid was collected by suction, recrystallized from water and dried.

C. 3 - Furfurylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

The sodium salt of 3 - furfurylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid (1 g.) was dissolved in water (50 ml.) at 50°C. and acetic acid (1 ml.) was added dropwise, while stirring. After cooling, the precipitated acid was collected by suction and recrystallized from aqueous ethanol. The melting point was 219—220°C.

EXAMPLE 66

3,4 - Dibenzylamino - 5 - sulphamyl - benzoic acid, and its sodium salt

A suspension of 3 - amino - 4 - benzylamino - 5 - sulphamyl - benzoic acid (1 g.) in water (20 ml.) was adjusted to a pH of 7.5 by the addition of 1N sodium hydroxide. To the solution benzyl bromide (0.54 g.) was added and, while stirring, the pH was kept at 7.5 by automatic titration with sodium hydroxide. After the base consumption had become negligible, the precipitated sodium salt

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of 3,4 - dibenzylamino - 5 - sulphamyl - benzoic acid was collected by suction and washed with a little water. The sodium salt was dissolved in aqueous ethanol (62 ml. containing 25% of ethanol) and the acid was precipitated by the addition of acetic acid (2 ml.). The acid was collected by suction and dried. The melting point was 205°C.

EXAMPLE 67

10 3 - Benzylamino - 4 - (β - phenylethylamino) - 5 - sulphamyl - benzoic acid

A mixture of 3 - amino - 4 - (β - phenylethylamino) - 5 - sulphamyl - benzoic acid (3.35 g.), benzyl bromide (5.3 g.), and anhydrous ethanol (30 ml.) was refluxed for 48 hours. After cooling, the precipitated ethyl ester was collected by suction, recrystallized from ethanol and saponified by heating in 1N sodium hydroxide (30 ml.) for 1 hour. The 3 - benzylamino - 4 - (β - phenylethylamino) - 5 - sulphamyl - benzoic acid was precipitated at room temperature by the addition of 4N hydrochloric acid until the pH was 2.5. After recrystallization from aqueous ethanol, the compound was obtained with a melting point of 203°C.

EXAMPLE 68

3 - Benzylamino - 4 - piperidino - 5 - sulphamyl - benzoic acid

30 A mixture of 3 - amino - 4 - piperidino - 5 - sulphamyl - benzoic acid (2.5 g.), benzyl bromide (1.4 g.), and dry ethanol (30 ml.) was refluxed for 3 days. The reaction mixture was evaporated *in vacuo*, and the residue was washed with petroleum ether. The crude ethyl 3 - benzylamino - 4 - piperidino - 5 - sulphamyl - benzoate obtained was saponified by the addition of 1N sodium hydroxide and heated on a steam bath for 1 hour. After cooling and adjusting the pH to 4 by means of 4N hydrochloric acid, 3 - benzylamino - 4 - piperidino - 5 - sulphamyl - benzoic acid precipitated. After collecting and recrystallizing from aqueous ethanol, the compound was obtained as a hemi-hydrate with a melting point of 195°C.

EXAMPLE 69

3 - Benzylamino - 4 - isopropylamino - 5 - sulphamyl - benzoic acid

50 A mixture of 3 - amino - 4 - isopropylamino - 5 - sulphamyl - benzoic acid (2.62 g.), benzyl bromide (4.28 g.), and anhydrous ethanol (25 ml.) was refluxed for 24 hours. The reaction mixture was evaporated *in vacuo*. 55 1N sodium hydroxide (30 ml.) was added and the mixture heated on a steam bath for 1 hour. After cooling and extracting with diethyl ether, the aqueous layer was adjusted to a pH of 3 by the addition of 4N hydrochloric acid. 60 The precipitated 3 - benzylamino - 4 - isopropylamino - 5 - sulphamyl - benzoic acid was collected by suction and recrystallized from aqueous ethanol. The melting point was 233—234°C.

EXAMPLE 70

3 - Benzylamino - 4 - (2 - methyl - 6 - pyridylamino) - 5 - sulphamyl - benzoic acid

A suspension of 3 - amino - 4 - (2 - methyl - 6 - pyridylamino) - 5 - sulphamyl - benzoic acid (0.5 g.) in water (25 ml.) was adjusted to a pH of 8 by addition of 1N lithium hydroxide. To the resulting solution benzyl bromide (0.2 g.) was added while, under stirring, the pH was kept at 8 by automatic titration with 1N lithium hydroxide. After the base consumption had become negligible, the crude 3 - benzylamino - 4 - (2 - methyl - 6 - pyridylamino) - 5 - sulphamyl - benzoic acid was precipitated from the reaction mixture by adjusting the pH to 5 by means of 1N hydrochloric acid. The compound was collected by suction, recrystallized from aqueous ethanol, and dried. The melting point of the compound was 168—170°C.

EXAMPLE 71

Ethyl 3 - benzylamino - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoate

A mixture of 3 - amino - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoic acid (1.82 g.), benzyl bromide (2 g.), and anhydrous ethanol (15 ml.) was refluxed for 7 hours. The solution was cooled and the precipitated ethyl 3 - benzylamino - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoate was collected by suction. After recrystallization from ethanol, the melting point was 166—168°C.

Ethyl 3 - benzylamino - 4 - (*p* - methoxyanilino) - 5 - sulphamyl - benzoate

By substituting 3 - amino - 4 - (*p* - methoxyanilino) - 5 - sulphamyl - benzoic acid (1.69 g.) for 3 - amino - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoic acid and extending the heating time to 20 hours, the compound was obtained with a melting point of 145°C.

Ethyl 3 - benzylamino - 4 - (*m* - methoxyanilino) - 5 - sulphamyl - benzoate

By substituting 3 - amino - 4 - (*m* - methoxyanilino) - 5 - sulphamyl - benzoic acid (1.69 g.) for 3 - amino - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoic acid and extending the heating time to 20 hours, the compound was obtained with a melting point of 149—152°C.

Ethyl 3 - benzylamino - 4 - (*p* - methoxyphenoxy) - 5 - sulphamyl - benzoate

By substituting 3 - amino - 4 - (*p* - methoxyphenoxy) - 5 - sulphamyl - benzoic acid (1.69 g.) for 3 - amino - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoic acid, the compound was obtained as a precipitate during the heating time. After collection by suction and recrystallizing from acetone, the compound had a melting point of 189—190°C.

