# PATENT SPECIFICATION

NO DRAWINGS

**826,921**

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**International Classification:—A61k. C07d.**

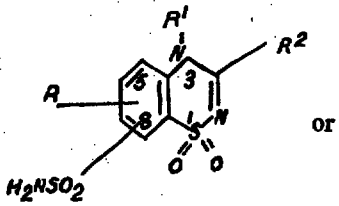
## COMPLETE SPECIFICATION

## Natriuretic Agents

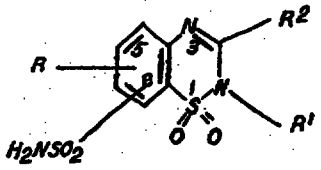
We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with novel benzothiadiazine-1,1-dioxide compounds containing a sulfamyl substituent in the benzenoid portion of the nucleus. In this specification and claims 'sulfamyl' is used to denote a $NH_2—SO_2—$ group, which is also termed 'sulphamoyl'.

In brief, this invention provides compounds having the general formula



or



in which R is a hydrogen atom, a halogen atom, typically chlorine, bromine, or fluorine, or a $C_{1-5}$ alkyl, $C_{1-5}$ alkoxy, nitro or amino radical, $R^1$ 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 group each containing one benzene ring which may or may not contain a $C_{1-5}$ alkyl, $C_{1-5}$ alkoxy, or halogen substituent, e.g. a benzyl, styryl, or phenyl group. The invention also provides sodium and potassium salts of the above compounds.

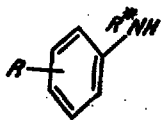
In those compounds of the invention having no organic substituent on either nitrogen in the benzothiadiazine-1, 1-dioxide nucleus, the double bond is tautomeric, i.e. it exists either between the 2- and 3-position atoms or between the atoms in the 3- and 4-positions. In those compounds having a organic substituent on the nitrogen atom in the 2-position, the double bond exists between the positions 3 and 4, and when substitution occurs on the $N^4$ atom, unsaturation exists between positions 2 and 3.

The new compounds of this invention are useful chemotherapeutic agents because of their diuretic, including natriuretic, properties. Accordingly, the invention also provides pharmaceutical compositions containing as active ingredient at least one compound of the above formula, together with a solid or liquid pharmaceutical diluent. Such compositions may be in the form of tablets, pills, capsules, or 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. 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.

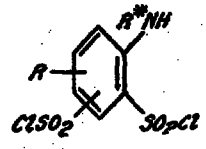
In accordance with the present invention, the benzothiadiazine-1, 1-dioxides of this invention can be prepared by a variety of methods.

[*Price 3s. 6d.*]

The first step in the preparation of the compounds involves the chlorosulfonation of a substituted aniline compound having the general formula

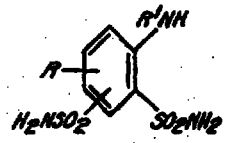


in which R is as defined above, and R* is a hydrogen atom, a $C_{1-5}$ alkyl radical, or an acetyl or $C_{3-6}$ alkanoyl group. This process, which forms part of the invention claimed in the specification of our copending Application No. 21905/58 (Serial No. 826,922), is carried out with chlorosulfonic acid in the presence of an alkali metal halide, which reacts with sulfonic acid formed during the reaction to produce an alkali metal sulfate and liberate a hydrohalic acid. Suitable alkali metal halides are the chlorides of sodium, potassium, and lithium. Sodium chloride is preferred in view of its cheapness and ready availability and the fact that the reaction proceeds quite smoothly in its presence. As the reaction is quite vigorous, it is preferred to add the aniline derivative to the chlorosulfonic 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° and 200° C., preferably in an oil bath, and there is obtained a disulfonyl chloride having the general formula

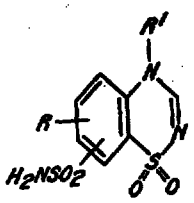


in which R and R* are as defined above. These disulfonyl chlorides form part of the invention claimed in the specification of our copending Application No. 21905/58 (Serial No. 826,922).

