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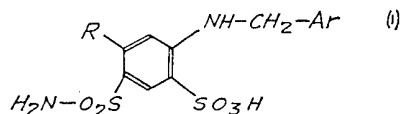


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 C2C 1470 1510 215 220 227 22Y 246
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 313 314 318 31Y 321 322 323 32Y
 332 338 339 364 36Y 373 37Y 385
 394 395 39Y 510 51X 532 536 620
 630 650 660 662 682 697 699 69X
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(54) 5-SULPHAMOYL-OR'THANILIC ACIDS AND PROCESS FOR THEIR PREPARATION

(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: 5

This invention provides a 5-sulphamoyl-or'thanilic acid of the general formula



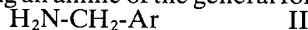
15 wherein R denotes a chlorine or bromine atom, a methyl group or a phenoxy or phenylthio radical which is unsubstituted or substituted by a chlorine or bromine atom or a methyl or methoxy group, and Ar denotes a furyl or thienyl radical. 15

The invention also provides a physiologically tolerable metal salt or ammonium or substituted ammonium salt, preferably an alkali metal salt.

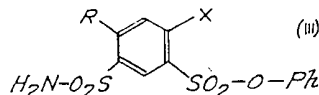
20 Compounds of the general formula I and physiologically tolerable salts thereof have diuretic and saluretic action. 20

There should especially be mentioned compounds of the general formula I in which R denotes a chlorine atom or a phenoxy or phenylthio group and in which Ar denotes a 2-furyl or 2-thienyl group, and, more especially, the sodium and potassium salts thereof.

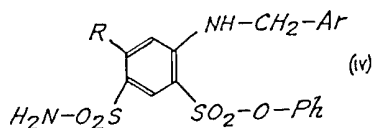
25 The invention also provides a process for the preparation of a compound of the general formula I or physiologically tolerable metal, ammonium or substituted ammonium salt thereof, which comprises reacting an amine of the general formula 25



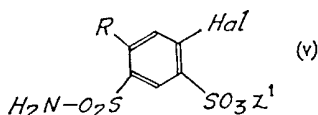
wherein Ar has the above-mentioned meaning, or a salt thereof, either (a) with a benzenesulphonate of the general formula 30



35 wherein R has the meaning given above, X denotes a halogen atom, but denotes a fluorine atom if R represents Cl or Br, and Ph denotes an unsubstituted or substituted aromatic radical, and the sulphonamide group is free or protected by a radical, suitably one which is easily detachable by hydrolysis, or with a salt thereof, and subsequently subjecting the 35
 40 resulting compound of the general formula 40

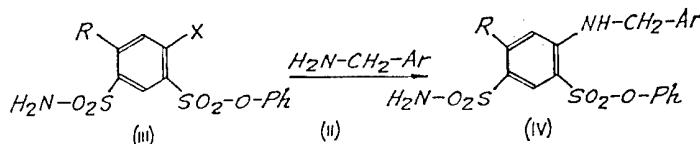


or salt thereof, to alkaline hydrolysis, or (b) with a benzenesulphonic acid of the general formula



wherein Hal denotes a halogen atom, Z' represents a hydrogen, metal, ammonium or tertiary ammonium ion, and R has the meaning given above, and the sulphonamide group is free or protected by a radical, suitably one which is easily detachable by hydrolysis, or with a salt thereof, and, if appropriate, detaching the sulphonamide protective group by hydrolysis, and, if desired, converting a compound obtained according to (a) or (b) into the free compound or into a physiologically tolerable metal, ammonium or substituted ammonium salt thereof.

According to variant (a), an amine of the general formula II is reacted, in the first stage, with a sulphonic acid ester of the general formula III to give a compound of the general formula IV.

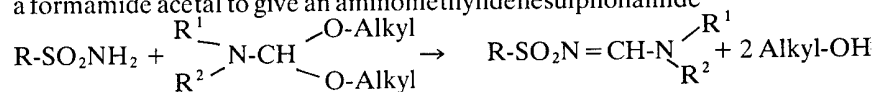


The phenolic component Ph of the sulphonic acid ester grouping in the compound of formula III is phenol or, preferably, a substituted phenol, for example *o*-, *m*- and *p*-cresol, 4-chlorophenol, 4-nitrophenol, 4-hydroxyanisole, 4-hydroxyphenetole, 3,5-dimethylphenol, 3,4-dimethylphenol or 3,5-dichlorophenol; the rate of saponification of the sulphonic acid ester group is increased by electron-attracting substituents (e.g. NO₂) in the phenol moiety and reduced by electron donors (e.g. OCH₃) and ortho-substituents in the phenol moiety.

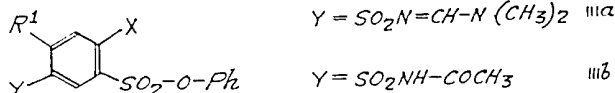
For example, the unsubstituted phenyl ester and the cresyl esters, which as a rule crystallise even better, are especially suitable. In place of the substituted phenols mentioned above, higher-molecular aromatic hydroxy compounds, such as, for example, 1- or 2-naphthol, 2-hydroxycarbazole, 4-hydroxydiphenyl or 6-hydroxyquinoline, may also be used.

The replaceable halogen atom X is preferably F or Cl. The fluorine compounds result in virtually quantitative yields when they are reacted with the amine of the general formula II, but they require a relatively high expenditure on synthesis. It is therefore industrially more advantageous to use the chlorine compounds as the starting material.

Before the condensation reaction with the base, the sulphonamide group in the compound of the general formula III may be protected by radical which is easily detachable by hydrolysis. Reactions suitable for this purpose are, above all, the condensation reaction with a formamide acetal to give an aminomethylidenesulphonamide

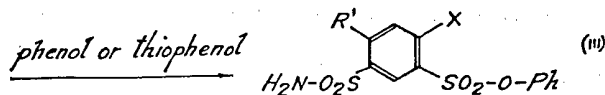
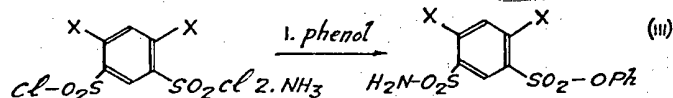


and the reaction with a carboxylic acid chloride or anhydride to give the corresponding monoacetylsulphonamide. The reaction with dimethylformamide dimethylacetal in dimethylformamide at 40 - 80°C to give III a and the reaction with acetic anhydride in pyridine to give III b are preferred.



