PATENT SPECIFICATION

NO DRAWINGS

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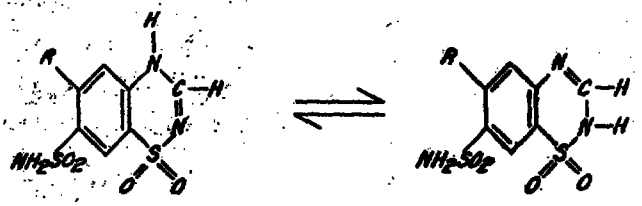
COMPLETE SPECIFICATION

Benzothiadiazine Derivatives

We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, 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 is concerned with certain novel benzothiadiazine - 1,1 - dioxide compounds containing a sulphamoyl substituent in the benzenoid portion of the nucleus.

In brief, this invention provides the new compounds 6 - chloro - 7 - sulphamoyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide, 6 - bromo - 7 - sulphamoyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide and 6 - methyl - 7 - sulphamoyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide which may be presented by the general formulae:

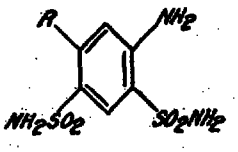


in which R is a chlorine or bromide atom or a methyl group. The compounds are tautomeric, i.e. they have a double bond that exists either in the 2(3) - position or the 3(4) - position.

The invention also provides sodium and potassium salts of the above compounds, and methods of preparing both the compounds and their sodium and potassium salts.

The new compounds of this invention are useful chemotherapeutic agents because of their diuretic, including natriuretic properties. Accordingly, the invention also provides diuretic compositions containing as active ingredient at least one compound of the above formulae, together with a solid or liquid pharmaceutical carrier. Compositions containing a solid carrier may be in the form of tablets, pills, or capsules; compositions containing a liquid carrier may be in the form of solutions, dispersions, or suspensions, e.g. in an aqueous medium. For intravenous injection pyrogen-free water is a suitable carrier. The compounds can be administered in therapeutic dosages as in conventional vehicles in the form of a tablet as these compounds are effective upon oral administration as well as upon injection. Tablets may, for example, be made by intimately dispersing the active ingredient in an orally administrable solid carrier, and compressing the resulting product into tablets. As the compounds of this invention also are readily soluble in a dilute alkaline medium and in polyethylene glycol solutions, injectable solutions can be prepared by dissolving the compound in the selected medium, to which preservatives can be added if desired.

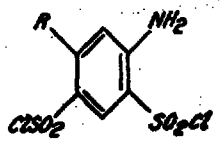
In accordance with the invention, the benzothiadiazine - 1,1 - dioxides of the invention can be prepared by heating a disulphamoyl - aniline compound having the formula:



in which R is a chlorine or bromine atom or a methyl group, with formic acid or ethyl orthoformate at from 100 to 150° C.

[Price 3s. 6d.]

Preferably, the disulphamoylaniline compound is prepared by treating with ammonia an aniline disulphonylchloride compound of formula



where R is a defined above, which compound is itself desirably prepared by the reaction of *m* - chloroaniline, *m* - bromoaniline, or *m* - toluidine, with chlorosulphonic acid in the presence of lithium chloride, sodium chloride or potassium chloride. These methods may in practice be carried out as set forth below.

The chlorosulphonation of the *meta* - substituted aniline is carried out in the presence of sodium, potassium, or lithium chloride. For all practical purposes sodium chloride can be used as it is readily available and cheap, and in its presence the reaction proceeds quite smoothly. As the reaction between these ingredients is quite vigorous, it is preferred to add the *meta* - substituted aniline derivative to the chlorosulphonic acid dropwise with stirring and cooling. After all of the aniline derivative has been added, the alkali metal chloride is added in small portions to allow for the evolution of hydrogen chloride at a moderate rate. Following this, the mixture is heated at between about 100° to 200° C. preferably in an oil bath.

