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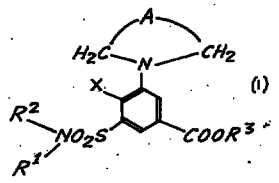
(19)

(54) SULPHAMOYLBENZOIC ACID DERIVATIVES AND PROCESSES FOR PREPARING THEM

(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt (Main) 80, Postfach 80 03 20, Federal Republic of Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to sulphamoylbenzoic acid derivatives and a process for their preparation.

The present invention provides a 5-sulphamoylbenzoic acid derivative of the general formula I



(I)

in which

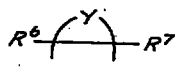
R^1 and R^2, which may be identical or different, each represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, and, if R^1 represents a hydrogen atom, R^2 may also represent an alkoxymethyl group having from 1 to 4 carbon atoms in the alkoxy radical, a phenoxymethyl group or a phenylthiomethyl group,

R^3 represents a hydrogen atom, a straight or branched chain alkyl group having from 1 to 4 carbon atoms, a cycloalkyl group, having 5 or 6 ring members, one of which may be replaced by an oxygen or sulphur atom, a phenyl or benzyl group which may be substituted in the phenyl nucleus by one or more substituents selected from nitro groups, alkyl groups having from 1 to 3 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms, or represents a benzhydryl group or an alkanoyloxymethyl group having 2 to 4 carbon atoms in the alkanoyl part,

X represents a halogen atom, a CF_3 or CCl_3 group, a straight or branched chain, saturated or unsaturated aliphatic hydrocarbon group having up to 6 carbon atoms, a benzyl group which may be substituted in the phenyl nucleus by one or more substituents selected from halogen atoms, hydroxy and amino groups, and lower alkyl and lower alkoxy groups, or represents one of the groups —O—R^4, —S—R^4, SO—R^4, SO_2—R^4 and NR^4R^5, in which R^4 represents a phenyl group which may be substituted by one or more substituents selected from halogen atoms, OH, CF_3 and amino groups, alkyl and alkoxy groups having from 1 to 4 carbon atoms, and SO_2NH_2 groups, or represents a straight or branched chain alkyl group having from 1 to 4 carbon atoms

which may be substituted by a phenyl, pyridyl, furyl or thienyl group, and R^5 represents a hydrogen atom, a straight or branched chain alkyl group having from 1 to 4 carbon atoms, and the group NR^4R^5 may also represent a saturated, heterocyclic, 5- or 6-membered ring which may be interrupted by an O-, N- or S-atom,

A represents a single bond, or an alkylene chain of 1 to 3 carbon atoms which may be unsaturated, interrupted by O-, N- or S-atoms or substituted by one or more substituents selected from halogen atoms, alkyl, alkoxy, aralkyl and aryl groups and mono-nuclear hetero-aromatic rings, or A represents an ortho-phenylene radical or the grouping

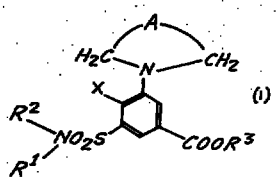


in which Y represents a single bond or an alkylene group having from 1 to 4 carbon atoms, and R^6 and R^7, which may be identical or different, each represents a hydrogen or halogen atom or an alkyl group having from 1 to 4 carbon atoms.

Preferred compounds of the formula I are those in which the radicals R^1 and R^2 both represent hydrogen atoms, or R^1 represents a hydrogen atom and R^2 represents a lower alkyl group; R^3 represents a hydrogen atom, a lower alkyl group or a benzyl group which may be substituted as above; X represents a benzyl, —OR^4, —SR^4, or —SO—R^4, R^4 preferably representing a phenyl radical the phenyl of which may be substituted in any position and once or several times, by substituents selected from chlorine atoms, OH and CF_3 groups, straight or branched chain alkyl groups having from 1 to 3 carbon atoms, alkylamino, dialkylamino or alkoxy of 1 or 2 carbon atoms or NH_2; and A represents a single bond or an alkylene chain of 1 or 2 carbon atoms which may be unsaturated and/or substituted once or several times by substituents selected from halogen atoms, phenyl and aralkyl groups, and lower alkyl and alkoxy groups.

The term "lower" is used herein to denote groups having up to 4 carbon atoms.

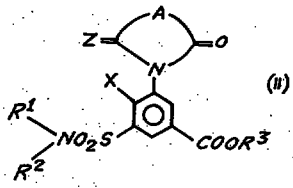
The invention also provides a process for preparing a compound of the general formula I



(I)

in which the radicals R^1 to R^3, A and X have the meanings given above, which comprises

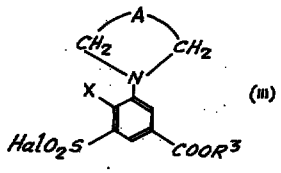
a) reducing a 3-substituted sulphamoylbenzoic acid derivative of the general formula II



(II)

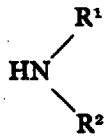
in which the radicals R^1 to R^3, A and X have the meanings given above, and in which any hydroxy or amino groups present may be blocked by customary protective groups, and Z represents two hydrogen atoms or one oxygen atom, by means of a boron hydride, for example, in the presence of a Lewis-acid by a boron hydride or by a complex boron hydride, or

b) reacting a 5-halogeno-sulphonylbenzoic acid derivative of the general formula III



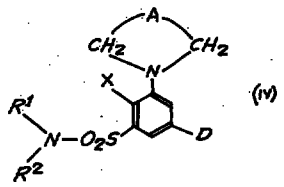
(III)

in which R^3, A and X have the meanings given above, and Hal represents a halogen atom, with an amine of the formula



in which R^1 and R^2 have the meanings given above, or

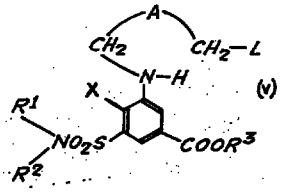
c) converting by hydrolysis or by a mild oxidation reaction a sulphamoyl compound of the general formula IV



(IV)

in which the radicals R^1 and R^2, A and X have the meanings given above and D represents a radical which may be transformed into a carboxylic acid group, into the corresponding 5-sulphamoylbenzoic acid of the formula I (R^3=H), or

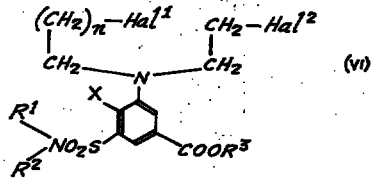
d) treating a sulphamoylbenzoic acid derivative of the general formula V



(V)

in which the radicals R^1 to R^3, A and X have the meanings given above and L represents a "leaving group", with an acid or base in order to eliminate HL, or

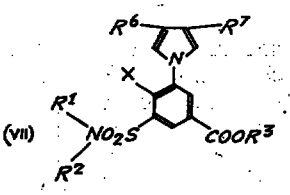
e) cyclizing a sulphamoyl benzoic acid derivative of the general formula VI



(VI)

in which the radicals R^1 to R^3 and X have the meanings given above, Hal^1 and Hal^2, which may be identical or different, each represents a halogen atom, preferably a chlorine or bromine atom, and n represents 0, 1 or 2, by a reaction known per se, for example, by reaction with a metal in accordance with the conditions of the Wurtz-Fittig synthesis or by reaction with a primary amine, NH_3 or H_2S to form a compound of the general formula I, or

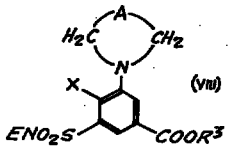
f) reducing the corresponding 3-N-pyrrolo-compound of the general formula VII



(VII)

or

g) hydrolyzing a compound of the general formula VIII



(VIII)

in which R^3, A and X are as defined above,

E represents the group



in which R^8, R^9 and R^{10} represent identical or different lower alkyl groups and in which R^8 may also represent a hydrogen atom, and/or two of the substituents R^8, R^9 and R^{10} may be linked and, together with the atom(s) to which they are attached form a ring, and, if desired, in a compound of the formula I obtained according to any one of the methods a) to g), carrying out any one or more of the following reactions h) to k):

h) hydrogenating any double bonds present or introducing double bond(s) by an elimination reaction,

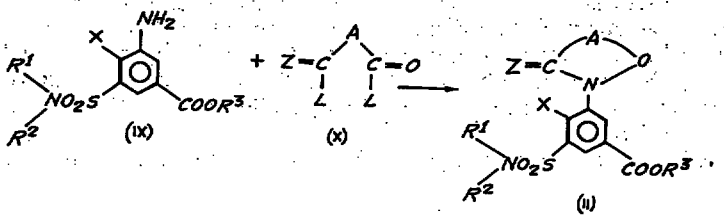
i) esterifying a free carboxylic acid of the formula I (R^3=H) or converting a carboxylic acid ester of the general formula I by hydrolysis or an elimination reaction into the corresponding carboxylic acid (R^3=H) and, if desired, forming a different ester,

j) setting free any protected hydroxy or amino groups by separation of the protective group, and

k) transforming a carboxylic acid of the formula I (R^3=H) by treating with a base or an acid into a salt, especially a physiologically tolerable salt thereof.

In the case of the process a) according to the invention, it is surprising that it is possible to reduce sulphamoylbenzoic acid derivative of the formula II by means of boron hydride or a complex borohydride in the presence of a Lewis acid without affecting the other groups in the molecule. The end products are obtained in good yields in this procedure.

The sulphamoylbenzoic acid derivatives of the formula II which are used in accordance with the invention may be prepared by various processes. For example, a 3-imido-5-sulphamoylbenzoic acid derivative of the formula II (Z represents an oxygen atom) is obtained from the corresponding known 3-amino-5-sulphamoylbenzoic acid derivative of the formula IX in which the radicals R^1 to R^3 and X have the meanings given above, by reacting this amino compound with a dicarboxylic acid derivative of the general formula X which is capable of forming an imide and in which A has the meaning given above, Z represents an oxygen atom and L denotes a "leaving group", preferably a halogen atom, a trialkylammonium group or the radical OR' of an activated ester. For this acylation reaction, any hydroxyl and/or amino groups in other positions of the molecule should be blocked by means of customary protective groups.

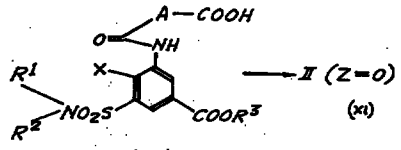


(IX) (X) (II)

Examples of dicarboxylic acids which can be converted into the corresponding dicarboxylic acid halides are succinic acid, methyl-succinic acid, 2,3-dimethylsuccinic acid, glutaric acid, 2-methylglutaric acid, phthalic acid, cis-cyclopropanedicarboxylic acid, cyclobutane-1,2-cis-dicarboxylic acid, cyclohexane-1,2-cis-dicarboxylic acid, bromosuccinic acid and diglycolic acid. The reaction of such a dicarboxylic acid derivative with an amino compound of the formula IX is generally carried out under the conditions of the known Schotten-Baumann reaction.

It is also possible to use an anhydride of a dicarboxylic acid. The carboxylic

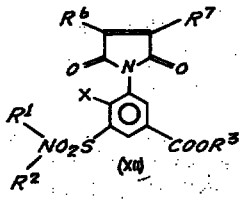
acid derivative of the formula XI which is formed initially in many cases, changes into the imido compound (II) directly, with elimination of water.



(XI)

The reaction can be followed easily by thin layer chromatography. Depending on the reaction conditions chosen, particularly if the reaction mixture is heated to a temperature of from 150 to 250°C, the cyclised product is obtained in high yields.

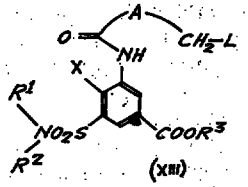
An anhydride is advantageously used in a substantial excess, for example, in a 2- or 3-fold excess, and the reaction is preferably carried out in the absence of a solvent. If an unsaturated dicarboxylic acid anhydride, for example, maleic anhydride, is used, a viscous oil is formed on reaction with the amino compound of the formula IX at a temperature from 150 to 200°C, and this oil changes after some time, with elimination of water, into the unsaturated imido compound of the formula XII



(XII)

in which the radicals R^1 to R^3, R^6, R^7 and X have the meanings given above. The double bond present in this imido compound makes possible a large number of reactions, for example, it can be hydrogenated to give an imido compound of the formula II in which Z represents an oxygen atom and A represents an ethylene group.

Compounds of the formula II in which Z represents two hydrogen atoms, may be prepared by various processes. Such a compound is produced, for example, from an amino compound of the formula IX by reaction with an ω-substituted carboxylic acid derivative of the formula X in which Z represents two hydrogen atoms, according to the conditions of the Schotten-Baumann reaction and subsequent cyclisation of the resulting amido compound of the formula XIII



(XIII)

with elimination of H—L.

The following are example carboxylic acid derivatives of the formula X: ω-chloroproprionic acid chloride, ω-chloropropionic acid bromide, ω-chlorobutyric acid chloride, ω-bromobutyric acid chloride, ω-bromobutyric acid phenyl ester and the chloride of trimethylammoniumbutyric acid chloride.

The base used for the elimination of the grouping H—L is preferably a tertiary organic base, for example, pyridine, triethylamine or N,N-dimethylaniline. The base may be used in a stoichiometric quantity or in a substantial excess, for example, when it is also used as the solvent.

An amido or imido derivative of the formula II may be used in the reduction according to the invention as the free acid or in the form of a salt which does not interfere with the reduction, for example, an alkali metal salt or an alkaline earth metal salt.

In order to obtain particularly pure reaction products in high yield, it is advantageous to use a 5-sulphamoylbenzoic acid ester for the reduction. Such an ester can be prepared from the corresponding acid by a known process. Suitable esters are especially alkyl esters having from 1 to 5 carbon atoms, for example, methyl, ethyl, propyl, butyl and *n*-pentyl esters, benzyl, *p*-methoxybenzyl and *t*-butyl esters, benzhydryl esters, and acyloxymethyl esters wherein the acyl radical represents the radical of a lower aliphatic carboxylic acid, for example, an acetyl or tert.-butyryl radical.

Suitable boron hydride reducing agents are complex borohydrides or diborane in the presence of Lewis acids, and diborane alone. In the reduction of a lactam of the formula II (Z=2 H), it is possible to use diborane in the presence of a Lewis acid. An imide (Z=0), on the other hand, requires the use of a complex borohydride in the presence of a Lewis acid in order to obtain a good yield. The reducing agent may be introduced into the reaction mixture while taking suitable protective measures, for example, the use of nitrogen as an inert gas. When diborane is used, it is simpler to take it up in a solvent and to use the resulting solution for the reduction. Suitable solvents are ethers, for example, tetrahydrofuran or diethylene glycol dimethyl ether.

The complex hydrides of boron used in this method of reduction are, for example, the alkali metal borohydrides, for example, lithium borohydride, sodium borohydride or potassium borohydride, the alkaline earth metal borohydrides, for example, calcium borohydride, and also zinc borohydride and aluminium borohydride. If a Lewis acid is added, this borohydride reduces the amide or imide groups present in the compound employed of formula II, and it is surprising that the carboxylic acid ester function is not appreciably attacked.

Suitably Lewis-acids within the meaning of the invention are especially aluminium chloride, titanium tetrachloride, tin tetrachloride, cobalt-II chloride, iron-III chloride, mercury-I chloride, zinc chloride, and boron trifluoride and its addition products, for example, boron trifluoride etherate. In this case there is the possibility that diborane may be formed *in situ* in the reaction of the boron trifluoride etherate, for example with sodium borohydride (c.f. Fieser, Fieser: Reagents for Organic Synthesis, John Wiley and Sons, Inc., New York, Vol. 1, page 199).

In order to obtain a particularly high yield and particular pure end products, it is advantageous first to introduce the Lewis acid together with the compound of the formula II and then to add the complex borohydride.

It is particularly advantageous to use the Lewis acid in excess and the complex borohydride in an at least stoichiometric quantity, relative to the amide group to be reduced. Thus, advantageous results are obtained by adding, for example in the case of titanium tetrachloride, three times the stoichiometric quantity of $NaBH_4$, and when using boron trifluoride etherate, by using the complex borohydride in the stoichiometric quantity, relative to the particular number of amide groups to be reduced.