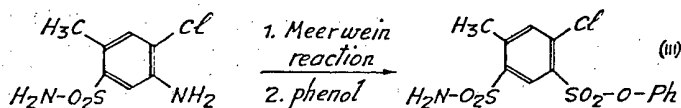
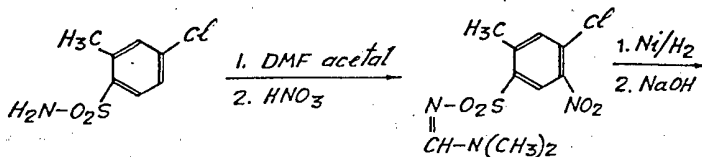
The derivatives mentioned above are split easily during the subsequent alkaline saponification, the unsubstituted sulphonamide being formed again.

The starting materials of the general formula III wherein R denotes an unsubstituted or substituted phenoxy or phenylthio radical, but not a methyl group, may be prepared, for example, in accordance with the equation given below (cf. Example 1):



(R' = unsubstituted or substituted phenoxy or phenylthio radical).

The compounds III in which R = CH₃ are advantageously synthesised in accordance with the equation given below (cf. Example 5):



When the reaction is carried out with compound III, at least 1 mole equivalent of the base of the formula II, preferably furfurylamine or 2-thienylamine, is used, and an acid-binding agent, such as, for example, pyridine, triethylamine, dimethylaniline, sodium carbonate or potassium carbonate, may also be used. Advantageously, either 2 to 3 mole equivalents of the base II are used and a water-miscible inert diluent, such as, for example, dimethylformamide, dimethylacetamide, diethylene glycol dimethyl ether, dioxan, hexamethylphosphoric acid triamide or tetramethylurea, is added, or more than 3 mole equivalents of II are used and the reaction is carried out without the addition of a diluent.

The reaction temperature is usually between 20 and 100°C when X = F and between 60 and 120°C when X = Cl.

For working up, the reaction mixture may be introduced into a dilute aqueous acid, preferably acetic acid, whereupon, in many cases, the end product separates out as crystals and can be purified by recrystallisation from methanol, ethanol, isopropanol or a mixture of one of these alcohols with water. Amorphous crude products are advantageously taken up in a suitable organic solvent, advantageously ethyl acetate, the dried solution concentrated and the end product precipitated as crystals by adding a non-solvent, such as, for example, diisopropyl ether, diethyl ether or petroleum ether, in portions, or the dried solution may be evaporated completely and the residue recrystallised from another organic solvent, such as, for example, toluene, xylene, nitromethane, cyclohexane or acetonitrile. Products which cannot be made to crystallise by these methods are advantageously chromatographed on a silica gel column.

The subsequent alkaline saponification of the intermediate of the general formula IV to give the end product of the general formula I is carried out with an inorganic base, advantageously with excess aqueous 1N to 5N sodium hydroxide solution or potassium hydroxide solution. The rate of saponification is influenced both by the Ph radical and by the R radical, so that the reaction times can vary, usually between 1 and 10 hours. In the case of higher-molecular radicals R and Ph it can be advantageous to add diethylene glycol dimethyl ether or dioxan to the mixture in order to obtain a homogeneous solution when hot.

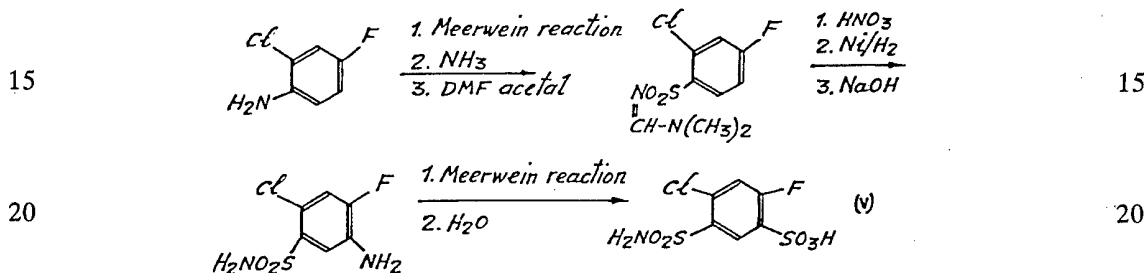
According to process variant b), a sulphonic acid of the general formula V or a salt thereof, is reacted with at least one mole equivalent of an amine of the general formula II, optionally with the addition of an acid-binding agent, and the product of the general formula I is obtained direct.

In the case of process variant b) also, it is possible, in principle, to protect the sulphonamide

group, as described above under a), by a radical which is easily detachable by hydrolysis and to detach this radical again, after the amine condensation reaction, by warming in aqueous alkaline solution.

Analogously to procedure a), the reaction can be carried out with or without a solvent. The reaction temperature is usually between 20 and 130°C when X = F and between 50 and 160°C when X = Cl and Br. The end product may be isolated in a conventional manner by diluting with water, neutralizing and, if necessary, concentrating the reaction mixture, and the compound of the formula I crystallises out as sulphonic acid salt of the amine II employed.

The preparation of the starting materials of the general formula V in which R = Cl or Br can be carried, for example, in accordance with a analogously to the equation given below (compare Example 8):



Starting materials of the general formula V in which R denotes a (substituted) phenoxy radical or CH_3 can be obtained in a simple manner by alkaline saponification of the sulphonic acid esters of the general formula III, described above.

In the form of the free sulphonic acids, the products are extremely readily soluble in water and, because of their highly acid reaction, are also unstable, especially when the basic radical denotes a furfurylamino radical. If such products are required in special cases, it is advantageous to pass an aqueous solution of any desired salt through a strongly acid ion exchanger in the H^+ form.