In accordance with the present invention, the disulfonyl chloride thus obtained then can be converted to a disulfonyl derivative having the general formula

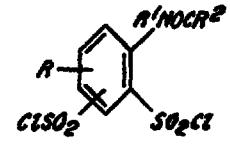


in which R and $R^1$ are as defined above, by treatment with ammonia which advantageously can be added in the form of aqueous or alcoholic ammonium hydroxide or liquid ammonia, or by dissolving the disulfonyl chloride in an organic solvent and bubbling ammonia gas into the solution to form the diamide compound. This step may be carried out so as to hydrolyse any alkanoyl group to a hydrogen atom. The diamide compound then is heated with formic acid or ethyl orthoformate, preferably at between about 100° and 150° C., after which the solvent is removed preferable by distillation thus forming a benzothiadiazine-1,1-dioxide compound having the general formula



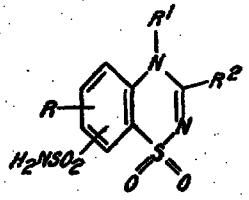
in which R and $R^1$ are as defined above.

Alternatively, the amino disulfonyl chloride compound can be acylated with an organic acid chloride or anhydride, the acid advantageously being a lower alkanoic acid such as acetic acid, propionic acid, or caproic acid or a mononuclear arylmonocarboxylic acid such as benzoic acid, phenylacetic acid, or cinnamic acid. This reaction proceeds quite smoothly at room temperature, yielding the N-acyldisulfonyl chloride derivative having the general formula



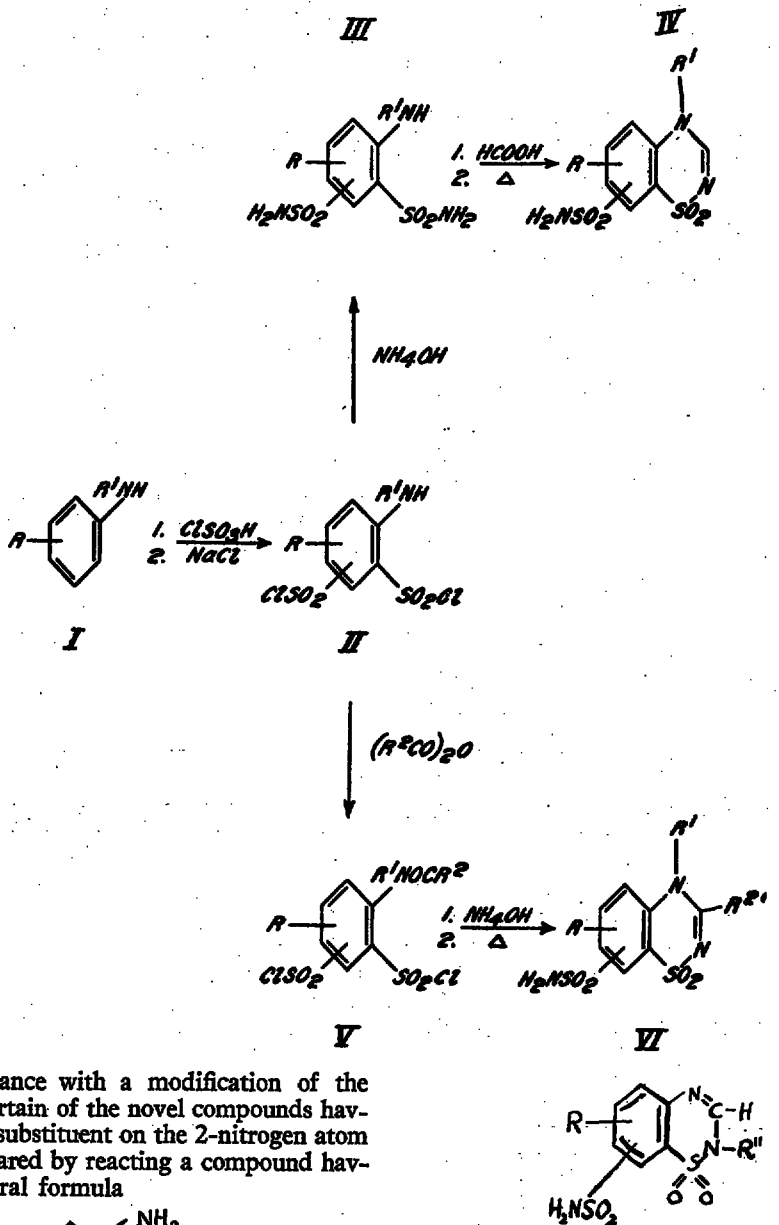
in which R, $R^1$, and $R^2$ are as defined above.