Ethyl 3 - benzylamino - 4 - cyclohexylamino - 5 - sulphamyl - benzoate

By substituting 3 - amino - 4 - cyclohexyl-

5 amino - 5 - sulphamyl - benzoic acid (1.5 g.) for 3 - amino - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoic acid and adding water (13 ml.) to the cooled reaction mixture, the compound was obtained with a melting point of 176—177°C.

Ethyl 3 - benzylamino - 5 - sulphamyl - 4 - (*m* - trifluoromethylanilino) benzoate

10 By substituting 3 - amino - 5 - sulphamyl - 4 - (*m* - trifluoromethylanilino) - benzoic acid (1.8 g.) for 3 - amino - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoic acid and increasing the amount of ethanol to 50 ml., the compound was obtained with a melting point of 189—190°C.

15 Ethyl 3 - benzylamino - 4 - (β - naphthylamino) - 5 - sulphamyl - benzoate

20 By substituting 3 - amino - 4 - (β - naphthylamino) - 5 - sulphamyl - benzoic acid (1.8 g.) for 3 - amino - 5 - sulphamyl - 4 - (*m* - trifluoromethylphenoxy) - benzoic acid and increasing the amount of ethanol to 25 ml., the compound was obtained with a melting point of 199—201°C.

25 EXAMPLE 72

Ethyl 3 - benzylamino - 5 - sulphamyl - 4 - (*m* - toluidino) - benzoate

30 A mixture of 3 - amino - 5 - sulphamyl - 4 - (*m* - toluidino) - benzoic acid (1.5 g.), benzyl bromide (2.5 g.), and anhydrous ethanol (50 ml.) was heated under reflux for 10 hours. The resulting solution was cooled and the precipitated ethyl 3 - benzylamino - 5 - sulphamyl - 4 - (*m* - toluidino) - benzoate collected by suction. After recrystallization from ethanol, the compound had a melting point of 169—170°C.

35 Ethyl 3 - benzylamino - 5 - sulphamyl - 4 - (*p* - toluidino) - benzoate

40 By substituting 3 - amino - 5 - sulphamyl - 4 - (*p* - toluidino) - benzoic acid for 3 - amino - 5 - sulphamyl - 4 - (*m* - toluidino) - benzoic acid, the compound was obtained with a melting point of 159—160°C.

45 Ethyl 3 - benzylamino - 4 - (*p* - chloroanilino) - 5 - sulphamyl - benzoate

50 By substituting 3 - amino - 4 - (*p* - chloroanilino) - 5 - sulphamyl - benzoic acid (2 g.) for 3 - amino - 5 - sulphamyl - 4 - (*m* - toluidino) - benzoic acid, the compound was obtained with a melting point of 187°C.

55 Ethyl 3 - benzylamino - 4 - (2,4 - dimethylanilino) - 5 - sulphamyl - benzoate

By substituting 3 - amino - 4 - (2,4 - dimethylanilino) - 5 - sulphamyl - benzoic acid (2 g.) for 3 - amino - 5 - sulphamyl - 4 - (*m* - toluidino) - benzoic acid, the compound was obtained with a melting point of 167—168°C.

60 EXAMPLE 73

Ethyl 3 - benzylamino - 4 - *n* - butylthio - 5 - sulphamyl - benzoate

65 A mixture of 3 - amino - 4 - *n* - butylthio - 5 - sulphamyl - benzoic acid (1.5 g.), benzyl bromide (2.1 g.), and anhydrous ethanol (20 ml.) was refluxed for 24 hours. After the first

7 hours of refluxing, benzyl bromide (0.7 g.) was added. After cooling, the precipitated ethyl 3 - benzylamino - 4 - *n* - butylthio - 5 - sulphamyl - benzoate was collected and recrystallized from ethanol, whereafter the compound was obtained with a melting point of 151—157°C.

Ethyl 3 - benzylamino - 4 - (*p* - carbethoxyanilino) - 5 - sulphamyl - benzoate

By substituting 3 - amino - 4 - (*p* - carboxyanilino) - 5 - sulphamyl - benzoic acid (1.7 g.) for 3 - amino - 4 - *n* - butylthio - 5 - sulphamyl - benzoic acid, the compound was obtained with a melting point of 161°C.

EXAMPLE 74

Ethyl 3 - benzylamino - 4 - morpholino - 5 - sulphamyl - benzoate

A mixture of 3 - amino - 4 - morpholino - 5 - sulphamyl - benzoic acid (3 g.), benzyl bromide (4 g.), and anhydrous ethanol (45 ml.) was refluxed. After 24 hours and again after 48 hours a solution of benzyl bromide (1.5 g.) in anhydrous ethanol (5 ml.) was added during 4 hours. After the second addition, the refluxing was continued for 24 hours. The reaction mixture was cooled and the precipitated ethyl 3 - benzylamino - 4 - morpholino - 5 - sulphamyl - benzoate was collected by suction and recrystallized from ethanol, whereafter the compound was obtained with a melting point of 185—186°C.

Ethyl 3 - benzylamino - 5 - sulphamyl - 4 - (*o* - tolylthio) - benzoate

By substituting 3 - amino - 5 - sulphamyl - 4 - (*o* - tolylthio) - benzoic acid for 3 - amino - 4 - morpholino - 5 - sulphamyl - benzoic acid, the compound was obtained with a melting point of 166—167°C.

EXAMPLE 75

Ethyl 3 - benzylamino - 5 - sulphamyl - 4 - (β,β,β - trifluoroethoxy) - benzoate

A mixture of 3 - amino - 5 - sulphamyl - 4 - (β,β,β - trifluoroethoxy) - benzoic acid (0.6 g.), benzyl bromide (1.2 g.) and dry ethanol (8 ml.) was refluxed for 5 hours. After cooling, the precipitated ethyl 3 - benzylamino - 5 - sulphamyl - 4 - (β,β,β - trifluoroethoxy) - benzoate was collected by suction and recrystallized from dry ethanol. After drying, the compound had a melting point of 163—165°C.