The disulphonyl chloride thus obtained then can be converted to the disulphamoyl derivative by treatment with ammonia, which can be added in a number of different ways. For example, aqueous or alcoholic ammonium hydroxide or liquid ammonia may be added to the disulphonyl chloride or a solution of it, or ammonia gas may be bubbled into a solution of the disulphonyl chloride in an organic solvent. All these methods result in production of the diamide compound. The diamide compound then is heated with formic acid or ethyl orthoformate at from 100° to 150° C. after which the solvent is removed preferably by distillation thus forming the benzothiadiazine - 1,1 - dioxide compound.

The sodium and potassium salts of the benzothiadiazine - 1,1 - dioxide compounds of this invention can be prepared by dissolving the selected compound in an aqueous or alcoholic solution of the alkali metal hydroxide and, if desired, isolating the salt by evaporating the solvent. The sodium and potassium salts can also be prepared by other methods known to organic chemists.

The preparation of the new compounds of the invention is more fully described in the following examples.

EXAMPLE 1.

6 - Chloro - 7 Sulphamoyl - 1,2,4 - Benzothiadiazine - 1,1 - Dioxide

Step a: 64 g. (0.5 mole) of *m* - chloroaniline was added dropwise with stirring to 375 ml. of chlorosulphonic acid in a 3 - litre round - bottom 3 - necked flask cooled in an ice bath. 350 g. of sodium chloride was added portionwise over a period of 1 to 2 hours and the mixture then heated gradually in an oil bath to 150° C. After 3 hours at 150—160° C. the flask was cooled thoroughly in an ice bath and the contents treated with a litre of cold water. The product was extracted with ether and the extract washed with water and dried over sodium sulphate. After renewal of ether on the steam bath, the residual 5 - chloroaniline - 2,4 - disulphonyl chloride, which may be crystallized from benzene - hexane m.p. 130—132° C. was cooled in an ice bath and treated with 150 ml. of 28% ammonium hydroxide in a 2 - litre Erlenmeyer flask. The mixture was heated on the steam bath for 1 hour and cooled, and the product was collected on the filter, washed with water, and dried. Upon crystallization from dilute alcohol, 5 - chloro - 2,4 - disulphamoylaniline was obtained as colourless needles, m.p. 251—252° C.

Step b: A solution of 88 g. of 5 - chloro - 2,4 - disulphamoylaniline in 1.1 litre of 88% formic acid was heated under reflux for 2 hours. After removal of 200 ml. of solvent by distillation, 1 litre of water was added and the product collected, washed with water and dried. Crystallization from dilute alcohol afforded 6 - chloro - 7 - sulphamoyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide as colourless needles, m.p. 342.5—343° C.

EXAMPLE 2.

6 - Bromo - 7 - Sulphamoyl - 1,2,4 - Benzothiadiazine - 1,1 - Dioxide

Step a: 86.0 g. (0.5 mole) of *m* - bromoaniline was added dropwise over a period of 1 hour to 375 ml. of chlorosulphonic acid cooled in an ice bath. 350 g. of sodium chloride was added portionwise over 2 hours and the mixture then heated in an oil bath at 150° C. for 3 hours. After thorough cooling in an ice bath, the reaction mixture was treated with 1 litre of ice water. The product was taken up in ether, washed with water and dried. After removal of solvent on the steam bath, the residue was cooled in an ice bath and treated with 150 ml. 28% ammonium hydroxide. After the initial vigorous reaction had subsided, the mixture was warmed on the steam bath for 1 hour and then cooled, and the precipitate was collected on the filter. Crystallization from dilute alcohol gave 5 - bromo - 2,4 - disulphamoylaniline as colourless needles, m.p. 265—267° C.

Step b: 5 g. of 5 - bromo - 2,4 - disulphamoylaniline was dissolved in 100 ml. of 98-100% formic acid by heating and the solution

heated on the steam bath for 2 hours. After dilution with water, the precipitate was collected on the filter and reprecipitated from 5% aqueous sodium hydroxide with acetic acid to give 6 - bromo - 7 - sulphamoyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide as colourless needles, m.p. 347—349° C. with decomposition (sample inserted at 250° C.).