In carrying out the reduction it is unimportant whether the substances to be reduced are introduced as imido compounds of the formula II i.e. Z represents an oxygen atom or as amido compounds i.e. Z represents two hydrogen atoms. Surprisingly, in a one-vessel reaction, an imido compound changes directly into the sulphamoylbenzoic acid derivative of the formula I. The reduction is carried out in a solvent. Examples of suitable solvents are ethers, for example, tetrahydrofuran and diethylene glycol dimethyl ether (diglym). The solvent in which the reduction is carried out may be the same as that in which the boron hydride is dissolved, but can also be different therefrom.

The reduction may be carried out within a wide range of temperatures, for example, at room temperature or at a slightly elevated temperature. While a secondary amine reacts with diborane and a lactam with diborane and a Lewis acid preferably at a slightly elevated temperature (40° to 60°C), the reduction with a complex borohydride and a Lewis acid, in particular with an imide, often proceeds favourably in the temperature range of from 0° to 20°C. If somewhat longer reaction times are acceptable, it is also possible to carry out the reduction in the cold. The duration of the reduction depends on the reaction components used and on the temperature selected.

In a preferred method of the process of the invention, the 5-sulphamoylbenzoic acid derivative of the formula II is first introduced together with the Lewis acid, in an inert solvent and then a solution of the complex borohydride or, if appropriate, a suspension of the complex borohydride in the same or different solvent is added at room temperature and the mixture is stirred for a short time. The complex borohydride can also be added directly in solid form. In order to accelerate the reaction, it may also be carried out at elevated temperature or the mixture may be heated to 50° to 80°C for about 1 hour after completing the addition of the reducing agent.

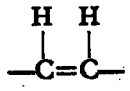
Another method comprises first introducing the substance to be reduced together with the complex borohydride and then adding the Lewis acid at room temperature. Sodium borohydride is particularly suitable as the complex borohydride. Here too, it may be advantageous, to achieve a faster conversion, to heat the mixture to 40°—70°C for about 1 hour after the end of the addition of the Lewis acid. With the aid of thin layer chromatography it is possible to follow the progress of the reaction by the appearance of the intensive light-blue fluorescence (in the region of 366 nm) of the resulting compound of the formula I. In the reduction according to the invention it is

possible that any double bonds which may be present in the group A may be reduced simultaneously.

The resulting compound of formula I can be isolated in several ways. A preferred method of working up comprises adding water and small quantities of an acid in order to free the solution of the reaction product from any reducing agent which may still be present and then precipitating the resulting 5-sulphamoylbenzoic acid ester by adding a non-solvent. When diethylene glycol dimethyl ether is used, a particularly suitable non-solvent is water. The resulting 5-sulphamoylbenzoic acid ester of the formula I generally crystallizes almost quantitatively with high purity. Subsequently, any substituents which are present in the radical X of the sulphamoylbenzoic acid derivatives of the general formula I and which are protected by protective groups may be liberated, for example, the *p*-hydroxyl group may be obtained in free form by saponifying the corresponding acetate.

It is also possible to obtain a 5-sulphamoylbenzoic acid of the formula I directly by partially concentrating the reaction mixture after decomposition of the excess of reducing agent, adding a dilute base and, if appropriate, heating for a short time. Sodium hydroxide solution, for example, may be used as the base. In this case, the 5-sulphamoylbenzoic acid of the formula I can be isolated directly in the form of a salt. The free acid may be obtained by acidification. Owing to the smooth course of the formation of the 3-imido- or 3-amido-5-sulphamoylbenzoic acid derivative of the formula II, the 5-sulphamoylbenzoic acid derivative of the formula I may be obtained according to method a) with high purity and with a high space-time yield.

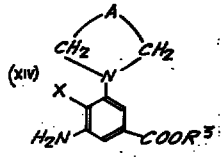
The reduction can be carried equally successfully with an imide or amide if the C—C chain contains substituents which are split off easily with formation of a carbon-carbon double bond. Thus, for example, a 3-pyrroline derivative of the formula I in which A represents a



group, is obtained when 2-bromosuccinic acid is used as the starting material for the reactant of the formula VIII.

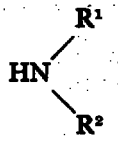
A Δ-3-pyrroline derivative can be modified chemically in known manner, for example, it may be hydrogenated catalytically to give a sulphamoylbenzoic acid derivative of the formula I in which A represents an ethylene group and with a heterocyclic substituent in the 3-position, or it may be subjected to the usual addition reactions.

A 5-halogenosulphamoylbenzoic acid derivative of the formula III required for method b) may be obtained in various ways, for example, from an aminobenzoic acid derivative of the formula XIV

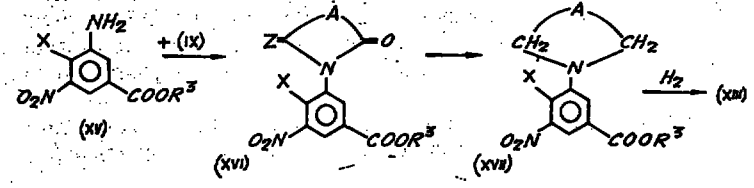


according to the reaction sequence described by Meerwein in J. pr. [2] 152, 251 (1939) or DBP 859,461.

The halogenosulphonylbenzoic acid derivative of formula III is reacted in known manner with an amine of the formula

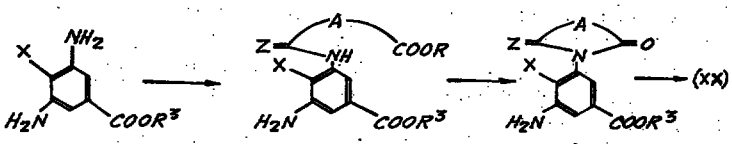


to give a compound of the formula I. An aminobenzoic acid derivative of the formula XIV may be obtained in various ways, for example, from a known amino-nitrobenzoic acid derivative of the formula XV according to the reaction scheme



by reacting the compound of formula XV with a carboxylic acid derivative of the formula X as described above and subsequently reducing the resulting compound of the formula XVI by means of a boron hydride e.g. diborane or a complex borohydride in the presence of a Lewis acid, to give a nitrobenzoic acid ester XVI. The nitro group of this compound is then reduced, advantageously by catalytic hydrogenation in the presence of Raney nickel or by another conventional reduction method.

The compound XIV can be prepared in a particularly advantageous manner as follows:



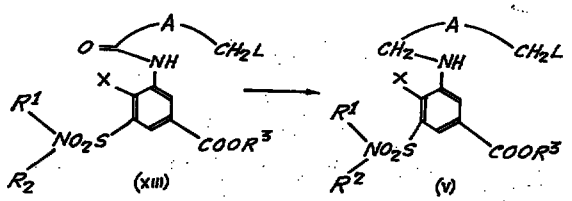
(XVII)

In the reduction of a 3-amido- or 3-imido-compound of the formula XVII or XVIII respectively, the same conditions can be used as those described under method a). In this respect it is surprising that the reduction proceeds specifically in the presence of a nitro group.

The compounds of the general formula IV used in method c) are accessible in various ways. For example, a compound in which D in formula IV represents a CH_2OH— group may be obtained from a carboxylic acid derivative of the formula I by means of an excess of reducing agent. This reaction can be observed as a side-reaction when treating an imido- or amido-derivative of the formula II according to method a) at too high a temperature for a prolonged period of time with an excess of reducing agent. Thus, according to method c), it is possible to reconvert a compound of the formula IV i.e. a compound of formula I which has been reduced too far into the desired compound of the formula I by treatment with an axidizing agent.

The method of conversion of a compound of the formula IV into a compound of the formula I depends on the nature of the substituent D. If D represents a CH_2-halogeno group, a CH_2OCOCH_3 group or a CH=O group, the desired products may be obtained by oxidation, as already described. If D represents a nitrile group, an amide is formed on alkaline hydrolysis and may subsequently be converted into the free carboxylic acid, for example, by further hydrolysis. Alternatively, reaction of a nitrile with alcoholic hydrochloric acid gives the imino-ester which can be converted by hydrolysis into the ester compound, and, if desired, into the corresponding carboxylic acid.

A sulphamoylbenzoic acid derivative of the formula V, used in method d), may be produced in various ways, for example, from a sulphamoylbenzoic acid derivative of the formula XIII



by reducing the amide group with a boron hydride alone or a complex borohydride in the presence of a Lewis acid in the manner already described. It is surprising in this reduction that the amide group is reduced without the "leaving group" L being affected. As the "leaving group" L, there is preferably used a halogen atom, an OH group, an active ester group, for example, a *o*-tosyl group, a trialkylammonium or pyridinium group.

The cyclization of a compound of the formula V with the elimination of HL, may be carried out under basic or acidic conditions. If, for example, L represents a halogen atom, preferably a chlorine or bromine atom, cyclization is effected by treatment with an alkali. In an acid medium, the cyclization is carried out according to the method described in Ber. dtsch. chem. Ges. *42*, 3427 (1909) (Summary in Chem. Rev. *63*. 55 (1963)), whereby a salt of a carboxylic acid of the formula I (R^3 represents a hydrogen atom), is formed. As the base which may be used in the separation reaction, there may be mentioned triethylamine, an alkali metal hydroxide, N,N-dimethylaniline or an alkali metal acetate.

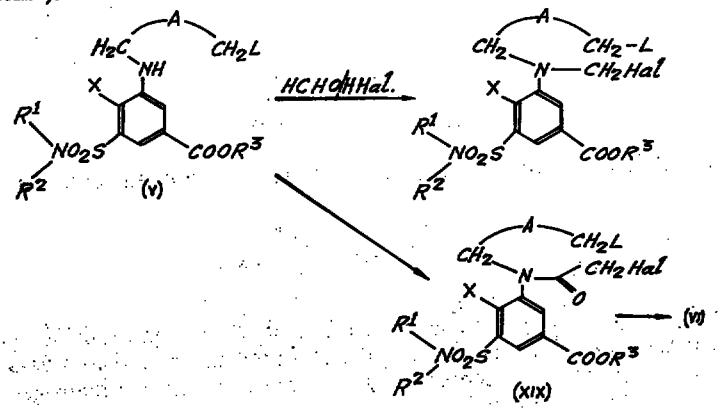
A compound of the formula I or II may also be prepared from a 3-amino-compound of the formula IX by reaction with a compound of the formula

$$L—CH_2—A—CH_2—L,$$

whereby the $—CH_2—A—CH_2—$ part of the molecule is cyclised with the 3-amino group of XV or XI with separation of 2 moles of HL to give a compound of the formula I or II.

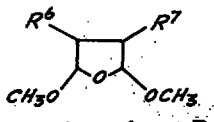
For this purpose, the compound IX is reacted in an organic solvent, for example, acetone, dimethylformamide, ethanol, or a mixture of such solvents, with an excess of the compound of the formula $L—CH_2—A—CH_2—L$, suitably by heating for several hours to days under reflux. It is advantageous, if L represents a bromine or chlorine atom, to add an excess of an alkali metal iodide to the reaction mixture. In some cases, an auxiliary base, for example, pyridine, triethylamine, $NaHCO_3$ or Na-acetate, accelerates the reaction.

A sulphamoylbenzoic acid derivative of the formula VI used in method e) may be prepared by various processes, for example, from a compound of the formula V in which A represents a single bond or an unsubstituted or substituted methylene or ethylene group, and L represents a halogen atom, preferably a chlorine or bromine atom, by reaction with formaldehyde and a hydrohalic acid or by a further reaction with an ω-halogenocarboxylic acid with formation of an amido compound of the formula XIX which is reduced in the manner already described (cf. the following reaction scheme).



The subsequent cyclization is effected in a known manner for example, according to the method described by Wurtz, by the reaction of a compound of the formula VI with metallic sodium or by the action of Zn on a boiling alcoholic solution of a compound of formula VI, as described in J. prakt. chem. *[2]36,* 300 (1887). This method is particularly suitable for the preparation of a compound of formula I having a 4-membered or 5-membered ring in the 3-position. It is also possible to react a compound of the formula VI with a nucleophilic compound, for example, a primary amine, NH_3 or H_2S, whereby the ring in the 3-position is closed with incorporation of the heteroatom of the nucleophilic reagent.

A compound of the formula VII used in method f) may be obtained from a 3-amino-5-sulphamoylbenzoic acid derivative of the formula IV by reaction in the usual manner with a 2,5-dimethoxytetrahydrofuran of the formula

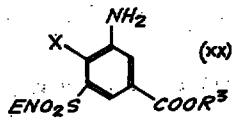


in which R^6, and R^7 have the meanings given above. Reduction of the resulting pyrrolo-compound VII is effected preferably by catalytic hydrogenation with a catalyst usually employed for such a purpose.

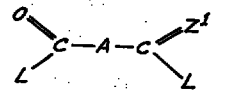
The benzoic acid derivatives of the formula VIII used in method g) and a process for preparing them are described and claimed in our Co-pending Application No. 37526/77.

The process for preparing the compound of formula VIII comprises

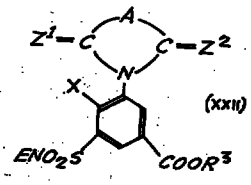
(a) (i) reacting a compound of formula XX



in which E, X and R^3 have the meanings given above, with a compound of the formula XXI

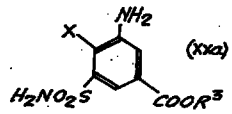

(xxi)

in which A and Z^1 have the meanings given above and L represents a "leaving group" or both symbols L together represent an oxygen atom, to give a compound of formula XXII

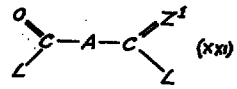

(xxii)

in which Z^1 represents an oxygen atom or two hydrogen atoms and Z^2 represents an oxygen atom, or

(a) (ii) reacting a compound of formula XXa


(xxa)

in which X and R^3 have the meanings given above, with a compound of formula XXI

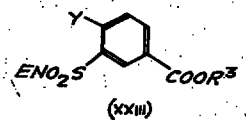

(xxi)

in which A, Z^1 and L have the meanings given above and introducing the group E, which has the meaning given above, into the resulting compound to give a compound of formula XXII in which Z^1 represents an oxygen atom or two hydrogen atoms and Z^2 represents an oxygen atom, and

(b) reducing the compound of formula XXII resulting from (a) (i) or (a) (ii) by means of a boron hydride to give the corresponding compound of formula VIII.

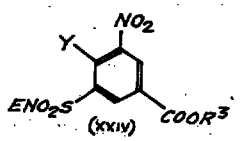
The compound of formula XX may be prepared by a process which comprises

(x) nitrating a sulphamoylbenzoic acid derivative of formula XXIII


(xxiii)

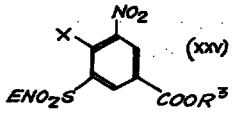
in which Y represents a halogen atom and E and R^3 are as defined above,

(y) reacting the resulting compound of formula XXIV


(xxiv)

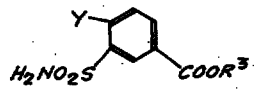
in which R^3, Y and E are as defined above, with a compound of formula XH in which X is as defined above

(z) reducing the resulting compound of formula XXV


(xxv)

in which E, X and R^3 have the meanings given above.

A compound of formula XXa may be prepared by carrying out the reactions (x), (y) and (z) described above using the corersponding, unprotected compound of formula XXIIIa



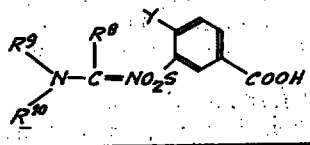
(XXIIIa)

as starting material. This process may be modified to produce a compound of formula XX by introducing the group E into any of the intermediates *i.e.* into the unprotected compounds corresponding to compounds XXIV, XV and XX.

The compound of formula XXIIIa is known, and the group E may be introduced into it or any other appropriate compound by any of the various known condensation methods.