The acylated compound then can be converted to the corresponding amide by the method described above using, advantageously, aqueous or alcoholic ammonium hydroxide, liquid, ammonia, or ammonia gas, and the N-acyldisulfamyl compound thus obtained is heated at from about 150° to about 250° C. to form the cyclized product having the general formula

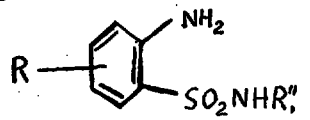


in which R, $R^1$ and $R^2$ are as defined above.

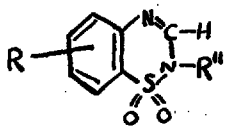
Practical methods of carrying out the method of the present invention are illustrated in the following reaction scheme, in which R, $R^1$ and $R^2$ are as defined above.




In accordance with a modification of the invention, certain of the novel compounds having an alkyl substituent on the 2-nitrogen atom may be prepared by reacting a compound having the general formula



where $R^{11}$ is a $C_{1-5}$ alkyl radical and R is a hydrogen or halogen atom or a $C_{1-5}$ alkyl or $C_{1-5}$ alkoxy, nitro or amino radical; with formic acid or ethyl orthoformate to produce a benzothiadiazine-1,1-dioxide compound having the general formula



and treating the latter with chlorosulphonic acid and then ammonia to produce a benzothiadiazine-1,1-dioxide compound having the general formula



The alkali metal 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. Any of the conventional alkali metal salts, such as the sodium, potassium, or lithium salt, can be prepared by this method or by other methods known to organic chemists.

The preparation of the benzothiadiazine-1,1-dioxide compounds of this invention is more fully described in the following examples.

EXAMPLE 1.

7-Sulfamyl-1,2,4-Benzothiadiazine-1,1-Dioxide

*Step a*: *o*-Chloroacetanilide (15.2 g.) was added portionwise to 120 ml. chlorosulfonic acid at room temperature followed by portion-

wise addition of 100 g. of sodium chloride over 1 hour. The mixture was then heated gradually to 150°C. in an oil bath over a 30 minute period and then maintained at 150° C. for 2 hours. After cooling thoroughly in an ice bath, the reaction mixture was treated with 500 ml. of ice water and the product, viz., 6-chloroacetanilide-2,4-disulfonyl chloride, was taken up in ether and washed with water and dried over sodium sulfate. After removal of ether by evaporation on the steam bath, the residual disulfonyl chloride was cooled in an ice bath and treated with 50 ml. of 28% ammonium hydroxide, which, in addition to converting the sulfonyl chloride groups to sulfamide groups, also hydrolysed the

$$-NH.CO.CH_3$$

group to an amino group. The ammoniacal solution was heated on the steam bath for 1 hour, cooled and the product collected on the filter. Crystallization from the dilute alcohol gave 6-chloro-2,4-disulfamylaniline as colorless needles, m.p. 242—244° C.