For therapeutic purposes, the alkali metal salts, which are readily soluble in water giving a neutral reaction, and are very stable, especially the sodium or potassium salts, are preferably used, and in general the sodium salts are more readily soluble in water than the potassium salts. For special purposes, calcium salts and magnesium salts can also be used under certain circumstances. Ammonium salts can also be therapeutically valuable.

Examples of salts having a particularly good solubility in water which may be mentioned are the diethanolammonium salt, the N,N,N-tris-hydroxymethylammonium salt and the glucoseammonium salt. Much more frequently it is desired to reduce the solubility in water by forming a salt with specific bases, in order, where appropriate, to achieve a protracted action in the case of oral administration. Suitable amine components for such salts are, for example, dicyclohexylamine, N,N'-dibenzylethylenediamine, 2-aminothiazole, 2-aminothiazoline, xanthinol and tetramisole.

Further salts of great pharmacological significance are the salts of the products with basic potassium-retaining compounds, such as, for example, amiloride or triamterene, or with basic antihypertensive agents, such as, for example, clonidine, dihydralazine or guanethidine.

As tests on rats and dogs have shown, the compounds of the general formula I and their physiologically tolerable salts are excellent salidiuretic agents with a very rapid onset of action and a period of action of 4 to 10 hours. A particular advantage of the compounds is the advantageous sodium/potassium ratio.

The high solubility in water of the compounds and the neutral pH of the aqueous solutions are also highly advantageous for therapeutic use. The products are therefore ideally suitable in particular for intravenous administration. The process products are reliably effective after oral administration also, in which case the action starts 1 - 2 hours after administration.

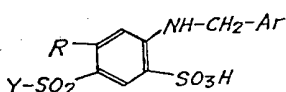
In human therapy, formulations which can be used are, preferably, aqueous injection solutions for intravenous administration with a total content of 0.1 to 50 mg of the alkali metal salts, and tablets, dragées or capsules for oral administration containing 1 to 200 mg of the active ingredient, and the conventional fillers and excipients.

In addition to the end products described in the Examples, the following sulphonic acid salts may, for example, be prepared:

Table 1

	R	Ar	Salt	
5	3-Chlorophenoxy	2-Thienyl	K	5
	3-Tolyloxy	2-Thienyl	K	
	3-Bromophenoxy	2-Furyl	K	
	4-Bromophenoxy	2-Furyl	K	
	3-Bromophenoxy	2-Thienyl	K	
10	3-Chlorophenylthio	2-Furyl	Na	10
	3-Tolylthio	2-Furyl	Na	
	2-Tolylthio	2-Furyl	Na	
	3-Methoxyphenylthio	2-Furyl	Na	

15 The present invention also provides a compound of the general formula IV or a salt thereof, and a compound of the general formula 15



20 in which Y represents a protected amino group and R and Ar have the meanings given above, or a salt thereof. 20

The following Examples illustrate the invention.

Example 1

25 *The sodium salt of N-(2-furylmethyl)-4-phenoxy-5-sulphamoylorthanilic acid* 25

a) 45.4 g (0.1 mole) of *p*-cresyl 2-chloro-4-phenoxy-5-sulphamoylbenzenesulphonate and 150 ml of freshly distilled furfurylamine are stirred at 80°C for one hour and the excess amine is then stripped off in vacuo. The evaporation residue is partitioned between 1.0 l of 10 per cent acetic acid and 0.3 l of ethyl acetate and the organic phase is separated off and washed 30 twice with 0.3 l of 5 per cent acetic acid and twice with 0.3 l of water. The dried ethyl acetate solution is evaporated and *p*-cresyl N-(2-furylmethyl)-4-phenoxy-5-sulphamoyl-orthanilate is isolated from the residue by recrystallising twice from ethanol. This gives 10.5 g (20% of theory) of colourless crystals having a melting point of 175-176°C. 30

b) 5.2 g (10 mmoles) of *p*-cresyl N-(2-furylmethyl)-4-phenoxy-5-sulphamoyl-orthanilate and 50 ml of 2N NaOH are heated under reflux for 2 hours. The pH of the clear reaction solution is then adjusted to 5 with 5N HCl, at room temperature, and the *p*-cresol is removed 35 by extracting by shaking with 50 ml of diisopropyl ether. After concentrating the aqueous solution to 30 ml and neutralizing with 2N HCl, the end product crystallises overnight at room temperature. It is dried at 60°C. This gives 3.4 g (75% of theory) of colourless crystals 40 having a decomposition point of 232°C. 40

Starting material:

101 g of triethylamine dissolved in 1.0 l of tetrahydrofuran are added dropwise in the course of one hour, at 5-10°C, whilst stirring, to a solution of 344 g (1.0 mole) of 1,3-dichlorobenzene-4,6-disulphonyl dichloride and 108 g of *p*-cresol in 4.0 l of tetrahydrofuran. 45 Ammonia gas is then passed in excess into the reaction mixture at 5-10°C. Water is then added in an amount such that the ammonium chloride and triethylamine hydrochloride go into solution, the solution is neutralized with HCl and concentrated in vacuo to one third its volume, and 3 l of water are added to the concentrate. The crude product, which has precipitated as an amorphous substance, is separated off by decanting off the supernatant liquor and dissolved in 1 l of ethanol with warming. After standing overnight at room 50 temperature, the bis-*p*-cresyl 1,3-dichlorobenzene-4,6-disulphonate which has separated out as crystals (about 75 g, by-product) is filtered off, 0.5 l of water is added in portions to the filtrate and the product is allowed to crystallise at room temperature for one day. After filtering off, it is dried on a steam bath. This gives 55 245 g (62% of theory) of *p*-cresyl 2,4-dichloro-5-sulphamoylbenzenesulphonate having a melting point of 155-157°C. 55

39.7 g (0.1 mole) of this ester are stirred with 11.3 g of phenol and 6.9 g of powdered potassium carbonate in 125 ml of dimethylformamide for 2 hours at 110°C. The solvent is then stripped off in vacuo and the residue is extracted twice with warm water. The undissolved crystalline constituent is filtered off and recrystallized from methanol. This gives 19.3 g 60 (43% of theory) of *o*-cresyl 2-chloro-4-phenoxy-5-sulphamoylbenzenesulphonate having a melting point of 157-159°C. 60

A further 8 g of the compound are obtained by evaporating the mother liquor and chromatographing the residue in a column of silica gel (300 g) soaked in toluene, using 65 toluene/ethyl acetate (0 to 10% of ethyl acetate). 65

The other starting materials of the formula III can be obtained in an analogous manner.