The following literature is cited by way of example of documents disclosing such methods: J. Org. Chem. *25* (1960), 352—356; Zh. Org. Khim. *8* (1972), 286—291; Liebigs Ann. Chem. *750* (1971), 42; Zh. Org. Khim. *6* (1970), 9,1855; B. *94* (1961), 2731—2737; Ang. Ch. *78* (1966), 147—148; Ang. Ch. *80* (1968), 281—282; B. *97* (1964), 483—389; B. *96* (1963), 802—812; J. Org. Chem. *27* (1962), 4566—4570; Ang. Ch. *74* (1962), 781—782, and Doklady Akad. SSSR *145* (1962), 584.

As the compound of the general formula XXIII, there may be used for example, any of the following derivatives:



Compound No.	R^8	R^9	R^{10}	Y
1	H	CH_3	CH_3	Cl
2	CH_3	CH_3	CH_3	Cl
3	H	C_2H_5	C_2H_5	Cl
4	C_4H_9	CH_3	CH_3	Cl
5	H	CH_3	CH_3	F
6	H	CH_3	CH_3	Br
7	CH_3	$-CH_2-CH_2-CH_2-CH_2-CH_2-$		Cl
8	$-CH_2-CH_2-CH_2-$		CH_3	Cl

A compound of the formula XXIII may be prepared according to any of the above methods described in the literature or by an analogous method. Instead of the acids listed above as compounds 1 to 7, there may be used, for example, the corresponding methyl or ethyl ester.

Nitration of the benzoic acid derivative of the formula XXIII can be effected in various ways. For example, the benzoic acid derivative may be introduced into one of the nitrating mixtures conventionally used for the nitration of inert aromatic substances (cf. manual "Organicum", page 288, Edition 1967). The process may also be carried out by dissolving the benzoic acid derivative of the formula XXIII in oleum and controlling the nitration by dropwise addition of nitric acid.

It is surprising that it is possible to nitrate a benzoic acid derivative of the general formula XXIII without modification of other groups in the molecule merely by the introduction of the protective group E into the sulphonamide radical.

The reaction temperature is relatively low; preferably, temperatures in the range of from 55° to 70°C are maintained.

It is advantageous first to introduce into a suitable vessel a nitrating acid of oleum and fuming nitric acid, then to add the compound of formula XXIII and to heat the reaction mixture to 55° to 60°C.

The course of the nitration can be followed by thin-layer chromatography. Isolation of the final product is carried out in the usual manner, for example by pouring the reaction mixture onto ice and separating by filtration the crystals that have precipitated.

As mentioned above, an acid or ester of the general formula XXIII may be used. When an ester is used small amounts of the acid of the formula XXIV (with R^3=H) are obtained in addition to the ester. Such a resulting mixture can be separated in the usual manner, for example, by treatment with aqueous sodium carbonate, A resulting acid of the formula XXIV (in which R^3 is hydrogen) is then esterified in the usual manner, for example, it is converted into its acid chloride which, upon addition of an alcohol, yields the corresponding ester of the formula XXIV.

Suitable alcohols for the esterification are, in particular, alkyl alcohols having from 1 to 4 carbon atoms, for example, methanol, ethanol, propanol, butanol, isopropanol or isobutanol, and aralkylalcohols, for example, benzyl-alcohols or benzhydrol. It is advantageous to use the alcohol in a 5- to 20-fold molar excess or to use it simultaneously as solvent. A tert. butyl ester or benzhydryl esters can be prepared according to other known methods.

In the next step, the ester of the formula XXIV is converted by reaction with a compound of the formula XH into a compound of the formula XXV. It is surprising that a compound of the general formula XXIV in which R^3 represents an alkyl group can be reacted under anhydrous conditions with good yields with compounds of the general formula XH.

As the compound of the formula XH, there may be used, for example, phenol, 4-methylphenol, 3-methylphenol, 2-methylphenol, 4-chlorophenol, 3-trifluoromethylphenol, 3,5-dimethylphenol, 2,4-dimethylphenol, 4-methoxyphenol, 3-methoxyphenol, 4-propylphenol; thiophenol or a thiophenol substituted in the same manner as the phenols listed above; N-methylaniline, benzenesulphinic acid, pyrrolidine, N-methylpiperazine , 5-methyl-2-mercapto-1,3,4-thiadiazole, or 1-methyl-5-mercapto-1,2,3,4-tetrazole. Any additionally present functional groups in XH as well as other OH-groups, NH_2- or mercapto-groups are blocked by the usual protective groups, for example by acylation.

Compounds of the general formula HOR^4 and HSR^4, in which the radical R^4 has the meanings given above, are of great importance. Among them, the thiophenol and phenol derivatives, which may be substituted as already indicated, are of particular importance.

The reaction may be carried out without solvent, but it is advantageous to use a solvent. Particularly suitable solvents are organic solvents, for example, ether and tert. carboxamide, in particular diglym, dimethylformamide or hexamethylphosphoric acid-tris-amide (HMPT).

The compound X—H may be used as such in the presence of a base or may be used in the form of an alkali metal salt or alkaline earth metal salt thereof. As the base, an alcoholate or an alkali metal amide may be used.

The thiophenol or phenol derivative is reacted in the form of the anions thereof, among these, the alkali metal salts, especially the sodium and potassium salts, have proved particularly useful.

The reaction may be carried out in the presence or in the absence of a solvent. Without a solvent, the components are heated, for example, to a temperature within the range of from 100° to 200°C, preferably from 140° to 180°C. The resulting product can be isolated in the usual manner, for example, by dissolving the molten products in a solvent and subsequently precipitating them by the addition of water or of an organic non-solvent.

The reaction with a phenolate or thiophenolate in a solvent at a temperature within the range of from 100° to 200°C, preferably from 120° to 160°C, however, is particularly advantageous.

As the solvent, there may be used an organic solvent, in particular a tertiary carboxyamide, polyester or high-boiling point solvent, for example, HMPT or tetramethylenesulphone. Particularly advantageous is the reaction of an ester of the formula IX in a tertiary carboxamide, for example, dimethylformamide or dimethylacetamide. Depending on the reaction temperature selected, the reaction is generally completed after 1 to 6 hours.

The isolation of the final product of the formula X is effected in the usual manner; for example, the inorganic salts are first filtered off and the reaction product is then precipitated by the addition of a non-solvent or the reaction mixture is poured into water or onto ice and the reaction product that has precipitated is isolated.

A compound of the formula XXV in which X represents a SOR^4 or SO_2R^4 group in the 4-position, may be obtained from the corresponding compound in which X represents SR^4 by oxidation according to a known method, for example, an S-oxide is obtained by oxidation with per-acetic acid in dimethylformamide at a low temperature, while an S-dioxide is formed upon addition of an excess of an oxidizing agent at a more elevated temperature.

The reduction of the nitro group in a benzoic acid derivative of the formula XXV may be effected in the usual manner, for example, by catalytic hydrogenation. As the catalyst, Raney nickel or a noble metal catalyst, for example, palladium on charcoal or platinum oxide, is preferably used (cf. for example Organokum, pages 271—277—pages 507—510).

As the solvent for the reduction, an organic solvent, for example, methanol or ethanol, ethyl acetate, dioxane or another polar solvent, in particular an amide, for example, dimethylformamide, dimethylacetamide or HMPT, is preferably used. Hydrogenation may be effected at room temperature and under normal pressure or at an elevated temperature and increased pressure, for example, at 50°C and 100 atmospheres gauge in an autoclave.

A 3-imidobenzoic acid derivative of the general formula XXII may be prepared in various ways. For example, it may be obtained by reacting the amino compound XX with a dicarboxylic acid derivative of the general formula XXI which is capable of forming an imide. The reaction is carried out in a manner analogous to the reaction described under method a) of the compounds IX and X to a compound of the formula II. The reaction can be easily followed by thin-layer chromatography, since the amino compounds XX fluoresce at 366 mμ, while the compounds of formula XXII show no fluorescence.

An amido-compound of the formula XXII in which Z represents 2 hydrogen atoms, may be prepared in a manner analogous to that described under method a) for the compounds II, in which Z stands for 2 H-atoms.

The carboxylic acid derivatives of the formula XXI correspond to the above-described compounds of the formula X.

In the reduction of a compound of the formula XXII, a benzoic acid derivative of the general formula VIII which is substituted heterocyclically in the 3-position, is obtained. In order to obtain a particularly pure product with high yield, it is advantageous to use a benzoic acid ester of the formula XXII. The reduction is effected as described under method a).

A 5-sulphamoyl-benzoic acid of the formula I (i.e. R^3 represents a hydrogen atom), may be obtained by alkaline hydrolysis of a compound of the general formula VIII by heating for several hours in a sodium or potassium hydroxide solution on a steam bath. Thereby, the ester is saponified and the protective group E as well as any other protective groups present are split off.

A 5-sulphamoylbenzoic acid of the formula I may also be obtained directly by partially concentrating the reaction mixture after destruction of the excess of reducing agent, adding a base and heating for a prolonged period of time. As the base, sodium hydroxide solution may be used. The 5-sulphamoylbenzoic acid of the formula I can therefore be isolated directly in the form of a salt and the free acid obtained by acidification.

Subsequent to the methods listed under a) to g), any double bonds which may be present in the compounds of the formula I of the invention may be hydrogenated in the customary manner, for example, by catalytic hydrogenation. Conversely, it is also possible subsequently to introduce double bond(s) by an elimination reaction, for example, by separating hydrogen halide from a halogenated compound, by separating water from a hydroxy compound or by any other conventional splitting reaction.

If a free carboxylic acid of the formula I is first obtained, this may be converted in a usual manner into esters. For this purpose, an alcohol of the formula R^3OH or a functional derivative thereof is used or esterification is carried out in another known manner. Conversely, if a carboxylic acid ester of the general formula I is first obtained, it may be converted into the corresponding free carboxylic acid. Hydrolysis is generally used for this purpose but, in suitable cases, hydrogenolysis or other elimination reactions may be used. It is therefore possible, for example, to split an alkyl ester by alkaline hydrolysis; an aralkyl ester, in particular a *p*-nitrobenzyl ester, by hydrogeno-

lysis; and a tert.-butyl ester by elimination of isobutylene upon treatment with trifluoroacetic acid.

A free carboxylic acid may be converted into a salt, especially a physiologically tolerable salt, by reaction with an appropriate base, for example, an alkali metal, alkaline earth metal or ammonium hydroxide or carbonate. Finally, it is possible to obtain a compound of the formula I by separating, in the last reaction stage, one of the customary protective groups used for protecting the hydroxyl and, amino groups, whereby, for example acylated hydroxyl groups are hydrolyzed in the customary manner. The protective groups of hydroxyl and, amino groups are required especially in the preparation of the starting materials of the formula II, in order to prevent acylation with the carboxylic acid derivative of the formula X at undesired positions. In this case, the reduction according to the invention by method a) is often carried out with the protected hydroxy and amino compounds and the separation of the protective group is only carried out, as described above, after the reduction. However, even in the other methods it may be suitable to block reactive substituents which are split off in the last reaction stage.

A large number of pharmacologically active agents can be prepared by the process of the invention, especially diuretics and saluretics, some of which are specified in the Table hereinafter:

3-N-azetidino-4-phenoxy-5-sulphamoylbenzoic acid
3-N-aziridino-4-phenoxy-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-chloro-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-chlorophenoxy-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(3′-methylphenoxy)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(2′-methylphenoxy)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(2′,4′-dimethylphenoxy)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(3′,5′-dimethylphenoxy)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(4′-hydroxyphenoxy)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(4′-methoxyphenoxy)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(4′-trifluoromethyl-phenoxy)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(3′-trifluoromethyl-phenoxy)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(4′-propylphenoxy)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-n-butoxy-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-n-pentoxy-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-phenylthio-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(4′-dimethylaminophenoxy)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(4′-aminophenoxy)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-phenylsulphoxy-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-phenylsulphonyl-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-trichloromethyl-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-trifluoromethyl-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(N-methyl-N-phenyl)-amino-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-benzyl-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(4′-methylbenzyl)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(4′-methoxybenzyl)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-(4′-chlorobenzyl)-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-methyl-5-sulphamoylbenzoic acid
3-N-pyrrolidino-4-n-butyl-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-chloro-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-*p*-chlorophenoxy-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(3′-methylphenoxy)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(2′-methylphenoxy)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(2),4′-dimethylphenoxy)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(3′,5′-dimethylphenoxy)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(4′-hydroxyphenoxy)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(4′-methoxyphenoxy)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(4′-trifluoromethyl-phenoxy)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(3′-trifluoromethyl-phenoxy)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(4′-propylphenoxy)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-n-butoxy-5-sulphamoylbenzoic acid

3-N-(3-methylpyrrolidino)-4-n-pentoxy-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-phenylthio-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(4′-dimethylaminophenoxy)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(4′-aminophenoxy)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-phenylsulphoxy-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-phenylsulphonyl-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-trichloromethyl-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-trifluoromethyl-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(N-methyl-N-phenyl)-amino-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-benzyl-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(4′-methylbenzyl)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(4′-methoxybenzyl)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-(4′-chlorobenzyl)-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-methyl-5-sulphamoylbenzoic acid
3-N-(3-methylpyrrolidino)-4-n-butyl-5-sulphamoylbenzoic acid
3-N-(3,3-dimethylpyrrolidino)-4-phenoxy-5-sulphamoylbenzoic acid
3-N-(3,3-dimethylpyrrolidino)-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid
3-N-(3,3-dimethylpyrrolidino)-4-benzyl-5-sulphamoylbenzoic acid
3-N-(3,4-dimethylpyrrolidino)-4-phenoxy-5-sulphamoylbenzoic acid
3-N-(3,4-dimethylpyrrolidino)-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid
3-N-(3,4-dimethylpyrrolidino)-4-benzyl-5-sulphamoylbenzoic acid
3-N-Δ3-pyrrolino-4-phenoxy-5-sulphamoylbenzoic acid
3-N-Δ3-pyrolino-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid
3-N-Δ3-pyrrolino-4-(4′-chlorophenoxy)-5-sulphamoylbenzoic acid
3-N-Δ3-pyrrolino-4-benzyl-5-sulphamoylbenzoic acid
3-[1-(3-phenylpyrrolidinyl)]-4-phenoxy-5-sulphamoylbenzoic acid
3-[1-(3-phenylpyrrolidinyl)]-4-(4′-methylphenoxy)-sulphamoylbenzoic acid
3-N-(3-chloropyrrolidino)-4-phenoxy-5-sulphamoylbenzoic acid
3-N-(3-bromopyrrolidino)-4-phenoxy-5-sulphamoylbenzoic acid
3-N-piperidino-4-chloro-5-sulphamoylbenzoic acid
3-N-piperidino-4-p-chlorophenoxy-5-sulphamoylbenzoic acid
3-N-piperidino-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid
3-N-piperidino-4-(3′-methylphenoxy)-5-sulphamoylbenzoic acid
3-N-piperidino-4-(2′-methylphenoxy)-5-sulphamoylbenzoic acid
3-N-piperidino-4-(2′,4′-dimethylphenoxy)-5-sulphamoylbenzoic acid
3-N-piperidino-4-(3′,5′-dimethylphenoxy)-5-sulphamoylbenzoic acid
3-N-piperidino-4-(4′-hydroxyphenoxy)-5-sulphamoylbenzoic acid
3-N-piperidino-4-(4′-trifluoromethyl-phenoxy)-5-sulphamoylbenzoic acid
3-N-piperidino-4-(4′-propylphenoxy)-5-sulphamoylbenzoic acid
3-N-piperidino-4-n-butoxy-5-sulphamoylbenzoic acid
3-N-piperidino-4-n-pentoxy-5-sulphamoylbenzoic acid
3-N-piperidino-4-phenylthio-5-sulphamyolbenzoic acid
3-N-piperidino-4-(4′-dimethylaminophenoxy)-5-sulphamoylbenzoic acid
3-N-piperidino-4-(4′-aminophenoxy)-5-sulphamoylbenzoic acid
3-N-piperidino-4-phenylsulphoxy-5-sulphamoylbenzoic acid
3-N-piperidino-4-phenylsulphonyl-5-sulphamoylbenzoic acid
3-N-piperidino-4-trifluoromethyl-5-sulphamoylbenzoic acid
3-N-piperidino-4-(N-methyl-N-phenyl)-amino-5-sulphamoylbenzoic acid
3-N-piperidino-4-(4′-methoxyphenoxy)-5-sulphamoylbenzoic acid
3-N-piperidino-4-(4′-methoxyphenoxy)-5-sulphamoylbenzoic(acid

the corresponding

5-N-methylsulphamoyl
5-N-ethylsulphamoyl
5-N-methoxymethylsulphamoyl, and
5-N-butoxymethylsulphamoyl, compounds;

benzoic acid methyl esters,

benzoic acid ethyl esters,
benzoic acid benzyl esters, and
benzoic acid tert.-butyl esters.