*Step b*: A solution of 5.72 g. (0.02 mole) of 6-chloro-2,4-disulfamylaniline in a mixture of 100 ml. of water and 35 ml. of 5% aqueous sodium hydroxide was hydrogenated in the presence of 2 g. of 5% palladium-on-charcoal until hydrogen absorption ceased (30 minutes). The solution was freed from catalyst and acidified to give 2,4-disulfamylaniline as colorless needles, m.p. 230—231.5° C.

*Step c*: A solution of 3.3 g. of 2,4-disulfamylaniline in 10 ml. of 98—100% formic acid was heated on the steam bath for 90 minutes. Upon cooling, the precipitate was collected, washed with water and crystallized from dilute alcohol to give 7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide as colorless needles, m.p. 319—320° C.

EXAMPLE 2.

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

*Step a*: 103.8 g. (0.5 mole) of 5-amino-2-chlorobenzenesulfonic acid was added dropwise over a period of 1 hour to 375 ml. of chlorosulfonic acid cooled in an ice bath. Sodium chloride (350 g.) 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 liter of ice water. The produce 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, cooled and the precipitate collected on the filter. Crystallization from dilute alcohol gave 4-chloro-2,5-disulfamylaniline, which was obtained as colorless needles, m.p. 289—290° C.

*Step b*: Two grams of 4-chloro-2,5-disulfamylaniline was dissolved in 50 ml. of 98—100% formic acid and treated in the manner described in Example 2 step *b* of Specification No. 37102/58 (Serial No. 826,923) to give 7-chloro-6-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxiode as colorless plates from acetone-petroleum ether, m.p. 327—330° C. (dec.).

EXAMPLE 3.

6 - Sulfamyl - 1,2,4 -Benzothiadiazine - 1,1-Dioxide

*Step a*: 4-Chloro-2,5-disulfamylaniline (described in Example 2, step *a*) (5.72 g., 0.02 mole) was hydrogenated in the presence of 5% palladium-on-charcoal catalyst by substantially the same procedure described in Example 1, step *b* to give 2,5-disulfamylaniline as colorless needles, m.p. 216—217° C.

*Step b*: By replacing the 2,4-disulfamylaniline employed in Example 1, step *c*, by 2,5-disulfamylaniline prepared as described above and following substantially the same procedure as described in Example 1, step *c*, 6-sulfamyl-1,2,4 -benzothiadiazine-1,1-dioxide was obtained as colorless needles, m.p. 311—314° C. (dec.).

EXAMPLE 4.

6 - Methoxy - 7 - Sulfamyl - 1,2,4 -Benzothiadiazine - 1,1 - Dioxide

*Step a*: Chlorosulfonic acid (150 ml.) was added dropwise over 30 minutes with stirring to 24.6 g. (0.2 mole) )of *m*-anisidine cooled in an ice bath. After addition of chlorosulfonic acid was complete, 140 g. of sodium chloride was added portionwise over 1 hour. The mixture was heated for two hours on the steam bath and then for three hours in an oil bath, 150—160° C., cooled thoroughly in an ice bath and treated with 500 ml. of ice water. The produce was taken up in ether, washed with water, dried and solvent evaporated on steam bath. The residue was cooled in an ice bath and treated with 100 ml. 28% ammonium hydroxide. The precipitate was collected on the filter, washed with water and recrystallized from water to give 2,4-disulfamyl-5-methoxyaniline as colorless needles, m.p. 252—253° C.

*Step b*: 2,4-Disulfamyl-5-methoxyaniline (4 g.) was dissolved in 100 ml. of hot 98—100% formic acid and heated on the steam bath for 90 minutes. After removal of 50 ml. of solvent by distillation, the reaction mixture was cooled, diluted with water and the product collected on the filter and washed with water. Crystallization from dilute alcohol afforded 6-methoxy-7-sulfamyl-1,2,4 -benzothiadiazine-1,1-dioxide as colorless needles m.p. 309—310°C. (dec.).

EXAMPLE 5.