Example 2

The sodium salt of N-(2-furylmethyl)-4-(4-tolyloxy)-5-sulphamoylorthanilic acid

5 a) 46.8 g (0.1 mole) of *p*-cresyl 2-chloro-4-(4-tolyloxy)-5-sulphamoyl-benzenesulphonate and 100 ml of furfurylamine are warmed at 80-85°C for one hour, whilst stirring, and the reaction solution is then worked up analogously to Example 1 a. The amorphous crude product is introduced, as a solution in 100 ml of toluene, onto a column of 500 g of silica gel soaked in toluene, and eluted first with toluene and subsequently with the addition of ethyl acetate (continuous, rising to a maximum of 8%). The fractions corresponding to the main product are evaporated and the crystalline residue in ground with diisopropyl ether and filtered off. The product is dried at 80°C/0.1 mm Hg. This gives 33 g (62% of theory) of *p*-cresyl *N*-(2-furylmethyl)-4-(4-tolyloxy)-5-sulphamoyl-orthanilate having a melting point of 136-138°C

10 b) 5.3 g (19 mmoles) of the ester from a) are warmed with 50 ml of 1N NaOH for 30 minutes, whilst stirring, on a steam bath. The saponification product is isolated analogously to Example 1 b and is recrystallized from 5 per cent aqueous NaCl solution and dried at 60°C/0.1 mm Hg. This gives 3.2 g (70% of theory) of colourless crystals which decompose above 236°C.

Starting material:

15 A mixture of 39.7 g (0.1 mole) of *p*-cresyl 2,4-dichloro-5-sulphamoylbenzenesulphonate, 120 ml of dimethylformamide, 6.9 g of powdered potassium carbonate and 10.8 g of *p*-cresol is stirred for one hour at 115°C. The dimethylformamide is then stripped off in vacuo, the evaporation residue is treated with 1 l of water and the amorphous precipitate is separated off and recrystallised from ethanol. This gives 19.2 g (41% of theory) of *p*-cresyl 2-chloro-5-sulphamoyl-4-(4-tolyloxy)-benzenesulphonate having a melting point of 223-225°C

Example 3

The sodium salt of N-(2-furylmethyl)-4-phenylthio-5-sulphamoylorthanilic acid

20 a) 47.0 g (0.1 mole) of *p*-cresyl 2-chloro-4-phenylthio-5-sulphamoylorthanilate and 120 ml of furfurylamine are stirred at 85 to 90°C for 2 hours and the reaction solution is then stirred into 1.2 l of 10 per cent acetic acid. The crude product, which has precipitated as crystals, is purified by recrystallisation from ethanol. This gives 41 g (89% of theory) of *p*-cresyl *N*-(2-furylmethyl)-4-phenylthio-5-sulphamoylorthanilate having a melting point of 151-153°C

25 b) 5.3 g (10 mmoles) of the ester from a) and 50 ml of 1N NaOH are heated under reflux for 2 hours. After cooling to room temperature, the pH of the clear reaction solution is adjusted to 2 with 0.5N HCl and the *p*-cresol is removed by extracting with 30 ml of diisopropyl ether. The end product crystallises out of the aqueous phase, which has been separated off, after neutralizing with 2N NaOH, on standing overnight at room temperature. It is dried on a steam bath. This gives 4.1 g (89% of theory) of colourless crystals which decompose above 236°C.

Starting material:

30 39.7 g (0.1 mole) of *p*-cresyl 2,4-dichloro-5-sulphamoylbenzenesulphonate, 120 ml of dimethylformamide, 6.9 g of powdered potassium carbonate and 11.2 g of thiophenol are stirred for one hour at 100°C, the mixture is then stirred into 1.5 l of water and the resin which has precipitated out is separated off and recrystallised from ethanol. This gives 20.5 g (44% of theory) of *p*-cresyl 2-chloro-4-phenylthio-5-sulphamoylorthanilate having a melting point of 199-201°C.

Example 4

The sodium salt of N-(2-thienylmethyl)-4-(4-tolyloxy)-5-sulphamoylorthanilic acid

35 a) 46.8 g (0.1 mole) of *p*-cresyl 2-chloro-5-sulphamoyl-4-(4-tolyloxy)-benzenesulphonate are dissolved in 75 ml of dimethylformamide and, after adding 55 g of thienylamine, the mixture is stirred at 90°C for one hour. The reaction solution is then stirred into 1 l of 10 per cent acetic acid and the crystalline precipitate is filtered off and, in the moist state in which it is obtained on the suction filter, recrystallised from methanol. This gives 23.5 g (43% of theory) of *p*-cresyl *N*-(2-thienylmethyl)-4-(4-tolyloxy)-5-sulphamoyl-orthanilate having a melting point of 180-181°C.

40 b) 5.4 g (10 mmoles) of the ester from a) are saponified analogously to Example 1 b) and the sodium salt is purified by recrystallisation from water. This gives 3.8 g (80% of theory) of colourless prisms having a melting point of 230°C with decomposition.

Example 5

The sodium salt of N-(2-furylmethyl)-4-methyl-5-sulphamoylorthanilic acid

45 a) 37.6 g (0.1 mole) of *p*-cresyl 2-chloro-4-methyl-5-sulphamoylbenzenesulphonate and 100 ml of furfurylamine are stirred at 90°C under nitrogen for 2 hours and the reaction solution is then worked up analogously to Example 1 a). The amorphous crude product is

50 55 60 65

recrystallised from toluene. This gives 32 g (73% of theory) of *p*-cresyl *N*-(2-furylmethyl)-4-methyl-5-sulphamoyl-orphanilate having a melting point of 143-144°C.

b) 4.4 g (10 mmoles) of the ester from a) are saponified analogously to Example 1 b) with NaOH and the sodium salt which has crystallised out from the aqueous solution is purified by recrystallisation from ethanol. This gives 2.8 g (75% of theory) of colourless crystals having a decomposition point of 235°C.