The sulphamoylbenzoic acid derivatives of the formula I and their physiologically tolerable salts are diuretics and saluretics which can be used as pharmaceutical agents in human and veterinary medicine.

The invention therefore provides a pharmaceutical preparation which comprises a compound of the general formula I or a physiologically tolerable salt thereof in admixture or conjunction with a pharmaceutically suitable carrier. The preparation may be in a form suitable for administration enterally, for example perorally by means of a sound, or parenterally, for example, by intravenous injection, intramuscular injection, or subcutaneous injection.

The preparations are preferably in unit dosage form, for example, as capsules, dragées, tablets or ampoules containing a solution of the active substance with various additives. There is advantageously from 0.5 to 100 mg of the active substance per unit dose.

The preparations, particularly for human beings, may comprise the active substance alone or in combination with another saliduretic substance having a different mode of action. A compound of the invention may be administered with various other medicaments, separately from them, alternatively with them or in combination with them. In this respect, there may be mentioned SPIRONOLACTON, TRIAMTEREN, AMILORID and other K^+-retaining compounds, alternating with long-acting salidiuretics of the type of CHLORTHALIDON or others, together with, or separately from, the potassium-containing compounds (salts or the like) which replace the loss of K^+ which is observed in salidiuresis.

The preparations of the invention are suitable for the treatment of oedematous diseases, for example, oedemas caused by various cardiac, renal and hepatic conditions and other similar disorders of the water balance and electrolyte metabolism.

The following Examples illustrate the invention. If not stated otherwise, temperatures are given degrees celsius.

Example 1

3-N-Pyrrolidino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

(a) 3-Nitro-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

34 g (~0.1 mol) of 3-nitro-4-phenoxy-5-sulphamoylbenzoic acid are dissolved in 150 ml of methanol and are heated to the boil. 5.4 ml of concentrated H_2SO_4 are then added slowly dropwise and the mixture is heated at reflux temperature for 10 hours. On cooling, 3-nitro-4-phenoxy-5-sulphamoylbenzoic acid methyl ester crystallises.

It can be recrystallised from methanol/acetone.

Melting point: 181—182°C.

(b) 3-Amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

35 g (~0.1 mol) of 3-nitro-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are suspended in 150 ml of methanol and are hydrogenated with Raney nickel (5—10%) in an autoclave at 40—50°C and 100 atmospheres gauge. The precipitated amino compound is dissolved by the addition of acetone on a steambath and the Raney nickel is removed by filtration.

On cooling, 3-amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester crystallises out cleanly.

Melting point: 179°C.

(c) 3-N-Succinimido-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

(i) 16.1 g (0.05 mol) of 3-amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are dissolved in 150 ml of absolute dioxane and the solution is heated to the boil.

A solution of 11.6 g (0.075 mol) of succinic acid dichloride in 50 ml of absolute acetone and a solution of 8 ml of pyridine in 50 ml of absolute acetone are then added dropwise at the same rate but separately, while stirring well, and the mixture is heated under reflux. The reaction is complete after about 2 hours. The mixture is concentrated and the residual oil is taken up in a little methanol. 3-N-Succinimido-4-phenoxy-5-sulphamylbenzoic acid methyl ester crystallises out after a short time.

Crystallisation is completeed by adding a little water.

Recrystallisation is carried out from methanol/acetone.

Melting point: 270°C.

(ii) 3-Amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester is fused with a 2—3-fold molar quantity of succinic anhydride, for about 2 hours at 160—180°C. On cooling and adding methanol, 3-N-succinimido-4-phenoxy-5-sulphamylbenzoic acid methyl ester crystallises out.

(d) 3-N-Pyrrolidino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

12.3 g (0.03 mol) of 3-N-succinimido-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are dissolved or suspended in 100 ml of absolute diglym. 9 g of boron trifluoride etherate are added direct to this and a solution of 2.4 g (~0.063 mol) of $NaBH_4$ in 80 ml of diglym is then added dropwise at room temperature and with good stirring. As the reaction proceeds exothermically, it is necessary to cool with ice water. The reaction is normally complete after the dropwise addition and a short period of stirring thereafter.

The excess reducing agent is then decomposed by means of a little water (foaming!), the solution is filtered and about 300 ml of water are added while stirring. The 3-N-pyrrolidino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester which has crystallised out is recrystallised from methanol.

Colourless crystals, melting point: 191—192°C.

NMR data: ($CDCl_3$, 60 MHz, TMS as internal standard) δ=1.73 (m; 4H), δ=3.26 (m; 4H), δ=3.91 (s; 3H), δ=5.0 (s; 2H), δ=6.6—8.0 (m; 7H) in ppm.

Example 2

3-N-Pyrrolidino-4-phenoxy-5-sulphamoylbenzoic acid

61 g of 3-N-pyrrolidino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are suspended in 350 ml of 1N NaOH and the suspension is heated for one hour on a waterbath. 3-N-Pyyrolidino-4-phenoxy-5-sulphamoylbenzoic acid is precipitated from the clear solution by means of 2 N HCl while stirring well. The almost pure crude product can be recrystallised from methanol/water.

Light yellow platelets, melting point: 225—227°, with decomposition.

NMR data: (D_6-DMSO, 60 MHz, TMS) δ=1.67 (quasi-s; 4H), δ=3.21 (quasi-s; 4H), δ=6.6—8.0 (m; 9H) in ppm.

Example 3

3-N-Piperidino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

(a) 3-N-Glutarimido-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

16.1 g of 3-amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are dissolved in 150 ml of absolute dioxane and the solution is heated to the boil. A solution of 16.8 g of glutaric acid dichloride in 50 ml of absolute acetone and a solution of 8 ml of pyridine in 50 ml of absolute acetone are then added dropwise at the same rate, while stirring well, and the mixture is heated under reflux. The reaction is complete after about 3 hours. The mixture is concentrated and the residue is taken up in a little methanol. 3-N-Glutarimido-4-phenoxy-5-sulphamoylbenzoic acid methyl ester crystallises out after a short time. It can be recrystallised from glycol monomethyl ether. Colourless crystals, melting point 312—314°C, with decomposition.

(b) 3-N-Piperidino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

15 g of 3-N-glutarimido-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are suspended in 200 ml of diglym (diethylene glycol dimethyl ether) and 10 ml of boron trifluoride etherate are added. A solution of 3 g of $NaBH_4$ in 150 ml of diglyme is then added slowly at room temperature with good stirring. The excess reducing agent is then decomposed with a little water, the solution is filtered and 500 ml of water are added, while stirring. The 3-N-piperidino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester which has crystallised out can be recrystallised from alcohol.

White crystals, melting point 198—199°C.

NMR data: (D_6-DMSO, 60 MHz, TMS) δ=1.1 (quasi-s; 6H), δ=2.86 (quasi-s; 4H), δ=3.92 (s; 3H), δ=6.7—8.1 (m; 9H) in ppm.

Example 4

3-N-Piperidino-4-phenoxy-5-sulphamoylbenzoic acid

8 g of 3-N-piperidino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are suspended in 50 ml of 1 N NaOH and the suspension is heated on a steam bath until a clear solution is formed. The resulting 3-N-piperidino-4-phenoxy-5-sulphamoylbenzoic acid is precipitated with 2 N HCl and is recrystallised from methanol/water.

White crystals, melting point 258—260°.

NMR data: (D_6-DMSO, 60 MHz, TMS) δ=1.08 (quasi-s; 6H), δ=2.9 (quasi-s; 4H), δ=6.65—8.2 (m; 9H) in ppm.

Example 5

3-N-isoindolinyl-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

(a) 3-N-Phthalimido-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

16 g of 3-amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are dissolved

in 200 ml of absolute dioxane and the solution is heated to the boil. A solution of 14 ml of phthalic acid dichloride in 50 ml of acetone and a solution of 9 ml of pyridine in 50 ml of acetone are then added dropwise at the same rate, while stirring well. The reaction is complete after 3 hours. The solution is concentrated and the residue is taken up in a little acetone and added dropwise, while stirring well, to a mixture of ice water and 2 N HCl. A light brown precipitate of the 3-N-phthalimido-4-phenoxy-5-sulphamoylbenzoic acid methyl ester is formed. Recrystallisation from methanol/acetone/H_2O gives colourless crystals, melting point 237—238°C.

(b) 3-N-Isoindolinyl-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

16 g of 3-N-phthalimido-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are dissolved or suspended in 150 ml of diglyme and 12 ml of boron trifluoride etherate are added. A solution of 3.6 g of $NaBH_4$ in 100 ml of diglym is then added dropwise at room temperature and the mixture is stirred for a further ½ hour at 60°C. On adding 400 ml of water a flocculent mixture of substances separates out. It is boiled up with methanol, during which the 3-N-isoindolinyl-4-phenoxy-5-sulphamylbenzoic acid methyl ester does not dissolve. It is filtered off and recrystallised from *n*-butanol/DMF.

White needles, melting point: 268—272°, with decomposition.

NMR data: (D_6-DMSO, 60 MHz, TMS) δ=3.92 (s; 3H), δ=4.66 (s; 4H), δ=6.6—8.1 (m; 13H) in ppm.

Example 6:

3-N-Isoindolinyl-4-phenoxy-5-sulphamylbenzoic acid

2.5 g of 3-N-isoindolinyl-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are suspended in 50 ml of 1 N NaOH and the suspension is heated on a steam bath until a clear solution is formed. The 3-N-isoindolinyl-4-phenoxy-5-sulphamylbenzoic acid is precipitated with 2 N HCl and is recrystallised from glacial acetic acid.

Light yellow crystals, melting point 259—261°, with decomposition.

NMR data: (D_6-DMSO, 60 MHz, TMS) δ=4.68 (s; 4H), δ=6.6—8.0 (m; 13H) in ppm.

Example 7

3-N-(3-Azabicyclo-[3,2,0]-heptano)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

(a) 3-N-(2,4-Dioxo-3-azabicyclo-[3,2,0]-heptano)-4-phenoxy-5-sulphamylbenzoic acid methyl ester

8.1 g of 3-amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are mixed with 6.3 g of *cis*-cyclobutane-1,2-dicarboxylic acid anhydride and 5 ml of diglym and the mixture is heated to 180°. In the course thereof the diglym evaporates off. The melt becomes solid after about 1 hour. Methanol is added while it is still warm. The solid mass disintegrates into a colourless mash of crystals. The crystalline powder is filtered off and recrystallised from glycol monomethyl ether.

Melting point: 284—285°C.

(b) 3-N-(3-Azabicyclo-[3,2,0]-heptano)-4-phenoxy-5-sulphamylbenzoic acid methyl ester

7.3 g of 3-N-(2,4-dioxo-3-azabicyclo-[3,2,0]-heptano)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are suspended in 70 ml of diglym and 6 ml of boron trifluoride etherate are added. A solution of 1.5 g of $NaBH_4$ in 70 ml of diglym is then added slowly dropwise, with ice cooling. The mixture is stirred for about 15 minutes more and the 3-N-(3-azabicyclo-[3.2.0]-heptano)-4-phenoxy-5-sulphamylbenzoic acid methyl ester is precipitated by adding water.

Recrystallisation is carried out from methanol or acetonitrile.

White crystals, melting point 176—177°C.

Eample 8

3-N-(3-Azabicyclo-[3,2,0]-heptano)-4-phenoxy-5-sulphamoylbenzoic acid

6.2 g of 3-N-(3-azabicyclo-[3,2,0]-heptano)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are suspended in 60 ml of 1 N NaOH and the suspension is heated on the waterbath until a clear solution is formed. The acid is then precipitated with 2 N HCl, while stirring well, and is recrystallised from glacial acetic acid.

Pale yellow platelets, melting point 254—255°C, with decomposition.

Example 9

3-N-Morpholino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

(a) 3-N-(3,5-Dioxo-morpholino)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

16 g of 3-amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are mixed with 15 g of diglycollic acid anhydride and 10 ml of diglym and the mixture is heated in an open flask to about 180°C. After 1—2 hours, methanol is added cautiously. The imide crystallises out on cooling.

White crystals from diglyme; melting point 295—297°C.

(b) 3-N-Morpholino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

9.4 g of 3-N-(3,5-dioxo-morpholino)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are suspended in 100 ml of diglyme and 6 ml of boron trifluoride etherate are added. A solution of 1.9 g of $NaBH_4$ in 100 ml of diglym is then added slowly dropwise, while cooling with ice and stirring well. The resulting 3-N-morpholino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester is precipitated by adding water.

Recrystallised from methanol; melting point 221—222°C.

Example 10

3-N-Morpholino-4-phenoxy-5-sulphamoylbenzoic acid

The corresponding methyl ester (Example 9) is heated with 1 N NaOH on a water bath until a clear solution is formed. The 3-N-morpholino-4-phenoxy-5-sulphamoylbenzoic acid is precipitated by adding 2 N HCl and is then recrystallised from methanol; brownish white crystals, melting point 194—197°, with decomposition.

Example 11

3-N-(4-Methylpiperidino)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

(a) 3-N-(4-Methylglutarimido)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

16 g of 3-amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester and 15 g of 4-methylglutaric anhydride are mixed, with the addition of a little diglym, to form a slurry which is heated to 160—180°C for 2—3 hours. The 3-N-(4-methylglutarimido)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester is precipitated by adding methanol; white crystals from glycol monomethyl ether; melting point 315°C.

(b) 3-N-(4-Methylpiperidino)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

10.3 g of 3-N-(4-methylglutarimido)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are suspended in 100 ml of diglyme and 6.5 ml of BF_3 etherate are added. A solution of 1.9 g of $NaBH_4$ in 100 ml of diglym is added dropwise at room temperature. After the dropwise addition, the mixture is stirred for a further 15 minutes and the 3-N-(4-methylpiperidino)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester is then precipitated with water; colourless crystals from methanol, melting point 143—144°C.

Example 12

3-N-(4-Methylpiperidino)-4-phenoxy-5-sulphamoylbenzoic acid

The corresponding methyl ester (Example 11) is heated with 1 N NaOH on a waterbath until a clear solution is formed. The 3-N-(4-methylpiperidino)-4-phenoxy-5-sulphamoylbenzoic acid is precipitated by adding 2 N HCl; white crystals from methanol/water, melting point 243—244°C.

Example 13

3-N-(3-Methylpyrrolidino)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

(a) 3-N-(3-Methylsuccinimido)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

16 g of 3-amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester and 15 g of 3-methylsuccinic anhydride are fused together with a little diglym in an open flask and the mixture is kept at approx. 180°C for about 2.5 hours. The 3-N-(3-methylsuccinimido)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester crystallises out on adding methanol.

Recrystallised from glycol monomethyl ether; white crystals, melting point 272°C.

(b) 3-N-(3-Methylpyrrolidino)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

17 g of 3-N-(3-methylsuccinimido)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are suspended in 150 ml of diglyme. 11 ml of BF_3 etherate are added and a solution of 3 g of $NaBH_4$ in 150 ml of diglym is then added dropwise while cooling with ice. After the dropwise addition, the resulting 3-N-(3-methylpyrrolidino)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester is precipitated with water; white crystals from methanol, melting point 145°C.