6 - Chloro - 3 - Methyl - 7 - Sulfamyl - 1,2,4 -Benzothiadiazine- 1,1 - Dioxide

A solution of 5 g. of 5-chloroaniline-2,4-

disulfonyl chloride in 15 ml. of acetic anhydride was allowed to stand at room temperature for 45 minutes. After cooling, the crystalline product was collected, treated with 50 ml. of 10% alcoholic ammonia and evaporated to dryness on the steam bath. The residue then was heated at 200° C. for 2 hours, cooled and recrystallized from dilute alcohol to give 6-chloro-3-methyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide as colorless needles, m.p. 332—333° C. (dec.).

EXAMPLE 6.

6 - Chloro - 3 - Phenyl - 7 - Sulfamyl - 1,2,4-Benzothiadiazine - 1,1 - Dioxide

*Step a*: A solution of 6.6 g. of 5-chloroaniline-2,4-disulfonyl chloride, prepared as described in Example 1, step *a*, of Specification No. 37102/58 (Serial No. 826,923) in 10 ml. of benzoyl chloride was allowed to stand at room temperature for 17 hours. The crystalline product was collected, washed with a small amount of benzene and crystallized from benzene-hexane to give N-benzoyl-5-chloroaniline-2,4-disulfonyl chloride as colorless needles, m.p. 171—173° C. (dec.).

*Step b*: N - benzoyl - 5 - chloroaniline-2,4-disulfonyl chloride (7.4 g.) was added to excess liquid ammonia (50—75 ml.) and allowed to evaporate to dryness at room temperature. The residue, which can be crystallized from dilute alcohol to afford N-benzoyl-5-chloro-2,4-disulfamylaniline, m.p. 266° C. (dec.), was heated at 200° C. for 2 hours, cooled and dissolved in 50 ml. of 5% aqueous sodium hydroxide and filtered. After acidification of the filtrate with dilute hydrochloric acid, the product was collected, washed with water and recrystallized from dimethylformamide-water mixture. 6 - Chloro - 3 - phenyl-7-sulfamyl-1,2,4 -benzothiadiazine-1,1-dioxide was obtained as colorless flakes, m.p. greater than 350° C.

EXAMPLE 7.

6 - Chloro - 3 - Propyl - 7 - Sulfamyl - 1,2,4-Benzothiadiazine-1,1-Dioxide.

*Step a*: A solution of 5.4 g. of 5-chloroaniline-2,4-disulfonyl chloride, prepared as described in Example 1, step *a*, of Specification No. 37102/58 (Serial No. 826,923) in a mixture of 10 ml. of butyric anhydride and 10 ml. of benzene was allowed to stand at room temperature for 1 hour. After cooling in an ice bath, the crystalline product was collected and crystallized from benzene-hexane to give N-butyryl-5-chloroaniline-2,4-disulfonyl chloride as colorless needles, m.p. 121—122° C.

*Step b*: N - Butyryl - 5 - chloroaniline-2,4-disulfonyl chloride (9.9 g.) was added portionwise to excess liquid ammonia (100 ml.) and allowed to evaporate to dryness at room temperature. The residue was dissolved in water and the solution acidified with dilute hydrochloric acid. The precipitate was collected and crystallized from dilute alcohol to give 6 - chloro - 3 - propyl - 7 - sulfamyl - 1,2,4-benzothiadiazine-1,1-dioxide as colorless needles, m.p. 302.5—303.5° C.

EXAMPLE 8.

3 - Amyl - 6 - Chloro - 7 - Sulfamyl - 1,2,4-Benzothiadiazine-1,1-Dioxide

*Step a*: 5 - Chloroaniline - 2,4 - disulfonyl chloride (5 g.), prepared as described in Example 1, step *a*, of Specification No. 37102/58 (Serial No. 826,923) was dissolved in 10 ml. of *n*-caproic anhydride by warming gently on the steam bath and allowed to stand at room temperature for 2 hours. The crystalline product was collected and recrystallized from hexane to give N-caproyl-5-chloroaniline-2,4-disulfonyl chloride as colorless needles, m.p. 91—93° C.

