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PATENT SPECIFICATION

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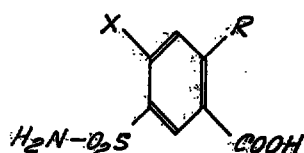
COMPLETE SPECIFICATION

Benzene-Sulphonamides and process of preparing them

We, FARBWERKE HOECHST AKTIEN-GESELLSCHAFT, vormals Meister Lucius & Brüning, a body corporate recognised under German law, of Frankfurt (M)-Hoechst, 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:—

The present invention relates to new sulphonamides and to a process for preparing them.

The present invention provides, as new compounds, benzene-sulphonamides of the formula I



in which X represents a chlorine or bromine atom and R represents a benzylamino, dibenzylamino, furfurylamino or thenylamino group, and the salts thereof.

The invention also provides a process for the manufacture of benzene-sulphonamides of the formula (I), wherein a compound of the formula



in which X has the meaning given above, is reacted with benzylamine, dibenzylamine, furfurylamine or thenylamine and, if desired, [Price 4s. 6d.]

the condensation product so obtained is converted into the corresponding carboxylic acid salt by means of an inorganic or organic base.

As starting substances of the formula (II) given above there may preferably be used 3-sulphamyl-4:6-dichlorobenzoic acid, 3-sulphamyl-4:6-dibromo-benzoic acid or 3-sulphamyl-4-chloro-6-bromo-benzoic acid.

The starting substances are advantageously obtained by heating the corresponding 2:4-dihalogeno-benzoic acids for several hours with four to six times their amount in weight of chlorosulphonic acid to temperatures between 160 and 180°C, by pouring the cooled reaction mixture into ice water and by subsequent reaction of the crystalline 4:6-dihalogeno-benzoic acid-3-sulphonic acid chlorides thus obtained, with concentrated aqueous ammonia solution at room temperature. On acidifying the ammoniacal solution the desired starting substances separate off in sufficiently pure state so that a further purification by recrystallization from ethanol/water can in most cases be dispensed with.

The reaction of the dihalogeno-sulphamyl-benzoic acids thus obtained with the above-mentioned amines is suitably effected in such a way that the starting substances are heated to a temperature within the range 120 to 180°C, if necessary in the presence of inert organic solvents or diluents, it being of advantage to use the basic reaction component in an amount of from twice to 4 times the theoretically necessary amount for the reaction, in order to bind the hydrogen halide set free in the reaction.

The reaction temperature depends to a high degree upon the type of the amine used. When using benzylamine it is favourable to use a temperature within the range 130 to 150°C, when using furfurylamine and

thenylamine the reaction mixture is advantageously heated to 135/145° C and when using dibenzylamine the most favourable temperatures are those within the range 160 to 180° C.

Instead of using an amount of amine in excess of that required for the reaction, it is also possible to use another basic agent for the purpose of binding the hydrogen halide set free in the course of the reaction, for instance, alkali metal bicarbonates, calcium oxide or tertiary organic bases as, for example, triethylamine, triethanolamine or dimethylaniline. It is surprising that the second halogen atom of the dihalogenated sulphamyl-benzoic acids, even when using a large excessive amount of the corresponding primary or secondary amine, does not participate in the reaction if the aforesaid temperatures are not considerably exceeded.

The reaction may be carried out with the reactants in the form of a melt as well as with the use of a solvent or diluent, for instance, water or inert solvents miscible with water as, for example, ethanol, propanol, ethylene-glycol, ethylene-glycol-monomethylether or diethylene-glycol-dimethylether. According to the type of the starting materials used, the reaction mixture is heated for a shorter or longer period under reflux, if necessary in a closed vessel. The reaction is generally performed within 1—4 hours, the reaction period can, however, be prolonged to 12—24 hours when it is suitable to operate at a temperature as low as possible, in order to avoid side reactions. After the reaction is terminated, the reaction mixture is poured into dilute acid, whereupon the desired final product generally precipitates in the form of crystals. The crude product can be purified by dissolving and recrystallizing it in normal sodium bicarbonate solution with hydrochloric acid and subsequent recrystallisation from an appropriate organic solvent miscible with water or a mixture of solvents as, for example, ethanol, dimethylformamide/water or ethanol/water.