Example 14

3-N-(3-Methylpyrrolidino)-4-phenoxy-5-sulphamoylbenzoic acid

9 g of 3-N-(3-methylpyrrolidino)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are heated in 1 N NaOH on a water bath until a clear solution is formed. The 3-N-(3-methylpyrrolidino)-4-phenoxy-5-sulphamoylbenzoic acid is then precipitated at room temperature with 2 N HCl and is recrystallised from CH_3OH/H_2O; white-yellow crystals, melting point 206—208°C.

Example 15

3-N-Pyrrolidino-4-phenoxy-5-sulphamylbenzoic acid methyl ester

4.1 g of 3-N-succinimido-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are dissolved in 40 ml of diglym and 2.5 ml of titanium tetrachloride are added. A solution of 1.1 g of $NaBH_4$ in 30 ml of diglym is then added dropwise slowly at room temperature and the mixture is stirred for about 1 hour more.

The resulting 3-N-pyrrolidino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester is precipitated with water and recrystallised from methanol. Melting point 191°C.

Example 16

3-N-Pyrrolidino-4-phenoxy-5-sulphamoylbenzoic acid

(a) 3-N-(ω-Chloro-butyramido)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

24 g of 3-amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester and 7.5 ml of pyridine in 100 ml of absolute dioxane and 21.2 g of ω-chlorobutyric acid chloride in 100 ml of absolute acetone are added dropwise, slowly and as nearly as possible at the same rate, over the course of about 2 hours into a vessel containing 100 ml of boiling absolute dioxane. The solution is stirred for 1 hour more and is then concentrated. The residual oil is taken up in a little acetone and added dropwise, with vigorous stirring, to ice water.

The 3-N-(ω-chloro-butyrylamino)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester is precipitated and is recrystallised from methanol. Melting point 151—153°C.

(b) 3-N-(ω-chlorobutylamino)-4-phenoxy-5-sulphamoyl-benzoic acid methyl ester

12 g of 3-N-(ω-chlorobutyrylamino)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are suspended in 150 ml of diglyme. 7 ml of boron trifluoride etherate are added. A solution of 2.2 g of $NaBH_4$ in 150 ml of diglym is slowly added dropwise at room temperature. Stirring is continued for some minutes and the product is then carefully precipitated with water. Recrystallisation from CH_3OH, m.p. 125°C.

(c) 3-N-pyrrolidino-4-phenoxy-5-sulphamoylbenzoic acid

Method C

3-N-(ω-chlorobutylamino)-4-phenoxy-5-sulphamoyl-benzoic acid methyl ester is suspended in 1N NaOH and heated on a steam bath until a clear solution is obtained.

3-N-pyrrolidino-4-phenoxy-5-sulphamoyl-benzoic acid (as in Example 2) is precipitated from the cold solution by means of 1N HCl.

Example 17

4-Chloro-3-pyrrolidino-5-sulphamoylbenzoic acid

(a) 4-Chloro-3-succinimido-5-sulphamoylbenzoic acid methyl ester

25.4 g of 4-chloro-3-amino-5-sulphamoylbenzoic acid methyl ester, m.p. 195—196°C, are thoroughly mixed with 25 g of succinic acid anhydride and melted for 6 hours at 180°C. The melt is allowed to cool slowly and CH_3OH is added carefully. The product crystallizes. A small amount of water added completes the crystallisation.

Recrystallisation from glycol monomethyl ether: m.p. 267—269°C.

(b) 4-Chloro-3-pyrrolidino-5-sulphamoylbenzoic acid

20 g of the imide produced in step (a) are suspended in 200 ml of diglyme and 17 ml of BF_3 etherate are added. A solution of 4 g of $NaBH_4$ in 200 ml of diglym is added dropwise to this suspension while cooling with ice. After the addition, stirring is continued for half an hour and the mixture is then carefully hydrolysed with a small amount of water. The solution is filtered, and 4-chloro-3-pyrrolidino-5-sulphamoylbenzoic acid methyl ester is precipitated with water. Recrystallisation from methanol: m.p. 189—191°C. The ester is hydrolysed in 1N NaOH on a steam bath until a clear solution has formed. Upon acidification at pH 4, the free acid precipitates.

Light yellow crystals are obtained from CH_3OH/H_2O. M.p. 259—261°C.

Example 18

3-N-Pyrrolidino-4-phenylthio-5-sulphamoylbenzoic acid

(a) 3-N-succinimido-4-phenylthio-5-sulphamoylbenzoic acid methyl ester

5.8 g of 3-amino-4-phenylthio-5-sulphamoylbenzoic acid methyl ester are mixed with 5.9 g of succinic anhydride and melted at 170°C. After 5 hours, CH_3OH is carefully added while cooling. The substance crystallizes and is recrystallised from glycol monomethyl ether.

M.p. 250—251°C.

(b) 3-N-Pyrrolidino-4-phenylthio-5-sulphamoylbenzoic acid

14.7 g of the imide produced in step (a) are suspended in 100 ml of diglyme and 10 ml of BF_3 etherate are added. 2.8 g of $NaBH_4$ dissolved in 100 ml of diglyme are then slowly added dropwise while cooling with ice. Stirring is continued for half an hour at room temperature and excess reducing agent is destroyed by adding a small amount of water. 3-N-pyrrolidino-4-phenylthio-5-sulphamoylbenzoic acid methyl ester is then precipitated with water and recrystallised from methanol. Yellow crystals having a melting point of 139—140°C are obtained. The ester is heated with 1N NaOH on a steam bath until a clear solution is obtained, and the acid formed is then precipitated with 1N hydrochloric acid at pH 3—4. Upon recrystallisation from methanol/water, yellow crystals are obtained, m.p. 238—239°C.

Example 19

3-(1-Pyrrolidinyl)-4-phenoxy-5-sulphamoylbenzoic acid

a) 3-N-succinimido-4-phenoxy-5-nitro-benzoic acid methyl ester

105 g of 3-amino-4-phenoxy-5-nitrobenzoic acid methyl ester are mixed with 210 g of succinic anhydride and heated for 2 hours to 180°C while stirring the reaction mixture is introduced, with stirring, into 3 l of water and extracted after some time with methylene chloride. The organic phase is isolated, dried and concentrated. The residue yields, after recrystallization from methanol, the desired compound melting at 152—154°C in a very good yield.

b) 3-(1-Pyrrolidinyl)-4-phenoxy-5-nitrobenzoic acid methyl ester.

A solution of 44.4 g of the ester obtained according to a) in 300 ml of diglym under nitrogen is reacted, while stirring at 0°C, with 34 g of boron trifluoro-dietherate and subsequently with a solution of 9.2 g of $NaBH_4$ in 200 ml of diglyme, while keeping the temperature below +15°C. After a further hour, water is added dropwise. After completion of the exothermic reaction, 500 ml of water are added. The desired compound thereupon separates in the form of orange coloured needles melting at 118°—120°C with a very good yield.

c) 3-(1-Pyrrolidinyl)-4-phenoxy-5-amino-benzoic acid methyl ester

A solution 30 g of the nitrobenzoic acid methyl ester obtained according to b) in 500 ml of dioxane is hydrogenated catalytically in the presence of Raney nickel. After completion of the absorption of hydrogen, the mixture is filtered and the filtrate is concentrated. The residue yields, on recrystallization from methanol, the desired compound in the form of colourless crystals melting at 153°—156°C in a very good yield.

d) 3-(1-Pyrrolidinyl)-4-phenoxy-5-chlorosulphonyl-benzoic acid methyl ester

A solution of 24.3 g of the amino ester obtained according to c) in 150 ml of concentrated hydrochloric acid is cooled to −5°C and diazotized with a solution of 5.46 g of $NaNO_2$ in 40 ml of water, while keeping the temperature below +5°C. After 15 minutes, the light brown solution of the diazonium salt is introduced into a mixture of 7.8 g of Cu^{II}-chloride dihydrate, 24 ml of concentrated hydrochloric acid and 200 ml of a saturated solution of SO_2 in glacial acetic acid at 0°C. After completion of the evolution of gas, the mixture is stirred for a short time, then combined with water, and the sulphochloride that has separated is extracted with methylene chloride. The organic phase is washed twice with water, dried and concentrated. The remaining oil yields, upon addition of diisopropyl ether, the desired compound melting at 108°—112°C with a very good yield.

e) 3-(1-Pyrrolidinyl)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester

25.0 g of the 5-chlorosulphonyl-benzoic acid methyl ester are introduced portionwise, while stirring, at room temperatures into a mixture of 150 ml of methylene chloride and 75 ml of 25% aqueous ammonia, the mixture is stirred for 1 hour, the

organic phase is separated and washed with water, dried over sodium sulfate and concentrated. The remaining oil is recrystallised from methanol and gives the 5-sulphamylbenzoic acid ester melting at 186—188°C with a very good yield.

Saponification of the ester to form the 3-(1-pyrrolidinyl)-4-phenoxy-5-sulphamoylbenzoic acid is effected in the manner described in Example 5. Melting point: 227—228°C.

Example 20

3-(1-Pyrrolidinyl)-4-phenoxy-5-sulphamylbenzoic acid

a) 3-(1-Pyrrolidinyl)-4-phenoxy-5-nitrobenzoic acid

50 g of 3-(1-pyrrolidinyl)-4-phenoxy-5-nitrobenzoic acid methyl ester (preparation cf. Example 19, step b) are saponified with heating with dilute sodium hydroxide solution.

The orange red solution is extracted twice with CH_2Cl_2, the aqueous phase is then acidified with concentrated hydrochloric acid. The desired acid is isolated in the form of light yellow crystals melting at 228°—230°C.

b) 3-(1-Pyrrolidinyl)-4-phenoxy-5-aminobenzoic acid

32.8 g of the nitrobenzoic acid prepared according to a) are dissolved in a solution of 8 g of NaOH in 200 ml of water, cooled to 0°C and combined with a solution of 90 g of sodium dithionite in 380 ml of water, while keeping the temperature below 10°C. The solution which at first is red-orange coloured changes to light yellow. The solution is stirred for 1 hour without cooling, then acidified to pH 1 by means of concentrated hydrochloric acid and concentrated until crystallisation begins. The hydrochloride of the desired aminobenzoic acid is obtained in the form of colourless crystals melting at 245°—247°C.

If the dithionite contains sulfate, there is obtained already before concentration of the aqueous solution the corresponding sulphate in the form of colourless crystals melting at 175°—176°C.

From both, the free amine melting at 100°—103°C can be obtained by neutralisation of the aqueous solution to pH 4—4.5.

c) 3-(1-Pyrrolidinyl)-4-phenoxy-5-chlorosulphonyl-benzoic acid

A solution of 8.35 g of the aminobenzoic acid hydrochloride prepared according to b) in 25 ml of concentrated hydrochloric acid is diazotized at 0°C with a solution of 1.75 g of sodium nitrite in 15 ml of water, while keeping the temperature below +5°C. After 15 minutes, the solution of the diszonium salt is introduced, while stirring, into a mixture cooled to 0°C of 2 g of Cu-dichloride-dihydrate, 2 ml of concentrated hydrochloric acid and 15 ml of a saturated solution of SO_2 in glacial acetic acid. After termination of the foam formation, the whole is stirred for 30 minutes, the reaction mixture is subsequently combined with 150 ml of water and extracted several times with ethyl acetate. The organic phase is washed with water, dried, concentrated and, after addition of ether and hexane, yields the crystalline sulphochloride melting at 163°—165°C.

If the aminobenzoic acid sulphate is used, the same sulphochloride is obtained with a somewhat smaller yield.

d) 3-(1-Pyrrolidinyl)-4-phenoxy-5-sulphamoylbenzoic acid

7.6 g of the chlorosulphonyl derivative prepared according to c) are introduced in 15 ml of liquid ammonia. The ammonia is removed by evaporation at room temperature and the residue is dissolved in a small amount of water. The solution is filtered and adjusted to pH 1 by means of concentrated hydrochloric acid. The desired sulphamoylbenzoic acid is thereupon obtained in the form of brownish crystals which, upon recrystallisation from methanol/water, yield pale yellow crystals melting at 225°C.

Example 21

4-Phenoxy-3-(1-pyrrolidinyl)-5-dimethylsulphamoylbenzoic acid

7.2 g (0.02 mol) of 4-phenoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid are dissolved in 100 ml of 1 N NaOH and combined with 10 ml of dimethylsulphate. The mixture is stirred well at room temperature. After about 30 minutes, a white flocculant substance precipitates. It is filtered off with suction and heated with 2N NaOH on a steam bath. When a clear solution is formed, the mixture is allowed to cool and the 4-phenoxy-3-(1-pyrrolidinyl)-5-dimethylsulphamoylbenzoic acid is precipitated with the aid of 2 N HCl. The substance can be recrystallized from methanol/water. Yellow fibers melting at 214°—215°C are obtained.

Example 22

4-Phenoxy-3-(1-pyrrolidinyl)-5-methylsulphamoylbenzoic acid

a) 4-Phenoxy-3-N-succinimido-5-methylsulphamoylbenzoic acid methyl ester

71 g of 3-amino-4-phenoxy-5-methyl-sulphamoylbenzoic acid methyl ester (M.p. 188°C) are fused with 87 g of succinic acid anhydride at 180°—190°C. After 5 hours, the molten mass is cautiously combined with methanol and thereafter with the same amount of water, whereupon the imide crystallises. The 4-phenoxy-3-N-succinimido-5-methylsulphamoylbenzoic acid methyl ester is obtained from methanol and is found to melt at 249°—250°C.

b) 4-Phenoxy-3-(1-pyrrolidinyl)-5-methylsulphamoylbenzoic acid methyl ester

67 g of 4-phenoxy-3-N-succinimido-5-methylsulphamoylbenzoic acid methyl ester are suspended in 300 ml of absolute diglym and combined with 40 ml of boron trifluoride etherate. The mixture is cooled to −10°C and a solution of 12.2 g of $NaBH_4$ in 300 ml of diglyme is added dropwise, while stirring well. The temperature should not rise above 10°C during that time. After the dropwise addition, the mixture is stirred for 10 minutes and then is cautiously combined with water (foaming). Upon further addition of water, the reaction product precipitates. The 4-phenoxy-3-(1-pyrrolidinyl)-5-methylsulphamoylbenzoic acid methyl ester melting at 138°—139°C is obtained by recrystallisation from methanol.

c) 4-Phenoxy-3-(1-pyrrolidinyl)-5-methylsulphamoylbenzoic acid

54 g of the methyl ester obtained according to b) are suspended in 50 ml of 1 N NaOH and heated, while stirring, on the steam bath. When a clear solution has formed, the mixture is allowed to cool and the free acid is precipitated with the aid of 1 N-HCl. The 4-phenoxy-3-(1-pyrrolidinyl)-5-methylsulphamoylbenzoic acid melting at 245°—248°C with decomposition is obtained by recrystallisation from methanol/water.