*Step b*: A solution of 5.2 g. of N-caproyl-5-chloroaniline-2,4-disulfonyl chloride in 25 ml. of concentrated ammonium hydroxide was heated on the steam bath for 90 minutes, cooled and acidified with dilute hydrochloric acid. The precipitate was collected and crystallized from dilute alcohol to give 3-amyl-6-chloro-7-sulfamyl-1,2,4 -benzothiadiazine - 1,1 - dioxide as colorless plates, m.p. 269—270° C.

EXAMPLE 9.

6 - Chloro - 4 - Methyl - 7 - Sulfamyl - 1,2,4-Benzothiadiazine-1,1-Dioxide

*Step a*: By replacing the *m*-chloroaniline employed in Example 1, step *a*, of Specification No. 37102/58 (Serial No. 826,923) by an equimolecular quantity of N-methyl-*m*-chloroaniline and then following the same procedures described in steps *a* and *b* of Example 1, of Specification No. 37102/58 (Serial No. 826,923) there was obtained 6-chloro-4-methyl - 7 - sulfamyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

EXAMPLE 10.

6 - Amino - 7 - Sulfamyl - 1,2,4 -Benzothiadiazine - 1,1 - Dioxide

6 - Bromo - 7 - sulfamyl - 1,2,4 -benzothiadiazine-1,1-dioxide (0.5 mole), obtained as described in Example 2 of Specification No. 37102/58) (Serial No. 826,923), was placed in a bomb with an excess of alcoholic ammonia and heated at 175° C. for two hours yielding 6-amino-7-sulfamyl-1,2,4 -benzothiadiazine-1,1-dioxide.

EXAMPLE 11.

3 - Benzyl - 6 - Fluoro - 7 - Sulfamyl - 1,2,4-Benzothiadiazine-~~1,1, Dioxide~~

*Step a*: By replacing the *m*-chloroaniline in Example 1, step *a*, of Specification No. 37102/58 (Serial No. 826,923) by an equimolecular quantity of *m*-fluoroaniline and following substantially the same procedure described in step *a* of Example 1 of Specification No. 37102/58 (Serial No. 826,923) for the preparation of 5-chloroaniline-2,4-disulfonyl chloride, 5-fluoroaniline-2,4-disulfonyl chloride was prepared.

*Step b*: 5 - Fluoroaniline - 2,4 - disulfonyl chloride was dissolved in phenylacetyl chloride and allowed to stand at room temperature for

17 hours. The product was collected and washed with benzene to give N-phenylacetyl-5-fluoroaniline-2,4-disulfonyl chloride.

*Step c*: N - Phenylacetyl - 5 - fluoroaniline-2,4-disulfonyl chloride was added to excess liquid ammonia and allowed to evaporate to dryness at room temperature. The residue was heated at 200° C. for 3 hours, cooled and the residue crystallised from dilute alcohol to give 3-benzyl-6-fluoro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide.

EXAMPLE 12.

2 - Methyl - 7 - Sulfamyl - 1,2,4-Benzothiadiazine-1,1-Dioxide

*Step a*: A mixture of 10 g. of *o*-aminobenzenesulfonmethylamide and 25 ml. of ethyl orthoformate was heated at 125—135° C. for 30 minutes. Solvent was then removed by distillation *in vacuo* and the residue crystallized from alcohol to give 2-methyl-1,2,4-benzothiadiazine-1,1-dioxide.

*Step b*: 2 - Methyl - 1,2,4 - benzothiadiazine-1,1-dioxide was treated with chlorosulfonic acid and heated on the steam bath for 2 hours, cooled and poured onto ice. Treatment of the product with 28% ammonium hydroxide gave 2-methyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide.

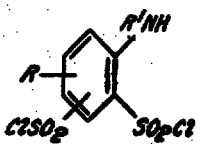
EXAMPLE 13.