EXAMPLE 76

4 - Substituted 3 - benzylamino - 5 - sulphamyl - benzoic acids by saponification of the corresponding ethyl esters

General procedure:

The corresponding ethyl ester (2 g.) prepared as in Examples 71 to 75, was dissolved in 1N sodium hydroxide (30 ml.) and heated on a steam bath for 1 hour. After cooling, the acid was precipitated by the addition of 4N hydrochloric acid until the pH was 2.5, collected by suction, recrystallized from aqueous ethanol, and dried at 115°C. *in vacuo*.

(0.7 g.)
precipitated
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and re-
the com-
point of
70
bethoxy-
oate
carboxy-
1 (1.7 g.)
- sulph-
md was
°C.
80
no - 5 -
holino -
benzyl
(45 ml.)
in after
(1.5 g.)
ed dur-
ion, the
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e pre-
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collected
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with a
95
1 - 4 -
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amino - 100
ic acid,
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1 - 4 - 105
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uction
After
int of 115
sulph-
of the
120
pre-
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) and
After 125
the
c pH
lized
5°C.
130

The following acids were obtained:

- 3 - Benzylamino - 5 - sulphamyl - 4 -
(*m* - toluidino) - benzoic acid with a
melting point of 226—227°C.
5 3 - Benzylamino - 5 - sulphamyl - 4 -
(*p* - toluidino) - benzoic acid with a
melting point of 217—218°C.
3 - Benzylamino - 4 - (*p* - methoxyanilino) -
5 - sulphamyl - benzoic acid with a melt-
ing point of 207—208°C.
10 3 - Benzylamino - 5 - sulphamyl - 4 -
(*m* - trifluoromethylanilino) - benzoic acid
with a melting point of 227—228°C. after
recrystallization from isopropanol.
15 3 - Benzylamino - 4 - (*p* - chloranilino) -
5 - sulphamyl - benzoic acid with a melt-
ing point of 245—246°C.
3 - Benzylamino - 4 - (2,4 - dimethyl-
anilino) - 5 - sulphamyl - benzoic acid
with a melting point of 245—246°C.
20 3 - Benzylamino - 4 - (*p* - carboxyanilino) -
5 - sulphamyl - benzoic acid prepared
from ethyl 3 - benzylamino - 4 - (*p* -
carbethoxyanilino) - 5 - sulphamyl -
benzoic acid and precipitated at a pH of
1.5 with a melting point higher than
300°C. and containing 1/2 mol of water
of crystallization.
25 3 - Benzylamino - 5 - sulphamyl - 4 - (*o* -
tolylthio) - benzoic acid with a melting
point of 227—228°C.
30 3 - Benzylamino - 4 - (*p* - methoxyphen-
oxy) - 5 - sulphamyl - benzoic acid with a
melting point of 230—232°C.
35 3 - Benzylamino - 5 - sulphamyl - 4 - (*m* -
trifluoromethylphenoxy) - benzoic acid
with a melting point of 220—222°C.
3 - Benzylamino - 4 - (β - naphthylamino) -
5 - sulphamyl - benzoic acid with a melt-
ing point of 261—263°C.
40 3 - Benzylamino - 4 - cyclohexylamino -
5 - sulphamyl - benzoic acid with a melt-
ing point of 249—250°C.
45 3 - Benzylamino - 4 - morpholino - 5 -
sulphamyl - benzoic acid with a melting
point of 237°C.
3 - Benzylamino - 4 - *n* - butylthio - 5 -
sulphamyl - benzoic acid with a melting
point of 210—211°C.
50 3 - Benzylamino - 5 - sulphamyl - 4 - (β , β , β -
trifluoroethoxy) - benzoic acid with a
melting point of 230—232°C.

EXAMPLE 77

4 - Anilino - 3 - butylamino - 5 - sulphamyl -
benzoic acid
A mixture of 3 - amino - 4 - anilino - 5 -
sulphamyl - benzoic acid (4 g.), *n*-butanol (50
ml.) and conc. H_2SO_4 (0.4 ml.) was boiled
under reflux with water separator for 5 days.
60 The resulting solution of butyl 4 - anilino - 3 -
butylamino - 5 - sulphamyl - benzoate was
saponified by addition of 2N sodium hydroxide
and boiling under reflux for 45 minutes. After
neutralisation with 4N hydrochloric acid, the
65 reaction mixture was evaporated *in vacuo*.

The residue was dissolved in hot water (50
ml.) and the 4 - anilino - 3 - butylamino -
5 - sulphamyl - benzoic acid was precipitated
by addition of 4N hydrochloric acid to pH 3.
The crude acid was dissolved in diethyl ether
(50 ml.) and undissolved impurities were
70 filtered off. The ethereal solution was
evaporated to dryness and the residue was re-
crystallized from acetone-water and aqueous
ethanol, whereafter the compound was
75 obtained with a melting point of 230—231°C.

EXAMPLE 78

3 - Benzylamino - 4 - butylamino - 5 -
sulphamyl - benzoic acid
A. 4 - Butylamino - 3 - nitro - 5 - sulphamyl -
benzoic acid 80

A mixture of 4 - chloro - 3 - nitro - 5 -
sulphamyl - benzoic acid (8.4 g.), *n* - butyl-
amine (8.7 g.) and water (25 ml.) was stirred
at 90°C. for 1.5 hour. After cooling, the pH
85 was adjusted to pH 2 and the precipitated
4 - butylamino - 3 - nitro - 5 - sulphamyl -
benzoic acid was collected by filtration. After
several recrystallizations from aqueous meth-
anol the melting point was 192.5°C.
90 B. 3 - Amino - 4 - butylamino - 5 - sulph-
amyl - benzoic acid

A suspension of 4 - butylamino - 3 - nitro -
5 - sulphamyl - benzoic acid (8.6 g.) in water
(175 ml.) was adjusted to pH 9.5 by addition
95 of 2N sodium hydroxide. The resulting solu-
tion was hydrogenated after addition of Pd
(0.5 g.) on-carbon-catalyst (10%). After the
hydrogen uptake had become negligible, the
catalyst was removed by filtration and the 3 -
100 amino - 4 - butylamino - 5 - sulphamyl -
benzoic acid was precipitated from the filtrate
by addition of 4N hydrochloric acid until
pH 3. After recrystallization from aqueous
methanol the melting point was 211—
105 211.5°C.