Starting material:

30.4 g (0.1 mole) of 2-chloro-4-methyl-5-sulphamoylbenzenesulphonyl chloride and 10.8 g of *p*-cresol are dissolved in 0.4 l of acetone and 10.1 g of triethylamine, dissolved in 50 ml of acetone, are added dropwise to the mixture at room temperature, whilst stirring. The acetone is then stripped off in vacuo, the residue is treated with water and the crystalline precipitate is filtered off and recrystallised from ethanol. This gives 31 g of *p*-cresyl-2-chloro-4-methyl-5-sulphamoylbenzenesulphonate having a melting point of 157-159°C.

Example 6

The sodium salt of N-(2-thienylmethyl)-4-methyl-5-sulphamoyl-orphanilic acid

a) 37.6 g (0.1 mole) of *p*-cresyl 2-chloro-4-methyl-5-sulphamoylbenzenesulphonate and 75 ml of thienylamine are stirred at 90°C under nitrogen for 3 hours and the reaction mixture is then introduced into 1 l of 10 per cent acetic acid. The crude product, which has precipitated out as crystals, is purified by recrystallisation from ethanol. This gives 36 g (80% of theory) of *p*-cresyl *N*-(2-thienylmethyl)-4-methyl-5-sulphamoyl-orphanilate having a melting point of 163-165°C.

b) 4.5 g (10 mmoles) of the ester from a) are saponified analogously to Example 1 b). After concentrating the aqueous-neutral solution, the sodium salt crystallises at room temperature. This gives 2.6 g (69% of theory) of slightly yellowish crystals having a melting point of 235°C with decomposition.

Example 7

The sodium salt of N-(2-thienylmethyl)-4-phenylthio-5-sulphamoyl-orphanilic acid

a) 47.0 g (0.1 mole) of *p*-cresyl 2-chloro-4-phenylthio-5-sulphamoyl-orphanilate are reacted analogously to Example 3 a) with 100 ml of 2-thienylamine and the condensation product is purified by recrystallisation from methanol. This gives 32 g (58% of theory) of *p*-cresyl *N*-(2-thienylmethyl)-4-phenylthio-5-sulphamoyl-orphanilate having a melting point of 153°C.

b) Saponification of 5.5 g of the ester from a) with NaOH, analogously to Example 3 b), gives 3.1 g (64% of theory) of the corresponding sodium sulphonate having a decomposition point of 214°C.

Example 8

The potassium salt of N-(2-furylmethyl)-4-chloro-5-sulphamoyl-orphanilic acid

A mixture of 16.3 g (50 mmoles) of 4-chloro-2-fluoro-5-sulphamoylbenzenesulphonic acid dihydrate, 50 ml of dioxan and 20 ml of furfurylamine is stirred for one hour at 85°C and the dioxan is then stripped off in vacuo. The evaporation residue is dissolved in 100 ml of 2N NaOH, the furfurylamine is removed from the solution by extracting three times by shaking with, in each case, 100 ml of ethyl acetate, and the solution is then neutralized with 5N HCl and evaporated to dryness. The evaporation residue, which has been dried at 100°C, is extracted twice with, in each case, 0.2 l of boiling ethanol. The end product crystallises out of the combined ethanol solutions, which have been concentrated to half their volume, overnight at room temperature. This gives 15.7 g (81% of theory); decomposition point 265°C.

Starting material:

185 g of phosphorus oxychloride are added in portions to a solution of 210 g (1.0 mole) of 2-chloro-4-fluorobenzenesulphonamide in 0.6 l of dimethylformamide, at room temperature, whilst stirring, and the mixture is then warmed at 90-95°C for 2 hours, whilst stirring, and subsequently stirred into 3 l of water. The condensation product, which has precipitated as crystals, is filtered off, washed with water and dried on a steam bath. This gives 230 g (87% of theory) of 2-chloro-4-fluoro-*N*-dimethylaminomethylidene-benzenesulphonamide having a melting point of 127-129°C.

84 ml of fuming nitric acid are allowed to run into 0.8 l of 20 per cent oleum at 20-30°C and 265 g of the above sulphonamide derivative are then introduced in portions. The mixture is stirred at 55°C for 2 hours and then added drop-wise to 5 kg of ice. The nitro compound, which has precipitated as crystals, is filtered off, washed well with water and dried at 60°C. This gives 290 g (94% of theory) of 4-chloro-5-dimethylaminomethylidene-sulphamoyl-2-fluoro-nitrobenzene having a melting point of 164-165°C.

155 g (0.5 mole) of the above nitro compound are dissolved in 3.0 l of tetrahydrofuran and hydrogenated in a shaking duck in the presence of palladium black. After 34 l of H₂ have been taken up, the hydrogenation ceases. The catalyst is separated off, the solution is evaporated and the residue is ground at room temperature with ethanol, whereupon the amino compound crystallises in the form of colourless platelets. After filtering off, the

product is recrystallised from nitromethane. This gives 125 g (90% of theory) of 4-chloro-dimethylaminomethylidene-sulphamoyl-2-fluoro-aniline having a melting point of 202-205°C.

5 56 g (0.2 mole) of the amino compound are stirred with a mixture of 0.4 l of 2N NaOH and 0.2 l of methanol at 40-45°C until a clear solution has formed and this solution is left to stand overnight at room temperature. The pH is then adjusted to 5 with HCl and the sulphonamide, which has precipitated as crystals, is filtered off, washed with water and dried on a steam bath. This gives 41 g (91% of theory) of 4-chloro-2-fluoro-5-sulphamoylaniline having a melting point of 176-179°C.

10 56 g (0.25 mole) of the aminosulphonamide are dissolved in a mixture of 0.1 l of concentrated HCl of 0.1 l of glacial acetic acid and the mixture is diluted with 0.1 l of water. A solution of 20 g of sodium nitrate in 0.1 l of water is then added dropwise at -3 to 0°C, whilst stirring, the mixture is stirred for a further 4 minutes at 0°C and the diazo solution is then introduced into a mixture, which has been prepared a short time previously, of 0.6 l of SO₂-saturated glacial acetic acid and 15 g of CuCl dihydrate in 50 ml of water, whilst stirring. After the evolution of nitrogen has ceased, the mixture is diluted with an equal volume of water and the crystalline precipitate is filtered off, washed well with water and dried in air. This gives 48 g (62% of theory) of 4-chloro-2-fluoro-5-sulphamoylbenzene-sulphonyl chloride having a melting point of 170-172°C.