6 - Nitro - 7 - Sulfamyl - 1,2,4 - Benzothiadiazine-1,1-dioxide

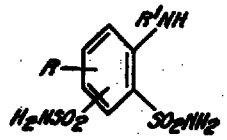
By carrying out the procedure described in Example 1, of Specification No. 37102/58 (Serial No. 826,923) except that the 0.5 mole of *m*-chloroaniline used in that Example is replaced by 69 g. (0.5 mole) of *m*-nitroaniline, 6 - nitro - 7 - sulfamyl - 1,2,4 - benzothiadiazine-1,1-dioxide may be obtained as colorless needles m.p. 338—339° C. with decomposition.

It should be noted that the compounds 6-chloro - 7 - sulfamyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide, 6 - bromo - 7 - sulfamyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide, and 6 - methyl - 7 - sulfamyl - 1,2,4-benzothiadiazine-1,1-dioxide and processes for preparing them are claimed in the specification of our copending Application No. 37102/58 (Serial No. 826,923), which has been divided from the present application. In this specification there are also described and claimed a method of preparing the sodium salt of 6-chloro-7-sulfamyl - 1,2,4 - benzothiadiazine-1,1-dioxide and a method of making a tablet containing 6 - chloro - 7 - sulfamyl - 1,2,4-benzothiadiazine-1,1-dioxide. It will be apparent to those skilled in the art that salts in accordance with the present invention and tablets containing compounds in accordance with the present invention may be made by analogous methods.

It should also be noted that compounds having the general formula



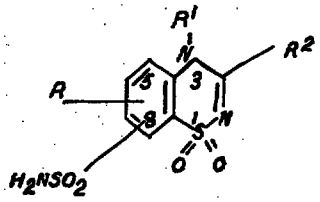
in which R is a halogen atom or a $C_{1-5}$ alkoxy or a nitro group; and $R^1$ is a hydrogen atom, a $C_{1-5}$ alkyl group, or a $C_{1-8}$ carboxylic acyl group, and processes for preparing them, are claimed in the specification of our copending Application No. 21905/58 (Serial No. 826,922), which has been divided from the present Application; and that compounds having the general formula



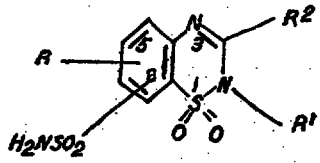
in which R is a halogen atom or a nitro, amino, or $C_{1-5}$ alkoxy radical and $R^1$ is a hydrogen atom, a $C_{1-5}$ alkyl group or a $C_{1-8}$ carboxylic acyl group and processes for preparing them are claimed in the specification of our copending Application No. 38885/58 (Serial No. 826,924), which has been divided from the present Application.

WHAT WE CLAIM IS:—

1. Thiadiazine compounds having one of the general structural formulae:

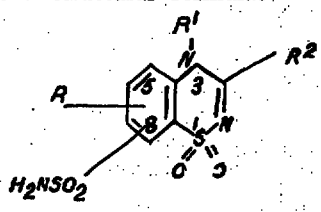


and



in which R is a hydrogen or halogen atom or a $C_{1-5}$ alkyl or $C_{1-5}$ alkoxy, nitro or amino radical; $R^1$ is a hydrogen atom or $C_{1-5}$ alkyl radical; and $R^2$ is a hydrogen atom, a $C_{1-5}$ alkyl group, or a phenyl, benzyl or styryl radical.

2. Thiadiazine compounds having one of the general structural formulae



and

17 hours. The product was collected and washed with benzene to give N-phenylacetyl-5-fluoroaniline-2,4-disulfonyl chloride.

*Step c*: N - Phenylacetyl - 5 - fluoroaniline-2,4-disulfonyl chloride was added to excess liquid ammonia and allowed to evaporate to dryness at room temperature. The residue was heated at 200° C. for 3 hours, cooled and the residue crystallised from dilute alcohol to give 3-benzyl-6-fluoro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide.

EXAMPLE 12.