The products obtained according to the process of the present invention may, if desired, be converted into the corresponding carboxylic acid salts by treatment with mineral or organic bases. As such, there may be used ammonia, alkali metal carbonates or alkali earth metal carbonates, alkali metal bicarbonates, alkaline earth metal bicarbonates, alkali metal hydroxides, alkaline earth metal hydroxides, alkali metal oxides and alkaline earth metal oxides. As organic bases there may be mentioned, for example, dicyclohexylamine.

With regard to the known state of the art it could not be expected that in the process according to the invention the selective exchange of an aromatically bound halogen atom for a substituted amino group would

occur even in the presence of an excess of a base, and this was the more surprising since the reaction proceeds without using catalysts and often even at a moderately elevated temperature. It is likewise surprising that practically only one of the two aromatically bound halogen atoms, that is, the halogen atom in ortho-position to the carboxy group, takes part in the reaction so that under the aforementioned reaction conditions there are obtained products that show a considerable degree of uniformity.

The previously proposed processes mentioned in the first part of the description cannot be used when compounds are to be prepared that are substituted at the nitrogen atom by a benzyl, furfuryl, or thenyl radical, since these radicals are likewise sulphonated in the reaction with chlorosulphonic acid or are oxidised during the oxidization with permanganate.

The new products obtained according to the process of the invention exhibit valuable therapeutic properties. They are particularly suitable as diuretics and saluretics. In animal experiments they cause, more especially, the secretion of sodium and chloride ions in approximately equivalent proportions, whereas the secretion of potassium is increased to a small extent only. By reason of this sodium-uretic efficacy the products obtained according to the process of the invention neither cause an acidosis nor an alkalosis of the cellular tissue and are, likewise owing to their excellent compatibility, particularly suitable, for example, for the therapy of oedema or, in combination with other hypotensively active compounds, they are suitable, for example, for the permanent therapy of essential hypertension.

The compounds are active in their free form as well as in the form of their salts in oral as well as in parental administration. They can be used as such or in the form of a pharmaceutical preparation comprising the active compound in admixture or conjunction with a pharmaceutical suitable carrier in solid or liquid form, for example, water, vegetable oils, starch, lactose, talcum or with auxiliary agents, for example, stabilizers, preserving, wetting or emulsifying agents. The preparations can be made up in the form of tablets, dragées, capsules, solutions, suspensions or emulsions. With particular advantage the preparations are orally administered in the form of tablets or dragées. For the therapy of human beings, there enter into consideration dosages in the range of 0.01 gram and 0.2 gram of the new products.

For the purpose of comparison the following Table shows the diuretic and saluretic values obtained by testing the new compounds of the invention, that is, 3-sulphamyl-4-chloro-6-benzylamino-benzoic acid (I) and

precipitate
ethanol/water

alkaline

pharmaceutically

3 - sulphamyl - 4 - chloro-6-furfurylamino- benzoic acid (II), in contradistinction to the known product 6-chloro-7-sulphamyl-3:4-dihydro - 1:2:4 - benzo - thiadiazine - 1:1-dioxide (III). 5

TABLE

Test Preparation	I		II		III	
dosage/per os	25 mg/kg	50 mg/kg	25 mg/kg	50 mg/kg	25 mg/kg	50 mg/kg
Lipschitz value L (T/U)	2.4	3.9	3.2	4.9	1.3	1.7
Saluresis T/U (Na)	2.7	3.3	3.1	3.1	1.4	1.5
T/U (K)	1.1	1.6	1.3	1.6	1.1	1.3
T/U (Cl)	2.5	3.2	3.0	3.0	1.5	1.6
(Cl) ⁻ — (Na) ⁺ + (K) ⁺	0.98	1.00	1.03	0.98	0.85	0.83

Elucidation regarding the above Table:—
When determining the Lipschitz value T/U the diuresis of a control group of rats to which, prior to the beginning of the test, urea was orally administered, was referred to the excretion of urine taking place upon application of the substance to be tested (T), in such a way that from the individual 5 hours' values (cc) a quotient $\frac{T}{U}$ was obtained.