C. 3 - Benzylamino - 4 - butylamino - 5 -
sulphamyl - benzoic acid.

A suspension of 3 - amino - 4 - butyl-
amino - 5 - sulphamyl - benzoic acid (6.5 g.)
110 in water (30 ml.) was adjusted to pH 7.5 by
addition of 1N sodium hydroxide. Benzyl-
bromide (3.87 g.) was added and under stir-
ring, the pH was kept at pH 7.5 by auto-
matal titration with 1N sodium hydroxide.
115 After the base consumption had become
negligible, the pH was adjusted to 3 by addi-
tion of diluted hydrochloric acid. The pre-
cipitated 3 - benzylamino - 4 - butylamino -
5 - sulphamyl - benzoic acid was collected and
120 recrystallized several times from aqueous
methanol, whereafter the compound was
obtained with a melting point of 198.5—
199°C.

EXAMPLE 79

5 - Acetylsulphamyl - 3 - benzylamino - 4 -
phenoxy - benzoic acid 125

A mixture of 3 - amino - 5 - acetylsulph-
amyl - 4 - phenoxy - benzoic acid (1 g.), benz-
aldehyde (0.3 g.) and acetic acid (40 ml.) was
130

heated on a steam bath for 2 hours. After cooling to room temperature, platinum oxide catalyst (0.035 mg.) was added and the reaction mixture hydrogenated at room temperature and at 1.1 atmosphere hydrogen pressure. After the hydrogen uptake had become negligible, the catalyst was removed by filtration, and the filtrate evaporated *in vacuo*. After several recrystallizations of the residue from aqueous ethanol, and after drying *in vacuo* at 76°C., the compound was obtained with a melting point of 241—243°C. The compound crystallized as a hemi-hydrate.

EXAMPLE 80

15 3 - Benzylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid

A mixture of 5 - acetylsulphamyl - 3 - benzylamino - 4 - phenoxy - benzoic acid (1 g.), ethanol (20 ml.), and 4N hydrochloric acid (5 ml.) was refluxed for 2.5 hours. Then 2N sodium hydroxide (15 ml.) was added and the reaction mixture was heated on a steam bath for 30 minutes. After cooling, the pH was adjusted to 2.5 by addition of 4N hydrochloric acid and the precipitated 3 - benzylamino - 4 - phenoxy - 5 - sulphamyl - benzoic acid was isolated by filtration. After recrystallization from aqueous ethanol and drying, the compound was obtained with a melting point of 264—265°C.

EXAMPLE 81

3 - Benzylamino - 5 - methylsulphamyl - 4 - phenoxy - benzoic acid

A. Ethyl 3 - benzylamino - 5 - methylsulphamyl - 4 - phenoxy - benzoate

A mixture of 3 - amino - 5 - methylsulphamyl - 4 - phenoxy - benzoic acid (1 g.), benzyl bromide (1.25 g.), and dry ethanol (15 ml.) was refluxed for 9 hours. After 3 hours and after 6 hours more benzyl bromide (0.6 g.) was added. After cooling, the precipitated ethyl 3 - benzylamino - 5 - methylsulphamyl - 4 - phenoxy - benzoate was collected by suction, recrystallized from ethanol, and dried *in vacuo*. The melting point of the compound was 162.5°C.

B. 3 - Benzylamino - 5 - methylsulphamyl - 4 - phenoxy - benzoic acid

Ethyl 3 - benzylamino - 5 - methylsulphamyl - 4 - phenoxy - benzoate (0.5 g.) was dissolved in 1N sodium hydroxide (8 ml.) and heated on a steam bath for 1 hour. After cooling, the 3 - benzylamino - 5 - methylsulphamyl - 4 - phenoxy - benzoic acid was precipitated by addition of 4N hydrochloric acid until a pH of 2.5. The precipitate was collected by suction and recrystallized from aqueous ethanol. After drying *in vacuo*, the melting point of the compound was 231—233°C.

EXAMPLE 82

3 - Benzylamino - 5 - dimethylsulphamyl - 4 - phenoxy - benzoic acid

A. Ethyl 3 - benzylamino - 5 - dimethylsulphamyl - 4 - phenoxy - benzoate

A mixture of 3 - amino - 5 - dimethylsulphamyl - 4 - benzoic acid (1.68 g.), benzyl bromide (2 g.), and ethanol (15 ml.) was refluxed for 5 hours. After cooling, the precipitated ethyl 3 - benzylamino - 5 - dimethylsulphamyl - 4 - phenoxy - benzoate was isolated and recrystallized from ethanol. After drying *in vacuo*, the compound was obtained with a melting point of 154—155°C.

B. 3 - Benzylamino - 5 - dimethylsulphamyl - 4 - phenoxy - benzoic acid

Ethyl 3 - benzylamino - 5 - dimethylsulphamyl - 4 - phenoxy - benzoate (1 g.) was heated on a steam bath with 1N sodium hydroxide (15 ml.) for 6 hours. From the resulting solution the 3 - benzylamino - 5 - dimethylsulphamyl - 4 - phenoxy - benzoic acid was precipitated by addition of 4N hydrochloric acid until a pH of 2.5. After isolating and recrystallizing from aqueous ethanol, the compound was obtained with a melting point of 205—206°C.

Ethyl 3 - benzylamino - 5 - n - butylsulphamyl - 4 - phenoxy - benzoate

By substituting in step A above 3 - amino - 5 - n - butylsulphamyl - 4 - phenoxy - benzoic acid (1.8 g.) for the 3 - amino - 5 - dimethylsulphamyl - 4 - phenoxy - benzoic acid, the title compound was obtained with a melting point of 149—149.5°C.

3 - Benzylamino - 5 - n - butylsulphamyl - 4 - phenoxy - benzoic acid

By substituting in step B above, ethyl 3 - benzylamino - 5 - n - butylsulphamyl - 4 - phenoxy - benzoate for ethyl 3 - benzylamino - 5 - dimethylsulphamyl - 4 - phenoxy - benzoate, and after recrystallization from ethanol the title compound was obtained with a melting point of 212°C.