Example 23

4-(4′-Methylphenoxy)-3-(1-pyrroldinyl)-5-sulphamoylbenzoic acid

a) 3-Nitro-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid

124 g (0.9 mol) of potassium carbonate are dissolved in 800 ml of water. To this solution, there are added portionwise 1.6 mols of p-cresol and subsequently 112 g (0.4 mol) of 2-chloro-3-nitro-5-carboxy-benzenesulphonamide and the solution is heated to 85°C. The solution is stirred for 16 hours at this temperature, cooled to 25°—30°C and acidified with concentrated hydrochloric acid to pH 1. The oil which thereupon separates is isolated from the aqueous phase and subjected to steam distillation. Alternatively, it is possible to adjust the pH to 8 to 9, to extract the excess phenol with ethyl acetate and then to acidify the aqueous phase. Afer having separated the excess *p*-cresol in this manner, the product crystallises upon cooling. By recrystallisation from acetone/H_2O, the 3-nitro-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid melting at 236°C is obtained.

b) 3-Nitro-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid methyl ester

The crude product obtained according to a) is dissolved in methanol and heated to the boiling temperature. Then, 5—10% of concentrated sulfuric acid (in relation to the benzoic acid used) are added and the whole is boiled for 8 hours under reflux. The solution is concentrated to one third and cooled to 5°—10°C. The methyl ester crystallises out: crystals melting at 161°—162°C.

c) 3-Amino-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid methyl ester

45 g of 3-nitro-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid methyl ester are suspended in 150 ml of ethyl acetate and hydrogenated for 5 hours with Raney nickel at 50°C and a hydrogen pressure of 100 atmospheres gauge. After cooling, the Raney nickel is separated and the solution is concentrated to dryness. The 3-amino-4-(4′-methylphenoxy)-4-sulphamoylbenzoic acid methyl ester is recrystallised from methanol/H_2O. Crystals melting at 183°—185°C.

d) 3-N-Succinimido-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid methyl ester

27 g (~0.08 mol) of 3-amino-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid methyl ester are fused with 24 g (0.24 mol) of succinic anhydride for 4 hours at 170°—190°C. During cooling of the molten mass, methanol and a small amount of water are added with care. The imide precipitates and is recrystallised from CH_3OH/H_2O. Crystals melting at 240°—241°C.

e) 4-(4′-Methylphenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid methyl ester
25.6 g of 3-N-succinimido-4-(4′-methylphenoxy)-5-sulphamoylbenzoic acid methyl ester are suspended in 150 ml of absolute diglym and 16 ml of BF_3-etherate are added. A solution of 4.6 g of $NaBH_4$ in 200 ml of absolute diglym is then added dropwise and slowly, while cooling with ice and stirring well. During that time, the temperature should not rise above 20°C. Stirring is continued for 15 minutes and eventually the product is precipitated with water. Recrystallisation from CH_3OH; crystals melting at 156°—157°C.

f) The methyl ester obtained according to e) is suspended in 1 N NaOH and heated on a steam bath until a clear solution has formed. The mixture is filtered and acidified to pH 3. The 4-(4′-methylphenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid that has precipitated is recrystallised from methanol; light yellow crystals melting at 230°—233°C with decomposition.

Example 24

4-(4′-Methoxyphenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid

a) 3-Nitro-4-(4′-methoxyphenoxy)-5-sulphamoylbenzoic acid
The reaction is carried out with *p*-methoxyphenol in a manner analogous to that described in Example 23a). The product is recrystallised from acetone/water and has a melting point of 233°—234°C.

b) 3-Nitro-4-(4′-methoxyphenoxy)-5-sulphamoylbenzoic acid methyl ester
This compound is produced in a manner analogous to that described in Example 23b). Recrystallisation from methanol; M.p. 150°—152°C.

c) 3-Amino-4-(4′-methoxyphenoxy)-5-sulphamoylbenzoic acid methyl ester
This compound is produced in a manner analogous to that described in Example 23c). Recrystallisation from methanol; M.p. 176°—177°C.

d) 3-N-succinimido-4-(4′-methoxyphenoxy)-5-sulphamoylbenzoic acid methyl ester
This compound is produced in a manner analogous to that described in Example 23d). M.p. 226°—227°C.

e) 4-(4′-Methoxyphenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid methyl ester.
This compound is produced in a manner analogous to that described in Example 23e). M.p. 190°—191°C.

f) 4-(4′-Methoxyphenoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid is prepared in a manner analogous to that described in Example 23f) and recrystallised from methanol/water. Light yellow crystals melting at 228°—229°C.

Example 25

4-(3′,5′-Dimethylphenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid

a) 3-Nitro-4-(3′,5′-dimethylphenoxy)-5-sulphamoylbenzoic acid.
The reaction is carried out with 3,5-dimethylphenol in a manner analogous to that described in Example 23a). The raw product so obtained is directly esterified.

b) 3-Nitro-4-(3′,5′-dimethylphenoxy)-5-sulphamoylbenzoic acid methyl ester
This compound is obtained in a manner analogous to that described under Example 23b), recrystallisation from methanol. M.p. 197°—198°C.

c) 3-Amino-4-(3′,5′-dimethylphenoxy)-5-sulphamoylbenzoic acid methyl ester
This compound is obtained in a manner analogous to that described under Example 23c), recrystallisation from methanol. M.p. 195°—196°C.

d) 3-N-Succinimido-4-(3′,5′-dimethylphenoxy)-5-sulphamoylbenzoic acid methyl ester
This compound is obtained in a manner analogous to that described under Example 23d), recrystallisation from methanol. M.p. sintering from 220°C onwards.

e) 4-(3′,5′-Dimethylphenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid methyl ester.
This compound is obtained in a manner analogous to that described under Example 23e), recrystallisation from methanol. M.p. 208°—209°C.

f) In a manner analogous to that described in Example 23f), 4-(3',5'-dimethylphenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid is obtained and recrystallised from methanol/water; M.p. 246°—248°C with decomposition.

Example 26

4-(4'-Chlorophenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid

a) 3-Nitro-4-(4'-chlorophenoxy)-5-sulphamoylbenzoic acid

This compound is prepared with *p*-chlorophenol in a manner analogous to that described in Example 23a). Recrystallisation from acetone/water; M.p. 248°C.

b) 3-Nitro-4-(4'-chlorophenoxy)-5-sulphamoylbenzoic acid methyl ester

In a manner analogous to that described in Example 23b) the above compound is obtained; recrystallisation from methanol; M.p. 171°—172°C.

c) 3-Amino-4-(4'-chlorophenoxy)-5-sulphamoylbenzoic acid methyl ester

In a manner analogous to that described in Example 23c) this compound is obtained; recrystallisation from methanol; M.p. 198°—199°C.

d) 3-N-Succinimido-4-(4'-chlorophenoxy)-5-sulphamoylbenzoic acid methyl ester.

In a manner analogous to that described in Example 23d) this compound is obtained; recrystallisation from methanol; M.p. 266°—267°C.

e) 4-(4'-Chlorophenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid methyl ester.

In a manner analogous to that described in Example 23e) this compound is obtained; recrystallisation from methanol/water; M.p. 200°C.

f) 4-(4'-Chlorophenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid

In a manner analogous to that described in Example 23d) this compound is obtained; recrystallisation from methanol; M.p. 253°—254°C.

Example 27

4-(3'-Trifluoromethylphenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid

a) 3-Nitro-4-(3'-trifluoromethylphenoxy)-5-sulphamoylbenzoic acid

This compound is obtained in a manner analogous to that described in Example 23a) with 3-trifluoromethylphenol. Recrystallisation from acetone/water. M.p. 210°C.

b) 3-Nitro-(3'-trifluoromethylphenoxy)-5-sulphamoylbenzoic acid methyl ester

This compound is obtained in a manner analogous to that described in Example 23b); recrystallisation from methanol; M.p. 141°—143°C.

c) 3-Amino-4-(3'-trifluoromethylphenoxy)-5-sulphamoylbenzoic acid methyl ester

This compound is obtained in a manner analogous to that described in Example 23c); recrystallisation from methanol; M.p. 186°—187°C.

d) 3-N-Succinimido-4-(3'-trifluoromethylphenoxy)-5-sulphamoylbenzoic acid methyl ester

This compound is obtained in a manner analogous to that described in Example 23d); recrystallisation from methanol; M.p. 227°—228°C.

e) 4-(3'-Trifluoromethylphenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid methyl ester

This compound is obtained in a manner analogous to that described in Example 23e); recrystallisation from methanol; M.p. 170°—171°C.

f) 4-(3'-Trifluoromethylphenoxy)-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid

This compound is obtained in a manner analogous to that described in Example 23f); recrystallisation from glacial acetic acid; M.p. 230°—234°C.

Example 28

3-(1-Pyrrolidinyl)-4-phenoxy-5-sulphamoylbenzoic acid

a) 3,5-Dinitro-4-phenoxy-benzoic acid methyl ester

30 g of 3,5-dinitro-4-phenoxy-benzoic acid in 200 ml of methanol are combined with 3 ml of concentrated sulphuric acid and the mixture is boiled for 3 hours under reflux. After evaporation of the solvent, the residue is dissolved in ethyl acetate, and traces of unreacted acid are destroyed with dilute sodium bicarbonate solution. After

drying of the ethyl acetate solution, the solvent is eliminated by evaporation, the residue is recrystallised from ethyl acetate/methanol. The desired ester melting at 171°—173°C is obtained with a very good yield.

b) 3,5-Diamino-4-phenoxy-benzoic acid methyl ester

25 g of 3,5-nidintro-4-phenoxy-benzoic acid methyl ester are dissolved in 250 ml of ethyl acetate, combined with 10 g of Raney nickel and hydrogenated. After absorption of the calculated amount of hydrogen, the catalyst is filtered off and the solvent is removed, whereupon the remaining oil crystallises. The raw product may be further reacted directly or may be recrystallized from methanol/water, whereby the diamino ester is obtained in form of colorless crystals melting at 140°—142°C in excellent yield. Alternatively, the hydrogenation is carried out in an autoclave at 50°C and 100 atmospheres gauge pressure. The reaction time is then 3 to 5 hours, depending on the reactivity of the Raney nickel.

c) 3-Succinylamino-4-phenoxy-5-amino-benzoic acid methyl ester

30 g of 3,5-diamino-4-phenoxy-benzoic acid methyl ester in 300 ml of chloroform or methylene chloride are stirred for 8 hours, at room temperature, with 12.8 g of succinic acid anhydride, whereupon the desired benzoic acid methyl ester separates in the form of a colourless precipitate. The crystals that have separated are isolated, washed with chloroform and recrystallised from methanol. The 3-succinylamino-4-phenoxy-5-amino-benzoic acid methyl ester melting at 190°—192°C is obtained in the form of colourless crystals.

d) 3-(1-Succinimido)-4-phenoxy-5-amino-benzoic acid methyl ester

30 g of 3-succinylamino-4-phenoxy-5-amino-benzoic acid methyl ester are introduced into a mixture of 260 ml of orthophosphoric acid and 60 g of P_2O_5, the mixture is heated for 2 hours to 50°C, then cooled and introduced into 750 ml of water. The 3-(succinimido)-4-phenoxy-5-amino-benzoic acid methyl ester is isolated in the form of colourless crystals melting at 200°C—201°C with almost quantitative yield.

e) 3-(1-Pyrrolidinyl)-4-phenoxy-5-aminobenzoic acid methyl ester

A solution of 24 g of 3-(1-succinimido)-4-phenoxy-5-aminobenzoic acid methyl ester in 180 ml of diglym is combined with 20 g of boron trifluoride-etherate and cooled to 10°C. A solution of 5.7 g of $NaBH_4$ in 125 ml of diglym is added dropwise, while cooling, to the reaction mixture in such a manner that the temperature does not rise above 15°C. After completion of the addition, the reaction mixture is stirred for 1 hour and then decomposed cautiously with 300 ml of water. The solid substance that has precipitated is isolated and crystallized from methanol. The 3-(1-pyrrolidinyl)-4-phenoxy-5-amino-benzoic acid methyl ester melting at 154°—156°C is isolated with excellent yield.

f) 3-(1-Pyrrolidinyl)-4-phenoxy-5-sulphamoylbenzoic acid

The reaction order described in Example 19 is repeated. Using the 3-(1-pyrrolidinyl)-4-phenoxy-5-chlorosulphonyl-benzoic acid methyl ester, there is obtained by reaction with concentrated ammonia the desired 3-(1-pyrrolidinyl)-4-phenoxy-5-sulphamoylbenzoic acid methyl ester (M.p. 186°—188°C) which can be converted by heating with sodium hydroxide solution and subsequent acidification into the desired 3-(1-pyrrolidinyl)-4-phenoxy-5-sulphamoylbenzoic acid melting at 226°—228°C.

Example 29

3-(1-Pyrrolidinyl)-4-phenoxy-5-sulphamoylbenzoic acid

Steps a) to c) of the reaction described in Example 28 are repeated, then, 10 g of the 3-succinylamino-4-phenoxy-5-aminobenzoic acid ester are stirred for 2 hours at 200°C. After cooling, the reaction mixture is recrystallised from methanol and 3-succinimido-4-phenoxy-5-amino-benzoic acid methyl ester is obtained with good yield. M.p. 199°—200°C.

The product so obtained is converted in the manner described in Example 28 into the desired 3-(1-pyrrolidinyl)-4-phenoxy-5-sulphamoylbenzoic acid melting at 227°—228°C.

Example 30

3-(1-Pyrrolidinyl)-4-phenoxy-4-sulphamoylbenzoic acid

The reaction sequence described in Example 28 is repeated to the end of step e).

51 g of 3-(1-pyrrolidinyl)-4-phenoxy-5-amino-benzoic acid methyl ester in 780 ml of 1N sodium hydroxide solution are boiled for 2 hours, whereupon a clear solution

forms. The reaction mixture is subsequently cooled, adjusted to pH 4 and the product that has precipitated is dissolved in 60 ml of 2N HCl. After standing for a short time, the hydrochloride of 3-(1-pyrrolidinyl)-4-phenoxy-5-aminobenzoic acid melting at 245°—257°C crystallises in beautiful crystals. Mixed melting point with the product of Example 20 (step b): 252°—254°C.

The hydrochloride of 3-(1-pyrrolidinyl)-4-phenoxy-5-aminobenzoic acid is converted in the manner described in Example 20 via 3-(1-pyrrolidinyl)-4-phenoxy-5-chlorosulphonyl-benzoic acid into the desired 3-(1-pyrrolidinyl)-4-phenoxy-5-sulphamylbenzoic acid melting at 225°—226°C.

Example 31

4-(4'-Methylphenoxy)-3-N-(3-methylpyrrolidinyl)-5-sulphamoylbenzoic acid

a) 3-N-(3-Methylsuccinimido)-4-(4'-methylphenoxy)-5-sulphamoylbenzoic acid methyl ester

20 g of 3-amino-4-(4'-methylphenoxy)-5-sulphamoylbenzoic acid methyl ester (cf. Example 28c)) are fused with 18 g of methylsuccinic anhydride for 3 hours at 180°C. During cooling of the molten mass, the product crystallises on addition of methanol. It is recrystallised from acetone/water. M.p. 229°—230°C.

b) 4-(4'-Methylphenoxy)-3N-(3-methylpyrrolidinyl)-5-sulphamoylbenzoic acid methyl ester

22 g of 3-N-(3-methylsuccinimido)-4-(4'-methylphenoxy)-5-sulphamoylbenzoic acid methyl ester are suspended in 200 ml of absolute diglyme and combined with 13 ml of BF_3-etherate. A solution of 3.3 g of $NaBH_4$ in 200 ml of diglym is then added dropwise and slowly, while stirring well, at −5° to 0°C. Stirring is continued for 1 hour and the product that has formed is precipitated with water. Recrystallisation from methanol/water M.p. 177°—178°C.

c) 4-(4'-Methylphenoxy-3-N-(3-methylpyrrolidinyl)-5-sulphamoylbenzoic acid

14 g of methyl ester (46 b)) are suspended in 150 ml of 1N-NaOH and heated on the steam bath, while stirring well. When a clear solution has formed, stirring is continued for 1 hour and the mixture is acidified with 2N-HCl to a pH of ~3, while cooling with ice. The product that has precipitated is filtered off with suction, washed thoroughly with water and recrystallised from methanol/water. M.p. 220°—221°C.

Example 32

4-Phenoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid

a) 4-Chloro-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid

90 ml (1.25 mol) of thionyl chloride are added dropwise, at −10°C, to a solution of 58.9 g (0.25 mol) of 4-chloro-5-sulphamoylbenzoic acid in 183 g (2.5 mols) of dimethylformamide (DMF). The solution is then allowed to reach room temperature, stirred for 2 hours and poured on ice, the precipitate is filtered off and washed with water until neutral. The 4-chloro-5-N,N-dimethylaminomethyleneamino-sulphonylbenzoic acid is obtained with very good yield in the form of crystals melting at 266°—267°C.

b) 3-Nitro-4-chloro-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid.