The secretion of water (diuresis) was tested on rats of an average weight of about 100 grams each. The rats were not given any food or drinking water for 24 hours prior to the starting of the test; they were divided into groups of 3 animals each having about the same body weight. The animals were given the test preparation by means of an oesophageal probe in a dosage of 25 or 50 milligrams/kilogram, suspended in a starch solution of 2% strength (0.5 cc). Each test animal was then orally given 5 cc of sodium chloride solution of 0.9% strength per 100 grams of body weight. The test animals were then placed into diuresis funnels. The quantity of urine excreted by each group of animals was hourly determined for 5 hours, in the measuring cylinder. During the examination of each test preparation a group of animals treated with urea (1 gram/kilogram) was simultaneously examined. Moreover, a comparison test with a known standard preparation was simultaneously carried out and there was likewise effected a control by means of sodium chloride (5 cc/100 grams of rat).

All tests were carried out with a double determination.

The total quantity of urine excreted by each group within the observation period of 5 hours was referred to 100 grams of body weight of the animals and the arithmetical mean was calculated. The quotient from the test group of the individual preparation (T) and the urea group (U) constitutes the Lipschitz value designated by L, L equalling T/U.

A test preparation may be considered an efficacious diuretic if, for instance, 25 milligrams of the substance result in a Lipschitz factor of lower than 1.

For testing the saluretic efficacy, rats of about 100 grams of body weight were also used as test animals. These animals were not fed for 24 hours prior to the beginning of the test but received drinking water. The animals were divided into groups of 3 animals each showing uniform weight. The test preparation as well as the known standard substance and the urea (1 gram/kilogram) were administered in the form of a suspension (0.5 cc) in a starch solution by means of an oesophageal probe. Three animals each were placed into the diuresis funnel (double control). The urine excretion was measured in the first five hours, the urine quantity of each group was collected and the amount of sodium-, potassium- and chlorine-ions contained therein was determined.

The saluretic efficiency of the test preparations was ascertained by determining Na and K (flame-photometrically) and Cl (argentometrically with potentiometric de-

45

50

55

60

65

70

75

80

termination of the final point). From the result of the analysis the excretion was calculated in millimols/kilogram for each ion. These values were designated by (Na)⁺, (K)⁺ and (Cl)⁻.

The excretion of ions (millimols/kilogram) after application of the test substance (T) was referred to the saluresis caused by urea (U). In this manner, there were obtained likewise for the excretion of sodium-, potassium- and chlorine-ions T/U values which were designated by T/U (Na), T/U (K) and T/U (Cl).

The quotient

$$\frac{(Cl)^-}{(Na)^+ + (K)^+}$$

shows the degree of efficiency. With a good saluretic agent the quotient should reach a value possibly near to 1, i.e. it should provoke the excretion of a great number of sodium and chlorine ions and of a small number of potassium ions.

It follows from the values given in the Table that the new compounds are considerably superior to the known preparation (III) as regards diuretic as well as saluretic efficacy.

The following Examples illustrate the invention:—

EXAMPLE 1

3 - sulphamyl - 4 - chloro - 6 - benzylamino-benzoic acid

a) A solution of 27 grams of 3-sulphamyl-4:6-dichloro-benzoic acid melting at 233—235° C in 42 cc of benzylamine and 50 cc of ethyleneglycol-monomethyl-ether were heated for 4 hours under reflux and then stirred into 600 cc of 2N-hydrochloric acid. 26 Grams of light-yellow crystals separated off melting at 232—235° C with decomposition. From ethanol of 96% strength (with addition of charcoal) the 3-sulphamyl-4-chloro-6-benzylamino-benzoic acid crystallized in the form of colourless prisms melting at 244.5° C with decomposition.

b) Dicyclohexylammonium salt of 3-sulphamyl - 4 - chloro - 6 - benzylamino - benzoic acid

6.8 Grams of 3-sulphamyl-4-chloro-6-benzylamino-benzoic acid and 3.6 grams of dicyclohexylamine were dissolved in 80 cc of ethanol and 100 cc of water were added to the clear mixture. On trituration, the salt started crystallizing. After standing for one day at 0° C it was filtered off with suction and precipitated from a mixture of acetone and water (1:2). 7.5 Grams of colourless prisms were obtained melting at 209—210° C.

c) Magnesium salt of 3-sulphamyl-4-chloro-6-benzylamino-benzoic acid

100 cc of water were added to 0.6 gram of finely pulverized magnesium oxide and

6.7 grams of 3-sulphamyl-4-chloro-6-benzylamino-benzoic acid, and the whole was heated for 20 minutes under reflux. After cooling to room temperature, any undissolved matter was filtered off and the filtrate was lyophilized. 6.9 Grams of the product were obtained in the form of an amorphous, non-hygroscopic powder which was easily soluble in water.