EXAMPLE 83

3 - Butylamino - 5 - n - butylsulphamyl - 4 - phenoxy - benzoic acid

3 - Amino - 5 - n - butylsulphamyl - 4 - phenoxy - benzoic acid was substituted for 3 - amino - 4 - phenoxy - 5 - sulphamyl - benzoic acid in Example 41. After the saponification the organic solvents were removed from the reaction mixture by azeotropic distillation. The aqueous solution obtained was adjusted to pH 2.5 by addition of 4N hydrochloric acid. The precipitated 3 - n - butylamino - 5 - n - butylsulphamyl - 4 - phenoxy - benzoic acid was isolated by filtration and several times recrystallized from aqueous ethanol. After drying *in vacuo* at 115°C., the compound had a melting point of 184—185°C.

EXAMPLE 84

4 - Anilino - 3 - benzylamino - 5 - phenylsulphamyl - benzoic acid

A. Ethyl 4 - anilino - 3 - benzylamino - 5 - phenylsulphamyl - benzoate

By substituting 3 - amino - 4 - anilino - 5 - phenylsulphamyl - benzoic acid (1.8 g.) for 3 - amino - 5 - sulphamyl - 4 - (m - trifluoro-

dimethyl-
, benzyl-
) was re-
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oate was
acl. After
obtained

phamyl - 75

Emethyl-
1 g.) was
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methylphenoxy) - benzoic acid in Example 71, the title compound was obtained with a melting point of 165°C.

B. 4 - Anilino - 3 - benzylamino - 5 - phenylsulphamyl - benzoic acid

- 5 Ethyl 4 - anilino - 3 - benzylamino - 5 - phenylsulphamyl - benzoate (3 g.) was dissolved in 1N sodium hydroxide (35 ml.), and the solution was heated on a steam bath for 1 hour. After cooling, the reaction mixture was adjusted to a pH of 2.5 by the addition of 4N hydrochloric acid. The precipitated 4 - anilino - 3 - benzylamino - 5 - phenylsulphamyl - benzoic acid was collected by suction and recrystallized from acetone/water. The compound was obtained with a melting point of 243°C.
- 10
- 15

EXAMPLE 85

Tablets containing free 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid

Ingredients:

- | | |
|--------------------------------|-------|
| 3 - Butylamino - 4 - phenoxy - | 3 g |
| 5 - sulfamyl - benzoic acid | 250 g |
| Corn starch | 250 g |
| Lactose | 250 g |
| Talc | 25 g |
- 25

The ingredients were mixed and screened through a 20 mesh per linear inch sieve and subsequently treated with an aqueous solution of gelatin (4 per cent) in sufficient amount to form a granulate. The granulate was dried and broken on a 16 mesh per linear inch sieve. After addition of talc, the granulate was compressed into tablets of 180 mg each, using 8 mm punches and dies, to afford 3000 tablets, each containing 1 mg of the free 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid.

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35

The effect of the tablets was tested as follows:

Nine healthy persons each received 1 tablet corresponding to 1 mg of the drug, whereafter the urinary excretion was observed for 24 hours. The average effect appears from the following Table II, in which is also tabulated the corresponding effects after administering to the same persons furosemide in the dose of 1 tablet containing 40 mg furosemide per person.

40

45

TABLE II

Average urinary volume and excretion of sodium and chloride in man after oral administration of 1.0 mg of 3-butyramino-4-phenoxy-5-sulfamyl-benzoic acid and of 40 mg of furosemide, respectively.

Treatment	Hours after administration										
	Sodium (mEq.)			Chloride (mEq.)			Volume (ml)			Potassium (mEq)	
	0—6	6—24	0—24	0—6	6—24	0—24	0—6	6—24	0—24	0—6	6—24
Tablets of the invention 1 mg., active substance	201	48	249	236	40	276	1784	577	2361	47	34
Furosemide tablets ~40 mg. active substance	215	45	260	243	33	276	1842	587	2429	51	29
Controls	57	94	151	66	80	146	387	607	994	32	33
											65

EXAMPLE 86

Capsules containing the free 3 - butyramino - 4 - phenoxy - 5 - sulfamyl - benzoic acid

5 Ingredients:

Micronized 3 - butyramino - 4 - phenoxy - 5 - sulfamyl - benzoic acid
Lactose

1.5 g
184 g

2 g

10 Magnesium stearate

The ingredients were mixed and passed through a 60 mesh per linear inch sieve and subsequently further mixed for 15 minutes.

The mixture was filled into No. 3 gelatin capsules (Parke, Davis and Co.) using a semi-automatic capsule-filling machine shaken by

vibrator. Each capsule contains 125 mg of the mixture, and in all 1500 capsules, each containing 1 mg of the free 3 - butyramino - 4 - phenoxy - 5 - sulfamyl - benzoic acid were obtained.

EXAMPLE 87

Tablets containing the potassium salt of 3 - butyramino - 4 - phenoxy - 5 - sulfamyl - benzoic acid

Ingredients:

3 - Butyramino - 4 - phenoxy - 5 - sulfamyl - benzoic acid
as the potassium salt

6 g
650 g
844 g

Lactose

Corn starch

30

The potassium salt was mixed with the other ingredients and granulated after moistening with a 10 per cent aqueous solution of polyvinyl pyrrolidone.

- 5 The granulate was dried and broken on a 16 mesh per linear inch sieve. After addition of 100 g of talc and 10 g of magnesium stearate, and mixing, the mixture was compressed into tablets, using 10 mm punches and dies, yielding 250 mg tablets, each containing the active substance corresponding to 1 mg of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid.

EXAMPLE 88

- 15 Capsules containing 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid and methyldopa

Ingredients:

- 20 3 - Butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid 0.4 g
Lactose 176 g
Talc 15 g
D,L-methyldopa 200 g

- 25 The ingredients were mixed and passed through a 60 mesh per linear inch sieve. The resultant mixture was subdivided and filled into capsules, each containing 0.2 mg of the free 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid and 100 mg of D,L-methyldopa.