15 31 g (0.1 mole) of the sulphonyl chloride are stirred with 1 l of water for 30 minutes on a steam bath and the clear reaction solution is then evaporated in vacuo. The product, which initially is amorphous, crystallises completely, radiating outwards, at room temperature. This gives 30 g (92% of theory) of 4-chloro-2-fluoro-5-sulphamoylbenzene-sulphonic acid dihydrate.

25 *Example 9*

The 2-thienylmethylammonium salt of N-(2-thienylmethyl)-4-chloro-5-sulphamoyl-orthanilic acid

30 32.6 g (0.1 mole) of 4-chloro-2-fluoro-5-sulphamoyl-benzenesulphonic acid dihydrate, 100 ml of dioxan and 45 g of 2-thienylmethylamine are warmed at 85°C for half an hour, whilst stirring, and the dioxan is then stripped off in vacuo. The evaporation residue is taken up in 0.4 l of water and the pH of the filtered solution is adjusted to 7.5 with 5N HCl. The end product starts to crystallise after grinding and is filtered off after standing for 4 hours at room temperature. This gives 25 g (50% of theory) of colourless crystals having a melting point of 202-204°C.

35 *Example 10*

The sodium salt of N-(2-furylmethyl)-4-(4-methoxyphenoxy)-5-sulphamoyl-orthanilic acid

40 a) 48.4 g (0.1 mole) of *p*-cresyl 2-chloro-4-(4-methoxyphenoxy)-5-sulphamoylbenzenesulphonate are reacted with 100 ml of furfurylamine, and the product is worked up and purified, analogously to Example 2 a. This gives 12 g (22% of theory) of *p*-cresyl *N*-(2-furylmethyl)-4-(4-methoxyphenoxy)-5-sulphamoyl-benzenesulphonate having a melting point of 117-120°C.

45 b) 5.4 g (10 mmoles) of the ester from a) and 50 ml of 1N NaOH are warmed for one hour, whilst stirring, on a steam bath. The saponification product is isolated analogously to Example 1 b. This gives 4.2 g (88% of theory) of colourless crystals which decompose above 225°C.

Starting material:

50 A mixture of 39.7 g (0.1 mole of *p*-cresyl 2,4-dichloro-5-sulphamoylbenzenesulphonate, 120 ml of dimethylformamide, 6.9 g of powdered potassium carbonate and 12.4 g of 4-hydroxy-anisole is stirred for one hour at 115°C. The dimethylformamide is then stripped off in vacuo, the evaporation residue is treated with 1 l of water and the product is filtered off and washed with water and hot ethanol. This gives 25.3 g (52% of theory) of *p*-cresyl 2-chloro-4-(4-methoxyphenoxy)-5-sulphamoylbenzenesulphonate having a melting point of 198-200°C.

Example 11

55 *The potassium salt of N-(2-furylmethyl)-4-phenoxy-5-sulphamoyl-orthanilic acid.*

60 a) 44.0 g (0.1 mole) of phenyl 2-chloro-4-phenoxy-5-sulphamoylbenzenesulphonate having a melting point of 180 - 181°C (from methanol) are stirred with 30 ml of furfurylamine and 100 ml of dimethylformamide for 2 hours at 90°C and the reaction solution is then evaporated in vacuo. The evaporation residue is boiled up with 0.5 l of water and the undissolved constituent is separated off by decanting off the supernatant liquor and is recrystallised from 0.25 l of methanol. This gives 16.0 g (32% of theory) of phenyl *N*-(2-furylmethyl)-4-phenoxy-5-sulphamoylorthanilate having a melting point of 176-178°C.

65 b) 12.5 g (25 mmoles) of the above ester and 125 ml of 1N KOH are boiled under reflux for 1.5 hours. After the clear reaction solution has cooled to room temperature and after neutralizing with 2N HCl, the end product rapidly crystallises out. After standing for one

hour at +10°C, the product is filtered off, washed with ice-water and diethyl ether and dried on a steam bath. This gives 9.7 g (84% of theory) of colourless platelets having a decomposition point of 217°C.

Example 12

5 The potassium salt of *N*-(2-furylmethyl)-5-sulphamoyl-4-(3-tolyloxy)-orphanilic acid 5

a) 10.3 g (22 mmoles) of *p*-cresyl 2-chloro-5-sulphamoyl-4-(3-tolyloxy)-benzenesulphonate and 25 ml of furfurylamine are warmed at 60°C for 2 hours, whilst stirring, and the reaction mixture is worked up analogously to Example 2 a. This gives 1.3 g of *p*-cresyl *N*-(2-furylmethyl)-5-sulphamoyl-4-(3-tolyloxy)-orphanilate having a melting point of 131-133°C. 10

b) The entire ester from a) is stirred with 40 ml of 2N KOH for 2 hours at 95°C and the pH of the saponification solution is adjusted to 6 with 5N HCl at room temperature. The end product crystallises immediately. After standing for one hour at room temperature, the product is filtered off and washed with a little ice-water and the colourless product is dried on a steam bath. This gives 1.0 g (85% of theory); decomposition point 218°C. 15