EXAMPLE 2

3 - sulphamyl - 4 - chloro - 6 - furfurylamino-benzoic acid

10.8 Grams of 3-sulphamyl-4:6-dichloro-benzoic acid (0.04 mol) and 11.7 grams of furfurylamine (0.12 mol) were heated in 30 cc of diethyleneglycol-dimethylether for 6 hours under reflux. On pouring the reaction mixture into 300 cc of 1N-hydrochloric acid, the reaction product was immediately separated off in the form of crystals. The light-yellow crude product was purified by dissolving it in 100 cc of warm 1N-sodium bicarbonate solution, precipitation by means of hydrochloric acid and subsequent recrystallization from ethanol/water, with addition of charcoal. Colourless prisms were obtained which decomposed at 206° C while undergoing a brown colouration, and with evolution of gas.

EXAMPLE 3

3 - sulphamyl - 4 - chloro - 6 - thenylamino-benzoic acid

10 Grams of 3-sulphamyl-4:6-dichloro-benzoic acid were reacted with 15.8 grams of thenylamine (0.14 mol) as described in Example 2 and the reaction product was purified as already indicated. The product according to the invention formed colourless prisms which decomposed at 201° C with evolution of gas and while undergoing a dark colouration.

EXAMPLE 4

3 - sulphamyl - 4 - chloro - 6 - dibenzylamino-benzoic acid

A mixture of 10.8 grams of 3-sulphamyl-4:6-dichloro-benzoic acid (0.04 mol), 27.6 grams of dibenzylamine (0.14 mol) and 50 cc of ethylene-glycol was heated for 3 hours to 170° C and then poured into 300 cc of normal sulphuric acid. After standing for several hours the precipitate was filtered off with suction, dissolved in 100 cc of 2N-sodium hydroxide solution, the solution was extracted with ether and decolorized at a raised temperature by means of charcoal.

The reaction product separated off on acidification with hydrochloric acid, was recrystallized from ethanol and formed colour-

less prisms melting at 206° C with decomposition.

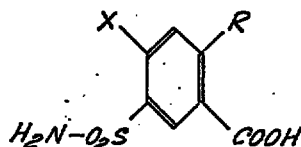
EXAMPLE 5

3-sulphamyl - 4 - bromo - 6 - benzylamino-benzoic acid

A mixture of 10.8 grams of 3-sulphamyl-4,6-dibromobenzoic acid (0.03 mol) melting at 242—243° C, 13.0 grams of benzylamine (0.12 mol) and 25 cc of ethyleneglycol-monomethyl ether were heated for 3 hours under reflux and then stirred into 500 cc of normal hydrochloric acid. The reaction product separated off in the form of a light-yellow resin, was freed from resinous by-products by dissolution in 100 cc of 1N-sodium-bicarbonate solution and was separated off in the form of crystals by the addition of concentrated hydrochloric acid. After recrystallization from ethanol the compound melted at 247° C with decomposition.

WHAT WE CLAIM IS:—

1. Benzene-sulphonamides of the formula



in which X represents a chlorine or bromine atom and R represents a benzylamino, dibenzylamino, furfurylamino or thenylamino group.

2. 3 - sulphamyl - 4 - chloro - 6 - benzylamino-benzoic acid.

3. 3 - sulphamyl - 4 - chloro - 6 - furfurylamino - benzoic acid.

4. 3 - sulphamyl - 4 - chloro - 6 - thenylamino - benzoic acid.

5. 3 - sulphamyl - 4 - bromo - 6 - benzylamino - benzoic acid.

6. 3 - sulphamyl - 4 - chloro - 6 - dibenzylamino - benzoic acid.

7. Salts of any one of the compounds claimed in any one of claims 1 to 6.

8. The dicyclohexylammonium salt of 3-sulphamyl - 4 - chloro - 6 - benzylamino-benzoic acid.

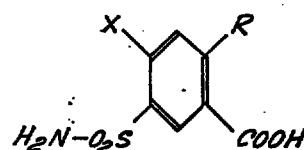
9. The magnesium salt of 3-sulphamyl-4-chloro-6-benzylamino-benzoic acid.

10. A pharmaceutical preparation for oral or parenteral administration, which comprises a benzene sulphonamide or a salt thereof as claimed in any one of claims 1 to 9 in admixture or conjunction with a pharmaceutically suitable carrier.