42 ml of fuming nitric acid are added dropwise, while cooling with ice, to 60 ml of 20% oleum, then 34.9 g (0.12 mol) of 4-chloro-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid are introduced slowly. After having stirred for 24 hours at 55°—60°C, the solution is cooled to room temperature, poured onto ice and the precipitate is washed with water until neutral. 3-Nitro-4-chloro-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid is obtained in the form of crystals melting at 274°—276°C.

c) 3-Nitro-4-chloro-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester

50.4 g (0.15 mol) of 3-nitro-4-chloro-5-N,N-dimethylaminomethylaneaminosulphonylbenzoic acid are boiled for 1 hour under reflux in a solution of 150 ml of thionyl chloride which contains 5 drops of DMF. After removal of the excess thionyl chloride under reduced pressure, the solid acid chloride is suspended in 200 ml of methanol. The suspension is boiled for 1/2 hour under reflux, then cooled, filtered and washed with cold methanol.

3 - Nitro - 4 - Chloro - 5 - N,N - dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester is obtained in the form of crystals melting at 168°—169°C.

d) 3-Nitro-4-phenoxy-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester

A solution of 105 g (0.3 mol) of 3-nitro-4-chloro-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester and 47.5 g (0.36 mol) of potassium phenolate in 600 ml of DMF is boiled for 2 hours under reflux. After cooling and removal of the potassium chloride by filtration, the solution is poured onto ice/water and stirred for 1 hour. The precipitate is filtered off, washed with water and dried.

After dissolution of the raw product in 900 ml of acetone, the solution is clarified with charcoal, evaporated to 500 ml and diluted with 1 litre of methanol. After having stirred for 1 hour at 10°C, the precipitate is filtered off and washed with cold methanol.

3-Nitro-4-phenoxy-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester is obtained in the form of crystals melting at 191°—193°C.

e) 3-Amino-4-Phenoxy-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester

61 g (0.15 mol) of 3-nitro-4-phenoxy-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester are hydrogenated with Raney nickel in methanol at room temperature and normal pressure for 8 hours. After filtration, the catalyst is suspended in warm DMF, filtered and the DMF filtrate is poured into a mixture of ice and water.

3-Amino-4-phenoxy-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester is obtained in the form of crystals melting at 255°—256°C.

f) 3-N-Succinimido-4-phenoxy-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester

30 g of 3-amino-4-phenoxy-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester are fused at 180°C with 25 g of succinic anhydride. After a reaction time of about 2 hours, the imide that has formed is precipitated with methanol. The imide melting at 283°—284°C is obtained with very good yield by recrystallisation from n-butanol.

g) 4-Phenoxy-3-(1-pyrrolidinyl)-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester

23 g (0.05 mol) of 3-N-succinimido-4-phenoxy-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester are suspended in 200 ml of diethylene glycol-dimethyl ether (diglym) and 13 ml of BF_3-etherate (0.1 mol) are added. Then, a solution of 3.8 g (0.1 mol) of $NaBH_4$ in 200 ml of diglyme is added dropwise and slowly, while cooling and keeping the temperature in the range of from −10° to +5°C. The mixture is allowed to warm to room temperature, whereupon a clear solution is formed. The reaction is completed after 1.25 hour. The product precipitates by the addition of water. By recrystallisation from methanol, there is obtained the 4 - phenoxy - 3 - (1 - pyrrolidinyl) - 5 - N,N - dimethylaminomethyleneaminosulphonyl-benzoic acid ester melting at 189°—190°C.

h) 4-Phenoxy-3-(1-pyrrolidinyl)-5-sulphamylbenzoic acid.

13 g (~0.03 mol) of 4-phenoxy-3-(1-pyrrolidinyl)-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester are suspended in 100 ml of 2N-NaOH and saponified at 80°—90°C, while stirring well. When a clear solution has formed, stirring is continued for 1 hour at the same temperature. The solution is cooled to 0°C and 110 ml of 2N-hydrochloric acid are slowly added, while well stirring. The whole is stirred more intensively for 1/2 hour and the product that has precipitated in fine form is filtered off sharply with suction. The substance is recrystallized from methanol/water. Light yellow platelets melting at 226°—228°C.

Example 33

The reaction sequence described in Example 32 is repeated to the end of step c) The resulting 3-nitro-4-chloro-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester is subsequently heated with potassium phenolate for 2 hours to 190°—200°C. The reaction mixture is cooled, dissolved in acetone and, after having removed inorganic components, worked up in the manner described in step d) of Example 32. 3-Nitro-4-phenoxy-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester is obtained which can be converted in the manner described in Example 32 into the desired final product.

Example 34

a) The reaction sequence described in Example 32 is repeated with the difference that the catalytical hydrogenation of the 3-nitro-4-phenoxy-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester is carried out in an autoclave at 50°C and 50 atmospheres gauge pressure. After cooling, the desired 3-amino-4-phenoxy-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid ester is isolated in the manner described in Example 32e).

b) The reaction sequence described in Example 32 is repeated with the difference that the catalytic hydrogenation of the 3-nitro-4-phenoxy-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester is carried out in dimethylformamide (DMF) with Raney nickel at room temperature and normal pressure. After removal of the catalyst by filtration, the DMF solution is poured onto ice. 3-Amino-4-phenoxy-5-N,N-dimethylaminomethyleneamino-sulphonyl-benzoic acid methyl ester is obtained; M.p. 255°—256°C.

Example 35

The reaction sequence described in Example 32 is repeated with the difference that 4-chloro-5-N,N-dimethylaminomethyleneamino-sulphonyl-benzoic acid methyl ester is used as starting compound.

a) 4-Chloro-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester

90 ml (1.25 mol) of thionyl chloride are added dropwise, at −10°C, to a solution of 74.9 g (0.3 mol) of 4-chloro-5-sulphamoylbenzoic acid methyl ester in 183 g (2.5 mols) of dimethylformamide and worked up as described in Example 32. 4-Chloro-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester melting at 174°—176°C is obtained.

b) 3-Nitro-4-chloro-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester

36.5 g (0.12 mol) of 4-chloro-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester are reacted under the same conditions as those described in Example 32b). A mixture of 3-nitro-4-chloro-5-N,N-dimethylaminomethyleneamino-sulphonyl-benzoic acid and 3-nitro-4-chloro-5-N,N-dimethylaminomethyleneamino-sulphonyl-benzoic acid methyl ester is obtained. The mixture is separated by treatment with 5% aqueous sodium carbonate. 3-Nitro-4-chloro-5-N,N-dimethylaminomethyleneamino-sulphonylbenzoic acid methyl ester melting at 168°—169°C and after acidification 3-nitro-4-chloro-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid melting at 270°—272°C are obtained; the latter can also be converted into the ester in the manner described in Example 32c).

The further reaction is then effected according to the reaction sequence described in Example 32.

Example 36

The nitration described in Example 32 is carried out with the difference that the ethyl ester is used instead of the methyl ester.

a) 4-Chloro-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid ethyl ester

90 ml (1.25 mol) of thionyl chloride is added dropwise at −10°C to a solution of 65 g (0.25 mol) of 4-chloro-4-sulphamylbenzoic acid ethyl ester in 183 g (2.5 mols) of DMF and worked up as described in Example 32. 4-Chloro-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid ethyl ester is obtained in the form of crystals melting at 119°—121°C.

b) 3-Nitro-4-chloro-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid ethyl ester

38.3 g (0.12 mol) of 4-chloro-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid ethyl ester are reacted under the same conditions as those described in Example 35. Separation of the nitro-ester and of the nitro-acid is effected as described in Example 35. 3-Nitro-4-chloro-5-N,N-dimethylaminomethylaminosulphonyl-benzoic acid ethyl ester is obtained in the form of crystals melting at 182°—184°C, and, after acidification of the aqueous solution, 3-nitro-4-chloro-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid is obtained in the form of crystals melting at 270°—272°C, which, according to melting point and mixture is identical with the carboxylic acid described in Example 32b).

Example 37

4-Phenoxy-3-(1-pyrrolidinyl)-5-sulphamoyl-benzoic acid methyl ester

36.2 g of 4-phenoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid are dissolved in 200 ml of methanol and 7 ml of concentrated H_2SO_4 and heated for 4 to 6 hours under reflux. Upon cooling, the ester crystallises. Recrystallisation from methanol; M.p. 191°C.

Example 38

4-Phenylmercapto-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid

The reaction sequence described in Example 32 for the preparation of 3-nitro-4-chloro-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester is repeated.

a) 3-Nitro-4-phenylthio-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester

A solution of 21 g (0.06 mol) of 3-nitro-4-chloro-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester, 7.7 g (0.07 mol) of thiophenol and 8.2 g (0.077 mol) of sodium carbonate in 100 ml of DMF is boiled for 2 hours under reflux. After cooling and filtration, the solution is poured onto a mixture of ice and water and stirred for 1 hour. The precipitate is filtered off, washed with water and dried. The raw product is recrystallised from acetone/methanol. 3-Nitro-4-phenylthio-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester is obtained in the form of crystals melting at 207°C.

b) 3-Amino-4-phenylthio-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester

2 g (0.0047 mol) of 3-nitro-4-phenylthio-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester are hydrogenated for 8 hours with Raney nickel in 30 ml of DMF at room temperature and normal pressure. The catalyst is removed by filtration with suction, washed with warm DMF and the DMF filtrate is poured onto a mixture of ice and water.

3-Amino-4-phenylthio-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester is obtained from acetone in the form of crystals melting at 214°—215°C.

c) 3-N-Succinimido-4-phenylthio-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester

35 g (0.089 mol) of 3-amino-4-phenylthio-5-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester are finely triturated with 26.6 g (0.2668 mol) of succinic anhydride and fused for 2 hours at 175°C. After cooling to 150°C, the whole is diluted with 100 ml of DMF and the solution is poured slowly onto a mixture of ice and water. The precipitate is filtered off with suction, dried and recrystallised from DMF/CH_3OH. M.p. 261°—263°C.

d) 4-Phenylthio-3-(1-pyrrolidinyl)-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester

A solution of 5.1 g of $NaBH_4$ in 135 ml of absolute diglym is added dropwise, at a temperature of 0°—10°C, while stirring well, to a solution of 32 g of 3-N-succinimido-4-phenylthio-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester and 17.5 ml of BF_3-etherate in 135 ml of absolute diglyme. After 2 hours, the whole is hydrolysed and the product is precipitated by further addition of water.

e) The raw product that has precipitated is heated under reflux with 2 N-NaOH until a clear solution is formed. The 4-phenylthio-3-(1-pyrrolidinyl)-5-sulphamoyl-benzoic acid is precipitated with the aid of 2N-HCl and recrystallised from CH_3OH/H_2O. M.p. 237°—238°C (see also Example 33).

Example 39

4-Phenylthio-3-[1-(3-methylpyrrolidinyl)]-5-sulphamoylbenzoic acid

a) 3-Amino-4-phenylthio-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester

A solution of 110 g of 3-nitro-4-phenylthio-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid methyl ester in 400 ml of DMF is hydrogenated for 8 hours over ~10 g of Raney nickel at 40°C and 100 atmospheres gauge pressure. The catalyst is filtered off and the solution is poured onto ice. The precipitate is filtered off, dried and recrystallised from acetone. M.p. 214°—215°C.

b) 3-N-(3-Methylsuccinimido)-4-phenylthio-5-N,N-dimethylaminomethyleneamino-sulphonyl-benzoic acid methyl ester.

40 g (0.1 mol) of 3-amino-4-phenylthio-5-N,N-dimethylaminomethyleneamino-sulphonyl-benzoic acid methyl ester are fused with 34 g (0.3 mol) of methylsuccinic anhydride for 2.5 hours at 175°C. After cooling to 150°C, the mixture is diluted with 100 ml of DMF and the solution is poured slowly onto a mixture of ice and water. The precipitate is filtered off with suction and recrystallised from CH_3OH. M.p. 206°—207°C.

c) 4-Phenylthio-3-[1-(3-methylpyrrolidinyl)]-5-N,N-dimethylaminomethyleneamino-sulphonyl-benzoic acid methyl ester.

A solution of 4.65 g of $NaBH_4$ in 120 ml of absolute diglyme is added dropwise, at 0—10°C, to a solution of 29.4 g of 3-N-(3-methylsuccinimido)-4-phenylthio-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester and 15.9 ml of BF_3-etherate in 120 ml of absolute diglym. After having stirred for 2 hours, the reaction product is precipitated cautiously with water. Recrystallisation from CH_3OH. M.p. 147°—148°C.

d) 4-Phenylthio-3-[1-(3-methylpyrrolidinyl)]-5-sulphamoylbenzoic acid

4 g of the ester of step c) are heated for 2 hours under reflux in 40 ml of 2N-NaOH. A clear solution is formed. After cooling and acidification with 2N-HCl to pH 2—3, the 4-phenylthio-3-[1-(3-methylpyrrolidinyl)]-5-sulphamoyl-benzoic acid precipitates. It is recrystallised from CH_3OH/H_2O. Yellow crystals melting at 216°—217°C.

Example 40

4-Phenoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid

a) 3-N-Pyrrolo-4-phenoxy-5-sulphamoylbenzoic acid

8 g of 3-amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester are heated under reflux with 5 g of 2,5-dimethoxytetrahydrofuran in 100 ml of glacial acetic acid. After 1.5 to 2 hours, the mixture is stirred into ice-water. The raw product which is thereby precipitated is heated on the steam bath with 1N NaOH until a clear solution has formed. Upon acidification with 2N-HCl the 3-N-pyrrolo-4-phenoxy-5-sulphamoyl-benzoic acid precipitates. It can be recrystallised from methanol or glacial acetic acid/water. White grey crystals melting at 214°C.

b) 8.8 g of 3-N-pyrrolo-4-phenoxy-5-sulphamoylbenzoic acid methyl ester (raw product) are dissolved in glacial acetic acid and hydrogenated under normal pressure with 1 g of Pd-black. After about 30 hours, the reaction is completed. If the hydrogenation is carried out in an autoclave at 40°—50°C and 100 atmospheres gauge pressure, the reaction is completed already after 5 hours.

The solution is filtered, concentrated and the solid residue is hydrolysed with 1N-NaOH on the steam bath. The clear solution is cooled and acidified with 2N HCl. The 4-phenoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid is recrystallised from CH_3OH/H_2O. M.p. 226—227°C.

Example 41

4-Phenoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid

a) 10 g of 3-amino-4-phenoxy-5-sulphamoylbenzoic acid methyl ester together with 25 g of 1,4-dibromobutane and 10 g of NaI in a mixture of acetone and DMF are heated for several days under reflux. The course of the reaction is followed by thin-layer chromatography. When the reaction is completed, the mixture is concentrated to dryness, the excess dibromobutane is extracted with ether, the mixture is decanted and the residue is saponified with 1N NaOH. The 4-phenoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid is precipitated from the clear solution with the aid of 2N-HCl.

b) 10 g of 3-amino-4-phenoxy-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester are heated for 5 hours under reflux together with 25 g of 1,4-dibromobutane in dimethylformamide. The reaction mixture is then concentrated to dryness, the excess of dibromobutane is extracted with ether, decanted and the remaining red oil is dissolved in a small amount of methanol. The 4-phenoxy-3-(1-pyrrolidinyl)-5-N,N-dimethylaminomethyleneaminosulphonyl-benzoic acid methyl ester crystallises upon standing. It is saponified as described above with sodium hydroxide solution and the 4-phenoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid is precipitated with HCl.

Example 42

4-Phenylsulfoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid

A solution of 7.8 g of 4-phenylthio-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid in 130 ml of glacial acetic acid and 20 ml of 30% H_2O_2 is stirred at room temperature. The course of the reaction is followed by thin-layer chromatography. After 20 hours, the solution is poured into 800 ml of ice-water. The precipitate is filtered off with suction and dried. Recrystallisation from methanol/water yields 4-phenylsulphoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid in the form of yellow crystals melting at 142°—144°C, with decomposition.