Example 13

The potassium salt of *N*-(2-furylmethyl)-4-(3-methoxyphenoxy)-5-sulphamoyl-orphanilic acid

a) 4.4 g (9 mmoles) *p*-cresyl 2-chloro-4-(3-methoxyphenoxy)-5-sulphamoylbenzenesulphonate having a melting point of 155°C are stirred with 20 ml of furfurylamine for 2 hours at 80-85°C and the reaction mixture is worked up analogously to Example 2 a. After evaporating those fractions obtained from column chromatography which correspond to the main product, *p*-cresyl *N*-(2-furylmethyl)-4-(3-methoxyphenoxy)-5-sulphamoyl-orphanilate is obtained in an amorphous form. The substance is a single compound according to chromatography. The NMR spectrum (in DMSO) corresponds to the structure. This gives 3.0 g (61% of theory) of colourless resin; thin layer chromatography (silica gel) using chloroform/methanol (10:1) as the solvent: *R*_f 0.75. 20

b) 3.0 g of the ester from a) are stirred with 40 ml of 2N KOH for 2 hours at 95°C and the clear reaction solution is then neutralized at room temperature with 2NHCl and concentrated to 40 ml in vacuo. After standing for two days at +5°C, the end product, which has precipitated as crystals, is filtered off, washed with a little ice-water and dried on a steam bath. This gives 0.8 g (29% of theory) of colourless crystals having decomposition point of 200°C. 30

Example 14

The potassium salt of *N*-(2-thienylmethyl)-4-phenoxy-5-sulphamoyl-orphanilic acid

a) 3.2 g (8 mmoles) of phenyl 2-chloro-4-phenoxy-5-sulphamoylbenzenesulphonate and 5.6 g of 2-thienylamine are warmed at 90°C for 2 hours, whilst stirring. The reaction solution is introduced into 0.2 l of 5 per cent acetic acid and the reaction product, which has precipitated in an amorphous form, is separated off by decanting off the supernatant liquor. 35

The crude product is crystallised from 30 ml of methanol as colourless prisms. This gives 2.1 g (51% of theory) of phenyl *N*-(2-thienylmethyl)-4-phenoxy-5-sulphamoyl-orphanilate having a melting point of 181-183°C. 40

b) 1.9 g of the above ester are stirred with 15 ml of 2N KOH for 4 hours at 95°C. The pH of the clear reaction solution is adjusted to 6 at room temperature with 5N HCl. The end product crystallises out of the solution, which at first is still clear, after grinding with a glass rod. After washing with water, the product is dried on a steam bath. This gives 1.1 g (62% of theory) of colourless platelets having a decomposition point of 248°C. 45

Example 15

The sodium salt of *N*-(2-furylmethyl)-4-(4-methoxyphenylthio)-5-sulphamoyl-orphanilic acid

a) 10.0 g of *p*-cresyl 2-chloro-4-(4-methoxyphenylthio)-5-sulphamoyl-orphanilate having a melting point of 188-190°C are stirred with 25 ml of furfurylamine for 1.5 hours at 70°C. The *p*-cresyl *N*-(2-furylmethyl)-4-(4-methoxyphenylthio)-5-sulphamoyl-orphanilate which has precipitated as crystals when the reaction solution is introduced into 0.3 l of 10 per cent acetic acid is washed thoroughly, on the suction filter, with water and then boiled up with 100 ml of ethanol and filtered off at room temperature. This gives 6.3 g (56% of theory) of yellowish crystals having a melting point of 159-161°C. 50

b) 5.6 g (10 mmoles) of the above ester are stirred with 50 ml of 1N KOH for one hour on a steam bath and the pH of the reaction solution is then adjusted to 7 at room temperature with 2N HCl. The end product crystallises immediately. After washing with water and ethanol, it is dried on a steam bath. This gives 5.0 g (98% of theory); decomposition point 205°C. 60

Example 16

The sodium salt of *N*-(2-furylmethyl)-4-(4-tolylthio)-5-sulphamoyl-orphanilic acid

a) 14.4 g (30 mmoles) of *p*-cresyl 2-chloro-5-sulphamoyl-4-(4-tolylthio)-orphanilate having a melting point of 181-183°C are reacted, analogously to Example 15 a, with 35 ml of furfurylamine and the *p*-cresyl *N*-(2-furylmethyl)-5-sulphamoyl-4-(4-tolylthio)-orphanilate 65

precipitated as crystals by dilute acetic acid is purified by recrystallisation from 0.3 l of ethanol. This gives 10.0 g (61% of theory) of yellowish crystals having a melting point of 169-171°C.

- 5 b) 9.8 g (18 mmoles) of the above ester are saponified by heating for one hour with 100 ml of 1N NaOH on a steam bath. The end product, which has been precipitated as crystals by neutralizing with 5N HCl at room temperature, is filtered off, after standing for a short time at room temperature, washed with water and diisopropyl ether and dried on a steam bath. This gives 5.6 g (65% of theory): decomposition point 233°C.

Example 17

- 10 The potassium salt of *N*-(2-furylmethyl)-4-(4-chlorophenylthio)-5-sulphamoyl-orthanilic acid

- a) 10.1 g (20 mmoles) of *p*-cresyl 2-chloro-4-(4-chlorophenylthio)-5-sulphamoyl-orthanilate having a melting point of 189°C are reacted, analogously to Example 15 a, with 25 ml of furfurylamine, and the *p*-cresyl 4-(4-chlorophenylthio)-*N*-(2-furylmethyl)-5-sulphamoyl-orthanilate precipitated as crystals by dilute acetic acid is recrystallised from 0.2 l of ethanol. This gives 7.6 g (67% of theory); melting point 152°C.

- 15 b) 7.4 g (13 mmoles) of the above ester are stirred with a mixture of 65 ml of 1N KOH and 15 ml of dioxan for 1 hour at 95°C and the reaction solution is then neutralized at room temperature with 2N HCl. The end product crystallises immediately. After standing for one hour at room temperature, it is filtered off, washed with water and ethanol and dried on a steam bath. This gives 6.1 g (91% of theory); decomposition point 233°C.

Example 18

The potassium salt of *N*-(2-furylmethyl)-4-(3-chlorophenoxy)-5-sulphamoyl-orthanilic acid

- 25 a) 8.0 g (16.5 mmoles) of *p*-cresyl 2-chloro-4-(3-chlorophenoxy)-5-sulphamoyl-orthanilate are stirred with 4.9 g of furfurylamine and 20 ml of dimethylformamide for 2 hours at 90°C. The crude product, which has precipitated in an amorphous form on introducing the reaction solution into 0.3 l of 10 per cent acetic acid, is chromatographed on a column of 100 g of silica gel in toluene/ethyl acetate (maximum 5% of ethyl acetate) and the main fraction (Rf 0.75, thin layer chromatography on silica gel in chloroform/methanol, 10 : 1, as the solvent; the by-products without exception have lower Rf values) is recrystallised from diisopropyl ether. This gives 1.2 g (13% of theory); melting point 151-153°C.