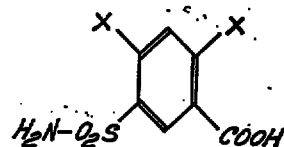
11. A pharmaceutical preparation as claimed in claim 10, which is in the form of tablets or dragées.

12. A pharmaceutical preparation as claimed in claim 10 or 11, which contains a dosage quantity of from 0.01 to 0.2 grams of the benzene sulphonamide compound or salt thereof.

13. A process for the manufacture of benzene-sulphonamides of the formula (I)



in which X represents a chlorine or bromine atom and R represents a benzylamino, dibenzylamino, furfurylamino or thenylamino group, by reacting a compound of the formula II



in which X has the meaning given above, with benzylamine, dibenzylamine, furfurylamine or thenylamine, and, if desired, converting the condensation product so obtained into the corresponding carboxylic acid salt by means of an inorganic or organic base.

14. A process as claimed in claim 13 and which is carried out substantially as described in any one of the Examples herein.

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less prisms melting at 206° C with decomposition.

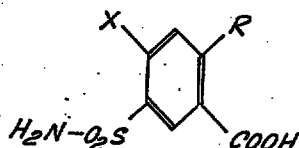
EXAMPLE 5

3-sulphamyl - 4 - bromo - 6 - benzylamino-benzoic acid

A mixture of 10.8 grams of 3-sulphamyl-4-bromobenzoic acid (0.03 mol) melting at 242—243° C, 13.0 grams of benzylamine (0.12 mol) and 25 cc of ethyleneglycol-monomethyl ether were heated for 3 hours under reflux and then stirred into 500 cc of normal hydrochloric acid. The reaction product separated off in the form of a light-yellow resin, was freed from resinous by-products by dissolution in 100 cc of 1N-sodiumbicarbonate solution and was separated off in the form of crystals by the addition of concentrated hydrochloric acid. After recrystallization from ethanol the compound melted at 247° C with decomposition.

WHAT WE CLAIM IS:—

1. Benzene-sulphonamides of the formula



in which X represents a chlorine or bromine atom and R represents a benzylamino, dibenzylamino, furfurylamino or thenylamino group.

2. 3 - sulphamyl - 4 - chloro - 6 - benzylamino-benzoic acid.

3. 3 - sulphamyl - 4 - chloro - 6 - furfurylamino - benzoic acid.

4. 3 - sulphamyl - 4 - chloro - 6 - thenylamino - benzoic acid.

5. 3 - sulphamyl - 4 - bromo - 6 - benzylamino - benzoic acid.

6. 3 - sulphamyl - 4 - chloro - 6 - dibenzylamino - benzoic acid.

7. Salts of any one of the compounds claimed in any one of claims 1 to 6.

8. The dicyclohexylammonium salt of 3-sulphamyl - 4 - chloro - 6 - benzylamino-benzoic acid.

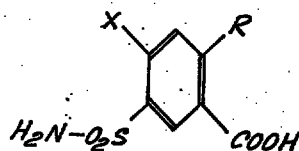
9. The magnesium salt of 3-sulphamyl-4-chloro-6-benzylamino-benzoic acid.

10. A pharmaceutical preparation for oral or parenteral administration, which comprises a benzene sulphonamide or a salt thereof as claimed in any one of claims 1 to 9 in admixture or conjunction with a pharmaceutically suitable carrier.

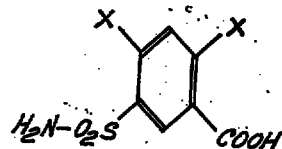
11. A pharmaceutical preparation as claimed in claim 10, which is in the form of tablets or dragées.

12. A pharmaceutical preparation as claimed in claim 10 or 11, which contains a dosage quantity of from 0.01 to 0.2 grams of the benzene sulphonamide compound or salt thereof.

13. A process for the manufacture of benzene-sulphonamides of the formula (I)



in which X represents a chlorine or bromine atom and R represents a benzylamino, dibenzylamino, furfurylamino or thenylamino group, and the salts thereof, by reacting a compound of the formula II



in which X has the meaning given above, with benzylamine, dibenzylamine, furfurylamine or thenylamine, and, if desired, converting the condensation product so obtained into the corresponding carboxylic acid salt by means of an inorganic or organic base.

14. A process as claimed in claim 13 and which is carried out substantially as described in any one of the Examples herein.

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