EXAMPLE 89

Ampoules containing the sodium salt of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid

- 35 Ingredients:
3 - Butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid 1 g
Sodium hydroxide 0.13 g
Sodium chloride 36 g
40 Sterile water up to 4000 ml

- 45 The acid was suspended into water, the suspension was adjusted to pH 7.5 with aqueous sodium hydroxide and then diluted up to 4000 ml. The resulting solution was sterilized by filtration. The sterile solution was thereafter filled into ampoules under aseptic conditions, yielding 2000 ampoules of 2 ml each.

EXAMPLE 90

- 50 Tablets containing 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid and reserpine

Ingredients:

- 55 3 - Butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid 5 g
Reserpine 1 g
Lactose 1249 g
Corn starch 1925 g

- 60 The reserpine was triturated with 100 g of lactose and the mixture was forced through a 30 mesh per linear inch sieve. Thereafter the other ingredients were incorporated, and the mixture was granulated with sufficient ethyl alcohol/water (60 per cent). The granulate was dried and broken on a 16 mesh per

linear inch sieve. After addition of 200 g of talc and 20 g of magnesium stearate, and mixing, the mixture was compressed into tablets, using 10 mm punches and dies, yielding tablets of 340 mg, containing 0.5 mg of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid and 0.1 mg of reserpine.

In a similar manner, tablets were prepared which contained 0.5 mg of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and 10 mg of hydralazine.

EXAMPLE 91

Tablets containing 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid and potassium chloride

Ingredients:

- Micronized 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid 10 g
Potassium chloride (passed through a 30 mesh per linear inch sieve) 2500 g
Talc 75 g
Polyvinyl pyrrolidone 50 g

The ingredients were thoroughly mixed and without granulation converted into tablets using 11 mm punches and dies, yielding 5000 tablets of 526 mg, each containing 2 mg of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid and 500 mg of potassium chloride.

EXAMPLE 92

Sustained-release tablets each containing 2.5 mg of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid in the form of its sodium salt

2700 g of lactose and 37.5 g of the sodium salt of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid were granulated with a 10 per cent gelatin solution, dried and screened through a 60 mesh per linear inch sieve. The granulate was mixed with 290 g of stearyl alcohol and 120 g of talc, and the mixture was converted into tablets using 8 mm punches and dies resulting in 15000 tablets each of 210 mg. The tablets were coated in a tablet coating machine operating on the air suspension principle with a solution of 70 g of methylcellulose in 1100 ml of chloroform and 900 ml of methanol. On completion of this coating process, the tablets were maintained suspended and circulating in the air stream while the temperature was raised to 75°C and then lowered. The increased temperature may be provided by increasing the temperature of the air, by radiation, by high frequency heating, or otherwise, whereby the stearyl alcohol of the tablet core is liquified and after cooling, tablets are provided in which the active material is embedded into a matrix of stearyl alcohol from which it is liberated slowly in the gastrointestinal tract by diffusion without disintegration of the tablet.

EXAMPLE 93

Sustained-release tablets containing 1.0 mg of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl -

30
650 g
844 g

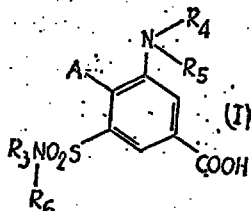
automatic capsule-filling machine shaken by Lactose Corn starch

benzoic acid as its sodium salt, and 0.1 mg of reserpine

Sustained-release tablets were prepared as described in Example 92, each containing 1.0 mg of the sodium salt of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid embedded in a matrix of stearyl alcohol. In a manner known per se the tablets were coated with saccharose containing reserpine. The coating was performed in a pan by successively adding an aqueous solution containing 65% saccharose, 0.6% gelatin, and 0.5% reserpine until the coating layer of each tablet contained 0.1 mg reserpine.

WHAT WE CLAIM IS:—

1. Compounds of the general formula I:



in which A stands for



R_2-O , R_2-S , R_2-OS or R_2-O_2S , and R_1 , R_2 , R_3 and R_6 are unsubstituted or substituted, saturated or unsaturated radicals and each represent an aliphatic radical, a cycloaliphatic radical, or an aromatically, cycloaliphatically or heterocyclically substituted aliphatic radical; in addition R_2 and R_3 may each represent an aromatic or heterocyclic radical; and when A is



R_1 and R_2 can together with the nitrogen atom represent a heterocyclic ring-system with from 5 to 8 ring members, and which may have one or more nitrogen, oxygen or sulphur atoms in the ring; R_3 represents a C_1 to C_8 alkyl radical, and R_6 represents a C_1 to C_8 alkyl radical or an acyl group; R_1 , R_3 , R_4 , R_5 and R_6 may each also be a hydrogen atom; and salts, esters and amides of these compounds.

2. Compounds according to claim 1, in which R_1 , R_3 and R_4 are hydrogen, R_2 is a mononuclear aryl radical, R_5 is an aliphatic radical or a mononuclear aralkyl radical, and R_6 is hydrogen or an acyl group, and salts or esters of these compounds.

3. Compounds according to claim 1, in which R_1 , R_3 and R_4 are hydrogen, R_2 is a substituted or unsubstituted phenyl radical, R_5 is an alkyl radical having from 3 to 6 carbon atoms, and R_6 is hydrogen, a methyl group, or a C_1 to C_8 aliphatic acyl group and the methyl esters of these compounds.

4. Compounds according to claim 1, in which R_1 , R_3 and R_4 are hydrogen, R_2 is a substituted or unsubstituted phenyl radical, R_5 is a benzyl, furfuryl or thienylmethyl radical, and R_6 is hydrogen, a methyl group, or a lower aliphatic acyl group, and the methyl esters of these compounds.

5. 3 - n - Butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

6. 3 - n - Pentylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

7. 3 - Benzylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

8. 3 - Furfurylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

9. 3 - Amino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

10. 3 - n - Butylamino - 4 - phenylthio - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

11. 3 - Benzylamino - 4 - phenylthio - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

12. 3 - n - Butylamino - 4 - anilino - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

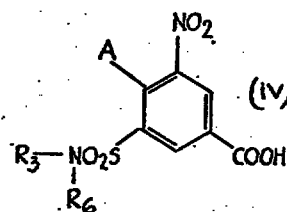
13. 3 - Benzylamino - 4 - isopropylamino - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

14. 3 - n - Butylamino - 4 - phenylsulphanyl - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

15. 3 - Benzylamino - 4 - n - butylsulphanyl - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

16. 3 - Benzylamino - 4 - phenoxy - 5 - methylsulfamyl - benzoic acid, and salts and esters thereof.