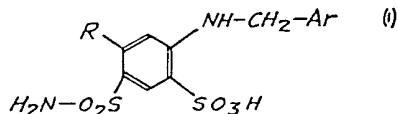
- 30 b) All of the *p*-cresyl 4-(3-chlorophenoxy)-*N*-(2-furylmethyl)-5-sulphamoyl-orthanilate from a) is warmed with 20 ml of 2N KOH for 15 minutes on a steam bath and the reaction solution is then neutralized at room temperature with 2N HCl. The end product, which has precipitated as crystals, is filtered off after standing for a short time at room temperature and is washed with water and dried on a steam bath. This gives 0.9 g (83% of theory) of colourless crystals which decompose above 250°C.

Example 19

- 40 The potassium salt of *N*-(2-furylmethyl)-4-(4-chlorophenoxy)-5-sulphamoyl-orthanilic acid is obtained analogously to Example 18, by saponifying the corresponding *p*-cresyl sulpho-nate (melting point 126-128°C after recrystallisation from isopropanol) with 2N KOH (4 hours on a steam bath). This gives Yield: 0.8 g (73% of theory); decomposition point 220°C.

WHAT WE CLAIM IS:

- 45 1. A 5-sulphamoyl-orthanilic acid of the general formula



wherein R denotes a chlorine or bromine atom, a methyl group or a phenoxy or phenylthio radical which is unsubstituted or substituted by a chlorine or bromine atom or a methyl or methoxy group, and Ar denotes a furyl or thienyl radical.

- 55 2. A compound as claimed in claim 1, in which R denotes a chlorine atom or a phenoxy or phenylthio group.

3. A compound as claimed in claim 1 or claim 2, in which Ar denotes a 2-furyl or 2-thienyl group.

- 60 4. A physiologically tolerable metal, ammonium or substituted ammonium salt of a compound claimed in any one of claims 1 to 3.

5. A salt as claimed in claim 4, which is an alkali metal salt.

6. A salt as claimed in claim 4, which is dicyclohexylamine, *N,N'*-dibenzylethylenediamine, 2-aminothiazole, 2-aminothiazoline, xanthinol or tetramisole salt.

- 65 7. A salt as claimed in claim 4, which is a salt of a basic potassium-retaining compound or

basic antihypertensive agent.

8. A salt as claimed in claim 7, which is an amiloride, triamterene, clonidine, dihydralazine or guanethidine salt.

9. A salt as claimed in claim 4, which is diethanolamine, N,N,N-trihydroxymethylamine or glucosamine salt.

10. A sodium or potassium salt of a compound as claimed in claim 1, in which R denotes a chlorine atom or a phenoxy or phenylthio group and Ar denotes a 2-furyl or 2-thienyl group.

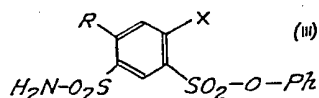
11. A salt as claimed in claim 4, which is specified in any one of the Examples 1 to 19 herein, or the corresponding free sulphonic acid.

12. A salt as claimed in claim 4, which is any one of those specified in Table 1 herein, or the corresponding free sulphonic acid.

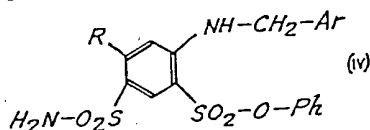
13. A process for the preparation of a compound as claimed in claim 1 or a physiologically tolerable metal, ammonium or substituted ammonium salt thereof, which comprises reacting an amine of the general formula



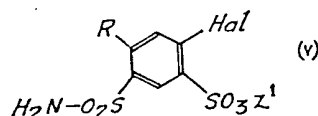
wherein Ar has the meaning given in claim 1, or a salt thereof, either (a) with a compound of the general formula



wherein R has the meaning given in claim 1, X denotes a halogen atom, but denotes a fluorine atom if R represents Cl or Br, and Ph denotes an unsubstituted or substituted aromatic radical and the sulphonamide group is free or protected, or with a salt thereof, and subjecting the resulting compound of the general formula



or salt thereof, to alkaline hydrolysis or (b) with a benzenesulphonic acid of the general formula



wherein Hal denotes a halogen atom, Z¹ denotes a hydrogen, metal, ammonium or tertiary ammonium ion, and R has the meaning given in claim 1, and the sulphonamide group is free or protected, or with a salt thereof, and, if appropriate, detaching the sulphonamide protective group by hydrolysis, and, if desired, converting the compound obtained according to (a) or (b) into the free compound or into a physiologically tolerable metal, ammonium or substituted ammonium salt thereof.

14. A process as claimed in claim 13, carried out substantially as described in any one of the Examples 1 to 19 herein.

15. A compound as claimed in claim 1, whenever prepared by a process as claimed in claim 13 or claim 14.

16. A physiologically tolerable metal, ammonium or substituted ammonium salt of a compound claimed in claim 1, whenever prepared by a process as claimed in claim 13 or claim 14.

17. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 12, 15 and 16, in admixture or conjunction with a pharmaceutically suitable carrier.

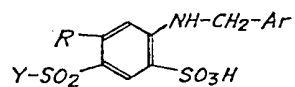
18. A pharmaceutical preparation as claimed in claim 17, which is in dosage unit form.

19. A pharmaceutical preparation as claimed in claim 18, which is in a form suitable for injection and contains from 0.1 to 50 mg of active ingredient per dosage unit.

20. A pharmaceutical preparation as claimed in claim 18, which is in a form suitable for oral administration and contains from 1 to 200 mg of active ingredient per dosage unit.

21. A compound of the general formula IV shown in claim 13, in which R and Ar have the meanings given in claim 1 and Ph has the meaning given in claim 13, or a salt thereof.

22. A compound of the general formula



5 wherein Y represents a protected amino group and R and Ar have the meanings given in claim 1, or a metal, ammonium or substituted ammonium salt thereof. 5

23. A compound as claimed in claim 21, which is specified in any one of the Examples 1 to 19 herein.

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