EXAMPLE 3.

6 - Methyl - 7 - Sulphamoyl - 1,2,4 - Benzothiadiazine - 1,1 - Dioxide

Step a: By replacing the *m*-bromoaniline used in Example 2, step *a*, by an equimolecular quantity of *m*-toluidine (53.5 gms.) and following substantially the same procedure described in step *a* of Example 2, 2,4 - disulphamoyl - 5 - methylaniline was obtained as colourless needles, melting point 246—247° C.

Step b: By substituting 5 g. of 2,4 - disulphamoyl - 5 - methylaniline for the 5 - bromo - 2,4 - disulphamoylaniline used in step *b* of Example 2 and following substantially the same procedure described in step *b* of Example 2, 6 - methyl - 7 - sulphamoyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide was obtained as colourless needles, m.p. 344—345° C. (dec.).

EXAMPLE 4.

Sodium salt of 6 - chloro - 7 - sulphamoyl - 1,2,4 - Benzothiadiazine - 1,1 - Dioxide

6 - Chloro - 7 - sulphamoyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide obtained as described in Example 1, was dissolved in alcoholic sodium hydroxide and the solvent then evaporated *in vacuo* yielding the sodium salt of 6 - chloro - 7 - sulphamoyl - 1,2,4-benzothiadiazine - 1,1 - dioxide.

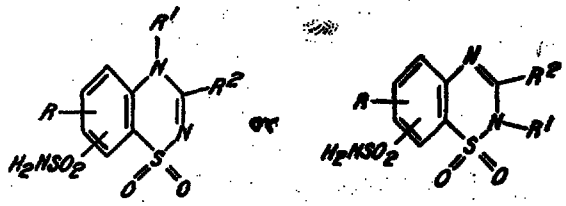
EXAMPLE 5.

Compressed Tablet Comprising 0.5 g. Active Ingredient

6-Chloro-7-Sulphamoyl-1,2,4-benzothiadiazine - 1,1-dioxide	500 g.
Starch paste 12.5% 100 cc. allow	12.5 g.
	512.5 g.
Starch U.S.P. Maize	25.0 g.
Magnesium stearate	5.5 g.
	543.0 g.

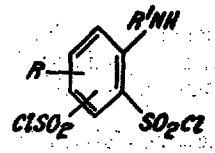
The 6 - chloro - 7 - sulphamoyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide is granulated with the starch paste and, while moist, passed through a No. 14 screen, dried at 45° C. for 20 hours, and then passed 3 times through a No. 14 screen. The starch then is passed through a No. 90 bolting cloth onto the granulation and all ingredients are blended thoroughly. Then the magnesium stearate is passed through a No. 90 bolting cloth onto the granulation and these ingredients are blended after which the granulation is compressed into tablets using a 14/32" flat, bevelled, scored punch having a thickness of 0.205 ± 0.005" yielding 1,000 tablets, each weighing 0.543 g. and having a hardness of 6 kgms. measured by the Monsanto Chemical Company tablet hardness tester apparatus and a disintegration time of 5 minutes when tested on the U.S.P. tablet disintegrating apparatus (U.S. Pharmacopeia, 15th Edition, page 937).

In the specification of our copending application No. 13921/57, (Serial No. 826,921) there are claimed compounds having the general formula:



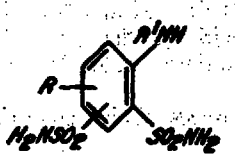
and their non-toxic alkali metal salts, where R is a hydrogen or halogen atom or a C_{1-5} alkyl, C_{1-5} alkoxy, nitro or amino group; R^1 is a hydrogen atom or a C_{1-5} alkyl radical and R^2 is a hydrogen atom, a C_{1-5} alkyl radical or an aryl, aralkyl, or aralkenyl radical containing one benzene ring which may or may not contain a C_{1-5} alkyl, C_{1-5} alkoxy or halogen substituent.