17. A process for the preparation of the compounds claimed in claim 1, consisting in reducing a compound of the general formula IV:



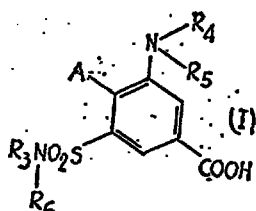
in which A, R_3 and R_6 have the meanings defined in claim 1; and salts esters and amides

benzoic acid as its sodium salt, and 0.1 mg of reserpine

Sustained-release tablets were prepared as described in Example 92, each containing 1.0 mg of the sodium salt of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid embedded in a matrix of stearyl alcohol. In a manner known per se the tablets were coated with saccharose containing reserpine. The coating was performed in a pan by successively adding an aqueous solution containing 65% saccharose, 0.6% gelatin, and 0.5% reserpine until the coating layer of each tablet contained 0.1 mg reserpine.

WHAT WE CLAIM IS:—

1. Compounds of the general formula I:



in which A stands for



R₂—O, R₂—S, R₂—OS or R₂—O₂S, and R₁, R₂, R₃ and R₄ are unsubstituted or substituted, saturated or unsaturated radicals and each represent an aliphatic radical, a cycloaliphatic radical, or an aromatically, cycloaliphatically or heterocyclically substituted aliphatic radical; in addition R₂ and R₃ may each represent an aromatic or heterocyclic radical; and when A is



R₁ and R₂ can together with the nitrogen atom represent a heterocyclic ring-system with from 5 to 8 ring members, and which may have one or more nitrogen, oxygen or sulphur atoms in the ring; R₃ represents a C₁ to C₈ alkyl radical, and R₄ represents a C₁ to C₈ alkyl radical or an acyl group; R₁, R₃, R₄, R₅ and R₆ may each also be a hydrogen atom; and salts, esters and amides of these compounds.

2. Compounds according to claim 1, in which R₁, R₃ and R₄ are hydrogen, R₂ is a mononuclear aryl radical, R₅ is an aliphatic radical or a mononuclear aralkyl radical, and R₆ is hydrogen or an acyl group, and salts or esters of these compounds.

3. Compounds according to claim 1, in which R₁, R₃ and R₄ are hydrogen, R₂ is a substituted or unsubstituted phenyl radical, R₅ is an alkyl radical having from 3 to 6 carbon atoms, and R₆ is hydrogen, a methyl group, or a C₁ to C₈ aliphatic acyl group and the methyl esters of these compounds.

4. Compounds according to claim 1, in which R₁, R₃ and R₄ are hydrogen, R₂ is a substituted or unsubstituted phenyl radical, R₅ is a benzyl, furfuryl or thienylmethyl radical, and R₆ is hydrogen, a methyl group, or a lower aliphatic acyl group, and the methyl esters of these compounds.

5. 3 - n - Butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

6. 3 - n - Pentylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

7. 3 - Benzylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

8. 3 - Furfurylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

9. 3 - Amino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

10. 3 - n - Butylamino - 4 - phenylthio - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

11. 3 - Benzylamino - 4 - phenylthio - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

12. 3 - n - Butylamino - 4 - anilino - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

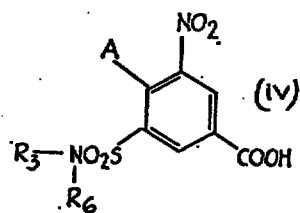
13. 3 - Benzylamino - 4 - isopropylamino - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

14. 3 - n - Butylamino - 4 - phenylsulphanyl - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

15. 3 - Benzylamino - 4 - n - butylsulphanyl - 5 - sulfamyl - benzoic acid, and salts and esters thereof.

16. 3 - Benzylamino - 4 - phenoxy - 5 - methylsulfamyl - benzoic acid, and salts and esters thereof.

17. A process for the preparation of the compounds claimed in claim 1, consisting in reducing a compound of the general formula IV:



in which A, R₃ and R₄ have the meanings defined in claim 1; and salts esters and amides





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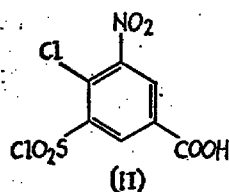
claim 1, in 45
gen, R₂ is a
nyl radical
om 3 to 6
n, a methyl
l group and 50
ands.
claim 1, in
en, R₂ is a
radical, R₁
hyl radical, 55
roup, or a
the methyl
noxy - 5 -
and esters 60
noxy - 5 -
and esters
oxy - 5 - 65
and esters
oxy - 5 -
and esters 70
sulfamyl -
ereof.
thio - 5 -
and esters 75
thio - 5 -
and esters
ro - 5 -
and esters 80
lamino -
alts and
phenyl- 85
cid, and
butyl-
cid, and 90
y - 5 -
alts and
of the
ating in 95
formula

thereof, to the compounds of claim 1, in which R₁ and R₂ are hydrogen, and the compounds in which R₁ and/or R₂ are different from hydrogen thereafter are obtained by alkylation.

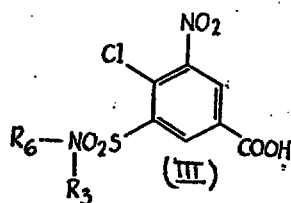
- 5 18. A process as claimed in claim 17 in which the alkylation is performed either,
a) by treatment with a compound of the formula R₄X, X being a halogen atom, a hydroxyl group, a sulphonyloxy group, an alkyl- or aryl-sulphonyloxy group, and if desired, followed by treatment with R₄X, or by a reductive alkylation, or
10 b) by subjecting the compound to a reductive alkylation using an aldehyde which is capable of introducing the R₄ radical whereafter, if desired, R₂ can be introduced as mentioned under a).
15 19. A process as claimed in claim 17 in which the reduction is performed by a catalytic hydrogenation using a noble metal catalyst or Raney-Nickel.

- 20 20. A process as claimed in claim 17 in which the reduction is performed with sodium dithionite or iron.