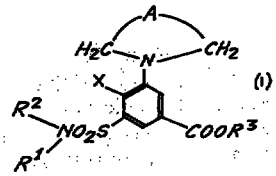
Example 43

4-Phenylsulphoxy-3-[1-(methylpyrrolidinyl)]-5-sulphamoylbenzoic acid

A solution of 6 g of 4-phenylthio-3-[1-(methylpyrrolidinyl)]-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid in 70 ml of glacial acetic acid and 15 ml of 30% H_2O_2 is stirred at 5°—20°C. After 20 hours, the solution is poured into ice-water. The residue is washed with water, dried and hydrolysed for 2 hours at 100°C with 30 ml of 2N-NaOH. The hydrolysate is filtered and acidified in the cold, while stirring, with 2N-HCl to pH 2—3; whereupon, 4-phenylsulphoxy-3-[1-(methylpyrrolidinyl)]-5-sulphamoylbenzoic acid precipitates. Recrystallisation from methanol/water yields yellow crystals melting at 143°—145°C with decomposition.

WHAT WE CLAIM IS:—

1. A 5-Sulphamoylbenzoic acid derivative of the general formula I



(I)

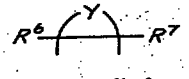
in which

R^1 and R^2, which may be identical or different, each represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, and, if R^1 represents a hydrogen atom, R^2 may also represent an alkoxymethyl group having from 1 to 4 carbon atoms in the alkoxy radical, a phenoxymethyl group or a phenylthiomethyl group,

R^3 represents a hydrogen atom, a straight or branched chain alkyl group having from 1 to 4 carbon atoms, a cycloalkyl group, having 5 or 6 ring members, one of which may be replaced by an oxygen or sulphur atom, a phenyl or benzyl group which may be substituted in the phenyl nucleus by one or more substituents selected from nitro groups, alkyl groups having from 1 to 3 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms, or represents a benzhydryl group or a alkanoyloxymethyl group having 2 to 4 carbon atoms in the alkanol part,

X represents a halogen atom, a CF_3 or CCl_3 group, a straight or branched chain, saturated or unsaturated alkyl group having from 1 to 6 carbon atoms, a benzyl group which may be substituted in the phenyl nucleus by one or more substituents selected from halogen atoms, hydroxy and amino groups, and lower alkyl and lower alkoxy groups, or represents one of the groups —O—R^4, —S—R^4, SO—R^4, SO_2—R^4 and NR^4R^5, in which R^4 represents a phenyl group which may be substituted by one or more substituents selected from halogen atoms, OH, CF_3, and amino groups, alkyl and alkoxy groups having from 1 to 4 carbon atoms, and SO_2NH_2 groups, or represents a straight or branched chain alkyl group having from 1 to 4 carbon atoms which may be substituted by a phenyl pyridyl, furyl or thienyl group, and R^5 represents a hydrogen atom, a straight or branched chain alkyl group having from 1 to 4 carbon atoms, and the group NR^4R^5 may also represent a saturated, heterocyclic, 5- or 6-membered ring which may be interrupted by an O-, N- or S-atom,

A represents a single bond, or an alkylene chain of 1 to 3 carbon atoms which may be unsaturated, interrupted by O-, N- or S-atoms or substituted by one or more substituents selected from halogen atoms, alkyl, alkoxy, aralkyl, and aryl groups, and mono-nuclear hetero-aromatic rings, or A represents an ortho-phenylene radical or the grouping



in which Y represents a single bond or an alkylene group having from 1 to 4 carbon

Example 42

4-Phenylsulfoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid

A solution of 7.8 g of 4-phenylthio-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid in 130 ml of glacial acetic acid and 20 ml of 30% H_2O_2 is stirred at room temperature. The course of the reaction is followed by thin-layer chromatography. After 20 hours, the solution is poured into 800 ml of ice-water. The precipitate is filtered off with suction and dried. Recrystallisation from methanol/water yields 4-phenylsulphoxy-3-(1-pyrrolidinyl)-5-sulphamoylbenzoic acid in the form of yellow crystals melting at 142°—144°C, with decomposition.

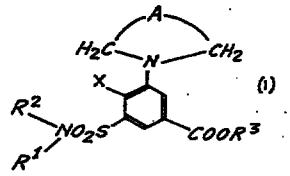
Example 43

4-Phenylsulphoxy-3-[1-(methylpyrrolidinyl)]-5-sulphamoylbenzoic acid

A solution of 6 g of 4-phenylthio-3-[1-(methylpyrrolidinyl)]-5-N,N-dimethylaminomethyleneaminosulphonylbenzoic acid in 70 ml of glacial acetic acid and 15 ml of 30% H_2O_2 is stirred at 5°—20°C. After 20 hours, the solution is poured into ice-water. The residue is washed with water, dried and hydrolysed for 2 hours at 100°C with 30 ml of 2N-NaOH. The hydrolysate is filtered and acidified in the cold, while stirring, with 2N-HCl to pH 2—3; whereupon, 4-phenylsulphoxy-3-[1-(methylpyrrolidinyl)]-5-sulphamoylbenzoic acid precipitates. Recrystallisation from methanol/water yields yellow crystals melting at 143°—145°C with decomposition.

WHAT WE CLAIM IS:—

1. A 5-Sulphamoylbenzoic acid derivative of the general formula I



(I)

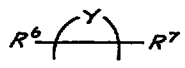
in which

R^1 and R^2, which may be identical or different, each represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, and, if R^1 represents a hydrogen atom, R^2 may also represent an alkoxymethyl group having from 1 to 4 carbon atoms in the alkoxy radical, a phenoxymethyl group or a phenylthiomethyl group,

R^3 represents a hydrogen atom, a straight or branched chain alkyl group having from 1 to 4 carbon atoms, a cycloalkyl group, having 5 or 6 ring members, one of which may be replaced by an oxygen or sulphur atom, a phenyl or benzyl group which may be substituted in the phenyl nucleus by one or more substituents selected from nitro groups, alkyl groups having from 1 to 3 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms and halogen atoms, or represents a benzhydryl group or a alkanoyloxymethyl group having 2 to 4 carbon atoms in the alkanol part,

X represents a halogen atom, a CF_3 or CCl_3 group, a straight or branched chain, saturated or unsaturated alkyl group having from 1 to 6 carbon atoms, a benzyl group which may be substituted in the phenyl nucleus by one or more substituents selected from halogen atoms, hydroxy and amino groups, and lower alkyl and lower alkoxy groups, or represents one of the groups —O—R^4, —S—R^4, SO—R^4, SO_2—R^4 and NR^4R^5, in which R^4 represents a phenyl group which may be substituted by one or more substituents selected from halogen atoms, OH, CF_3, and amino groups, alkyl and alkoxy groups having from 1 to 4 carbon atoms, and SO_2NH_2 groups, or represents a straight or branched chain alkyl group having from 1 to 4 carbon atoms which may be substituted by a phenyl pyridyl, furyl or thienyl group, and R^5 represents a hydrogen atom, a straight or branched chain alkyl group having from 1 to 4 carbon atoms, and the group NR^4R^5 may also represent a saturated, heterocyclic, 5- or 6-membered ring which may be interrupted by an O-, N- or S-atom,

A represents a single bond, or an alkylene chain of 1 to 3 carbon atoms which may be unsaturated, interrupted by O-, N- or S-atoms or substituted by one or more substituents selected from halogen atoms, alkyl, alkoxy, aralkyl, and aryl groups, and mono-nuclear hetero-aromatic rings, or A represents an ortho-phenylene radical or the grouping



in which Y represents a single bond or an alkylene group having from 1 to 4 carbon

atoms, and R^6 and R^7, which may be identical or different, each represents a hydrogen or halogen atom or an alkyl group having from 1 to 4 carbon atoms.

2. A compound as claimed in claim 1, in which X represents a benzyl, phenoxy, phenylthio, phenylsulphoxy, phenylsulphonyl or anilino group the phenyl ring of which may be substituted by one or more substituents selected from halogen atoms, OH and CF_3 groups, alkyl groups having from 1 to 4 carbon atoms, alkoxy groups having from 1 to 3 carbon atoms, and alkyl- and dialkyl-amino groups.

3. A compound as claimed in claim 1, in which A represents a $-CH_2-CH_2-$ or $-CH=CH-$ group which may be substituted by one or more substituents selected from halogen atoms, lower alkyl, lower alkoxy, and aralkyl groups or by a phenyl group.

4. A compound as claimed in claim 1, in which X and A have the meanings specified in claims 2 and 3 respectively.

5. 3-N-Pyrrolidino-4-phenoxy-5-sulphamoylbenzoic acid or its methyl ester.

6. 3-N-Δ3-Pyrrolino-4-phenoxy-5-sulphamoylbenzoic acid or its methyl ester.

7. 3-N-Piperidino-4-phenoxy-5-sulphamoylbenzoic acid or its methyl ester.

8. 3-N-Pyrrolidino-4-benzyl-5-sulphamoylbenzoic acid or its methyl ester.

9. 3-N-Pyrrolidino-4-(4'-methylphenoxy)-5-sulphamoylbenzoic acid or its methyl ester.

10. 3-N-(3-Methyl-pyrrolidino)-4-phenoxy-5-sulphamoylbenzoic acid or its methyl ester.

11. 3-N-(3-Methyl-pyrrolidino)-4-(4'-methylphenoxy)-5-sulphamoylbenzoic acid or its methyl ester.

12. 3-N-Pyrrolidino-4-(4'-hydroxyphenoxy)-5-sulphamoylbenzoic acid or its methyl ester.

13. 3-N-Pyrrolidino-4-(4'-methylbenzyl)-5-sulphamoylbenzoic acid or its methyl ester.

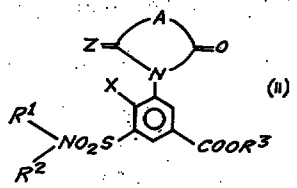
14. A compound as claimed in claim 1 and which is described in any one of the Examples herein, with the exception of the compounds claimed in claims 5 to 13.

15. A salt of a compound as claimed in any one of claims 1 to 14.

16. A physiologically tolerable salt of a compound as claimed in any one of claims 1 to 14.

17. A process for preparing a compound of the general formula I as claimed in claim 1 which comprises

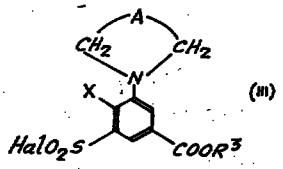
a) reducing a 3-substituted sulphamoylbenzoic acid derivative of the general formula II



(II)

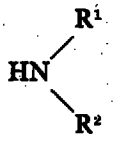
in which the radicals R^1 to R^3, A and X have the meanings given in claim 1, and in which any hydroxy or amino groups present may be blocked by customary protective groups, and Z represents two hydrogen atoms or one oxygen atom, by means of a boron hydride, or

b) reacting a 5-halogeno-sulphonylbenzoic acid derivative of the general formula III



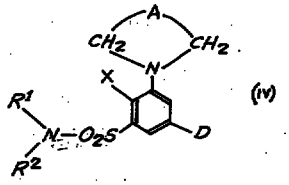
(III)

in which R^3, A and X have the meanings given in claim 1 and Hal represents a halogen atom, with an amine of the formula



in which R^1 and R^2 have the meanings given in claim 1, or

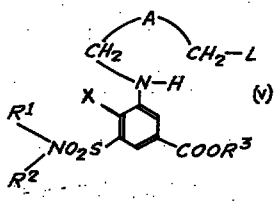
c) converting by hydrolysis or by mild oxidation a sulphamoyl compound of the general formula IV



(IV)

in which the radicals R^1 and R^2, A and X have the meanings given in claim 1 and D represents a radical which may be transformed into carboxylic acid groups, into the corresponding 5-sulphamoylbenzoic acid of the formula I, or

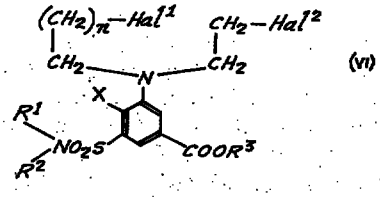
d) treating a sulphamoylbenzoic acid derivative of the general formula V



(V)

in which the radicals R^1 to R^3, A and X have the meanings given in claim 1 and L represents a "leaving group", with an acid or base in order to eliminate HL, or

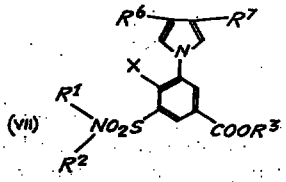
e) cyclizing a sulphamoylbenzoic acid derivative of the general formula VI



(VI)

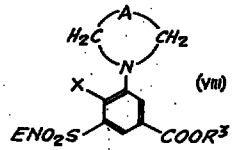
in which the radicals R^1 to R^3 and X have the meanings given in claim 1, Hal^1 and Hal^2, which may be identical or different, each represents a halogen atom and *n* represents the number 0, 1 or 2, by a method known *per se* to form compounds of the general formula I, or

f) reducing the corresponding 3-N-pyrrolo-compound of the general formula VII



(VII)

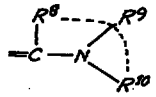
g) hydrolyzing a compound of the general formula VIII



(VIII)

in which R^3, A and X are as defined above,

E represents the group



in which R^8, R^9 and R^{10} represent identical or different lower alkyl groups and in which R^8 may also represent a hydrogen atom, and/or two of the substituents

R^8, R^9 and R^{10} may be linked and, together with the atom(s) to which they are attached, form a ring,

if desired, in a compound of the formula I obtained according to any one of the methods a) to g), carrying out any one or more of the following reactions h) to k):

h) hydrogenating any double bonds present or introducing double bond(s) by an elimination reaction,

i) esterifying a free carboxylic acid ester of the formula I or converting a carboxylicoxylic acid ester of the formula I by hydrolysis or an elimination reaction into the corresponding free carboxylic acid, and, if desired, forming a different ester,

j) setting free any protected hydroxy, and/or amino groups by separation of the protective group, and

k) converting a carboxylic acid of the formula I by treatment with a base or an acid into a salt thereof.

18. A process as claimed in claim 17, wherein the boron hydride is used in the presence of a Lewis acid.

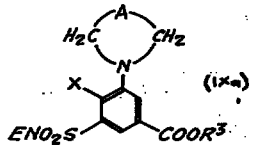
19. A process as claimed in claim 18, wherein the boron hydride is a complex borohydride.

20. A process as claimed in claim 17, wherein the compound of formula VI is cyclised by reaction with a metal in accordance with the conditions of the Wurtz-Fittig synthesis or by reaction with a primary amine, NH_3 or H_2S.

21. A process as claimed in claim 17, conducted substantially as described in any one of the Examples herein.

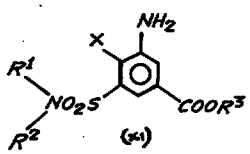
22. A compound as claimed in claim 1 whenever produced by a process as claimed in any one of claims 17 to 21.

23. A process for preparing a sulphamoylbenzoic acid of the formula I as claimed in claim 1 which comprises hydrolyzing a compound of the formula IXa



in which A, E, X and R^3 have the meanings given in claim 17 and, if desired, esterifying a resulting acid.

24. A process for preparing a sulphamoylbenzoic acid of the formula I as claimed in claim 1, which comprises reacting a compound of the formula



with a compound of the formula

$$L—CH_2—A—CH_2—L$$

in which formulae L, A, R^1 to R^3, X and E have the meanings given in claim 17.

25. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 14, claim 16 or claim 22 in admixture or conjunction with a pharmaceutically suitable carrier.

26. A pharmaceutical preparation as claimed in claim 25, in a form suitable for enteral administration.

27. A pharmaceutical preparation as claimed in claim 25, in a form suitable for parenteral administration.

28. A pharmaceutical preparation as claimed in claim 26 or claim 27 in unit dosage form.

29. A pharmaceutical preparation as claimed in claim 28 which comprises from 0.5 to 100 mg of the compound per unit dose.

30. A pharmaceutical preparation as claimed in any one of claims 25 to 29 which also comprises one or more other pharmaceutically active compounds.

* C L M S *

31. A pharmaceutical preparation as claimed in claim 30, wherein the other compounds are salidiuretics and/or potassium containing compounds.

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* C L M S *