In the specification of our copending Application No. 21905/58 (Serial No. 826,922) there are claimed compounds having the general formula;



in which R is a halogen atom or a C_{1-5} alkoxy or a nitro group, and R^1 is a hydrogen atom, a C_{1-5} alkyl group, or a C_{1-8} carboxylic acyl group.

In the Specification of our copending Application No. 38885/58 (Serial No. 826,924) there are described and claimed compounds having the general formula:



in which R is a halogen atom, a C_{1-5} alkoxy group, or a nitro or amino group, and R_1 is a hydrogen atom, a C_{1-5} alkyl group, or a C_{1-8} carboxylic acyl group.

WHAT WE CLAIM IS:—

1. 6 - Chloro - 7 - sulphamoyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

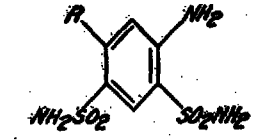
2. 6 - Bromo - 7 - sulphamoyl - 1,2,4, - benzothiadiazine - 1,1 - dioxide.

3. 6 - Methyl - 7 - sulphamoyl - 1,2,4, - benzothiadiazine - 1,1 - dioxide.

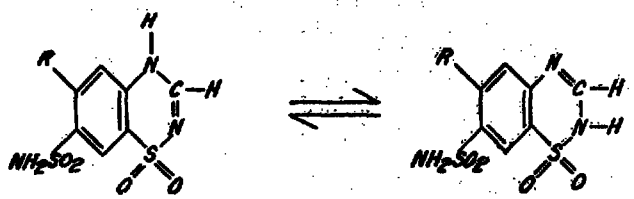
4. The sodium salt of a compound as claimed in any one of Claims 1—3.

5. The potassium salt of a compound as claimed in any one of Claims 1—3.

6. The process comprises heating a disulphamoylaniline compound having the formula:

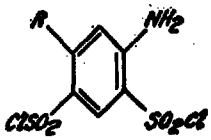


in which R is chlorine or bromine atom or a methyl group, with formic acid or ethyl orthoformate at from 100 to 150° C. to produce a tautomeric compound



7. A process as claimed in Claim 6, in which the conversion of the 5 - substituted - 2,4 - disulphamoylaniline to the 6 - substituted - 7 sulphamoyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide is effected by refluxing with formic acid.

8. A process as claimed in Claim 6 or 7, including the step of preparing the disulphamoylaniline compound by treating with ammonia an aniline disulphonylchloride compound of formula:



where R is as defined in Claim 6.

9. A process as claimed in Claim 8 in which the ammonia is used in aqueous solution.

10. A process as claimed in Claim 8 or 9 including the step of preparing the aniline disulphonyl chloride compound by the reaction of a compound of formula:



where R is a defined in Claim 6, with chlorosulphonic acid in the presence of lithium chloride, sodium chloride, or potassium chloride.

11. The process which comprises treating a compound as claimed in Claim 1, 2 or 3 with the hydroxide of sodium or potassium in aqueous or alcoholic solution so as to produce the sodium or potassium salt of the said compound.

12. A pharmaceutical composition comprising, as active ingredient, a compound as claimed in any one of Claims 1—5, together with a solid or liquid pharmaceutical carrier.

13. A composition as claimed in Claim 12 in the form of a tablet.

14. A process for preparing tablets containing as active ingredient a compound as claimed in Claim 1, 2 or 3, which comprises intimately dispersing the active ingredient in an orally administrable solid carrier, and compressing the resulting product into tablets.

15. A process as claimed in Claim 6, substantially as described in any one of the Examples 1—3 hereinbefore.

16. A process as claimed in Claim 11, substantially as described in Example 4 hereinbefore.

17. A process as claimed in Claim 14, substantially as described in Example 5 hereinbefore.

18. A compound as claimed in Claim 1, 2 or 3, when prepared by a process as claimed in any one of Claims 6—10 and 15 or an obvious chemical equivalent of such a process.

19. A compound as claimed in Claim 4 or 5, when prepared by a process as claimed in Claim 11 or 16 or an obvious chemical equivalent of such a process.

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* C L M S *

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