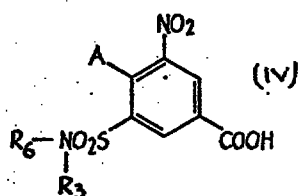
- 25 21. A process for the preparation of the compounds claimed in claim 1, consisting in reacting the compound of formula II:



- 30 with ammonia or an amine of the formula R₃>NH, R₃ being as defined in claim 1, and R₄ being hydrogen or a C₁ to C₈ alkyl group, to produce an intermediate of formula III:



- 35 which compound is treated either as the free acid or an ester, salt or amide thereof with a compound of the formula A-H, A being as defined in claim 1, thereby yielding the compound of formula IV:

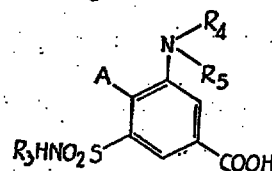


in which A, R₃ and R₄ have the above given meanings, or a salt, or an ester or amide thereof, whereafter a reduction of the nitro group yields the compounds of claim 1, in which R₁ and R₂ are hydrogen, whereafter the compounds in which R₁ and/or R₂ are different from hydrogen are obtained by alkylation as defined in claim 18 and the compounds in which R₄ is an acyl group are obtained by an acylation of resulting compounds of formula I or of intermediates of formula IV in which R₄ is hydrogen.

22. A process according to claim 21 whereby compounds of formula I of claim 1, in which A is R₂-OS or R₂-O₂S, are obtained by oxidizing the corresponding compounds in which A is R₂-S.

23. A process according to claim 22 in which the oxidizing agent is hydrogen peroxide.

24. A process for the preparation of compounds of the general formula



in which A, R₃, R₁ and R₂ are as defined in claim 1, consisting in deacylation of compounds of formula 1 as defined in claim 1 in which R₄ is an acyl group.

25. A process for the preparation of compounds of formula 1 as defined in claim 1 whereby the corresponding esters or amides are subjected to hydrolysis.

26. A pharmaceutical preparation in dosage unit form for the oral or enteral treatment of patients suffering from hypertension or oedemas, which comprises as an active ingredient a compound of formula I, or a salt thereof with a pharmaceutically acceptable base, or an ester or an amide thereof, and an atoxic pharmaceutically acceptable carrier, the quantity of the said active compound being between 0.1 and 25 mg.

27. A preparation as claimed in claim 26 wherein the dosage unit contains from 0.1 to 10 mg. of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid or a salt thereof with a pharmaceutically acceptable inorganic or organic base.

28. A preparation as claimed in claim 26 or 27 wherein the dosage unit is in the form of a tablet.

29. A preparation as claimed in claim 26 or 27 wherein the dosage unit is in the form of a capsule.

30. An injectable pharmaceutical preparation in dosage unit form, containing from 0.1 mg. to 25 mg. of a compound of claim 1 in the form of a salt with a pharmaceutically acceptable base, dissolved in an aqueous medium.

anings
mides 100

31. An injectable pharmaceutical preparation in dosage unit form, containing from 0.1 mg. to 25 mg. of a compound of claim 1 in the form of an ester, dissolved or suspended in a non-toxic, pharmaceutically acceptable vehicle.
32. A pharmaceutical preparation for oral treatment in form of a sustained-release preparation in dosage unit form of a compound of claim 1, in which the dose of the active compound is between 0.1 to 25 mg.
33. A preparation as claimed in any one of claims 26 to 32 in which the dosage unit additionally contains other hypotensors or potassium-sparing diuretics.
34. A preparation as claimed in any one of claims 26 to 33 in which the dosage unit additionally contains Rauwolfia alkaloids, veratrum alkaloids, hydralazine, methyl dopa, or triamterene or 3,5 - diamino - 6 - chloropyrazinoylguanidine or other potassium-sparing diuretics.
35. A pharmaceutical preparation in oral unit form as claimed in Claim 27 or 35, which wherein each unit contains from 0.1 to 10 mg. of the 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid as an alkali metal salt.
36. A pharmaceutical preparation in dosage unit form as claimed in Claim 27 or 36, which contains, as a diuretic, 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid or a salt thereof with a pharmaceutically acceptable inorganic or organic base, and, as a hypotensor, Rauwolfia serpentina alkaloid, including reserpine, and veratrum alkaloids, together with an atoxic pharmaceutically acceptable carrier, the quantity of the diuretic being between 0.1 and 10 mg., calculated as the free 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and the quantity of hypotensor being between 0.05 and 0.5 mg.
37. A pharmaceutical preparation in dosage unit form as claimed in Claim 27 or 35, which contains, as a diuretic, 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid or a salt thereof with a pharmaceutically acceptable inorganic or organic base, and, as a hypotensor, hydralazine, together with an atoxic pharmaceutically acceptable carrier, the quantity of

the diuretic being between 0.1 and 10 mg., calculated as the free 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and the quantity of hydralazine being from 10 to 50 mg.

38. A pharmaceutical preparation in dosage unit form as claimed in Claim 27 or 35, which contains, as a diuretic, 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid or a salt thereof with a pharmaceutically acceptable inorganic or organic base, and, as a hypotensor, methyl dopa, together with an atoxic pharmaceutically acceptable carrier, the quantity of the diuretic being between 0.1 and 10 mg., calculated as the free 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid, and the quantity of methyl dopa being between 100 and 500 mg.

39. A pharmaceutical preparation in dosage unit form as claimed in any one of Claims 36 to 38, which also contains 2:2 - di-(carbamoyloxymethyl) - pentane in an amount between 100 and 400 mg.

40. An injectable pharmaceutical preparation in dosage unit form as claimed in Claim 27 or 35, in which the unit contains from 0.2 to 2 mg. of 3 - butylamino - 4 - phenoxy - 5 - sulfamyl - benzoic acid in the form of a salt with a pharmaceutically acceptable base, dissolved in an aqueous medium.

41. A compound of the general formula defined in Claim 1 substantially as hereinbefore described in any one of Examples 1 to 84 of the foregoing Examples.

42. A process for the preparation of a compound of the general formula defined in Claim 1 substantially as hereinbefore described in any one of Examples 1 to 84 of the foregoing Examples.

43. A pharmaceutical preparation in dosage unit form substantially as hereinbefore described in any one of Examples 85 to 93 of the foregoing Examples.

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