2 - Methyl - 7 - Sulfamyl - 1,2,4-Benzothiadiazine-1,1-Dioxide

*Step a*: A mixture of 10 g. of *o*-aminobenzenesulfonmethylamide and 25 ml. of ethyl orthoformate was heated at 125—135° C. for 30 minutes. Solvent was then removed by distillation *in vacuo* and the residue crystallized from alcohol to give 2-methyl-1,2,4-benzothiadiazine-1,1-dioxide.

*Step b*: 2 - Methyl - 1,2,4 - benzothiadiazine-1,1-dioxide was treated with chlorosulfonic acid and heated on the steam bath for 2 hours, cooled and poured onto ice. Treatment of the product with 28% ammonium hydroxide gave 2-methyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide.

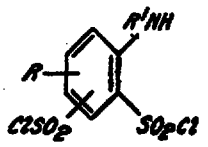
EXAMPLE 13.

6 - Nitro - 7 - Sulfamyl - 1,2,4 - Benzothiadiazine-1,1-dioxide

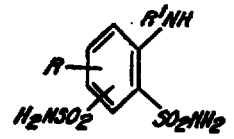
By carrying out the procedure described in Example 1, of Specification No. 37102/58 (Serial No. 826,923) except that the 0.5 mole of *m*-chloroaniline used in that Example is replaced by 69 g. (0.5 mole) of *m*-nitroaniline, 6 - nitro - 7 - sulfamyl - 1,2,4 - benzothiadiazine-1,1-dioxide may be obtained as colorless needles m.p. 338—339° C. with decomposition.

It should be noted that the compounds 6-chloro - 7 - sulfamyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide, 6 - bromo - 7 - sulfamyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide, and 6 - methyl - 7 - sulfamyl - 1,2,4-benzothiadiazine-1,1-dioxide and processes for preparing them are claimed in the specification of our copending Application No. 37102/58 (Serial No. 826,923), which has been divided from the present application. In this specification there are also described and claimed a method of preparing the sodium salt of 6-chloro-7-sulfamyl - 1,2,4 - benzothiadiazine-1,1-dioxide and a method of making a tablet containing 6 - chloro - 7 - sulfamyl - 1,2,4-benzothiadiazine-1,1-dioxide. It will be apparent to those skilled in the art that salts in accordance with the present invention and tablets containing compounds in accordance with the present invention may be made by analogous methods.

It should also be noted that compounds having the general formula



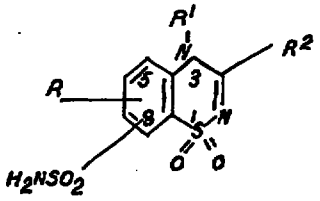
in which R is a halogen atom or a $C_{1-5}$ alkoxy or a nitro group; and $R^1$ is a hydrogen atom, a $C_{1-5}$ alkyl group, or a $C_{1-8}$ carboxylic acyl group, and processes for preparing them, are claimed in the specification of our copending Application No. 21905/58 (Serial No. 826,922), which has been divided from the present Application; and that compounds having the general formula



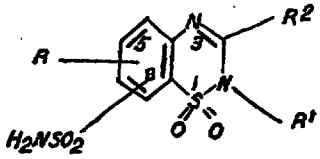
in which R is a halogen atom or a nitro, amino, or $C_{1-5}$ alkoxy radical and $R^1$ is a hydrogen atom, a $C_{1-5}$ alkyl group or a $C_{1-8}$ carboxylic acyl group and processes for preparing them are claimed in the specification of our copending Application No. 38885/58 (Serial No. 826,924), which has been divided from the present Application.

WHAT WE CLAIM IS:—

1. Thiadiazine compounds having one of the general structural formulae:

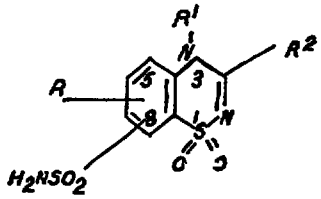


and

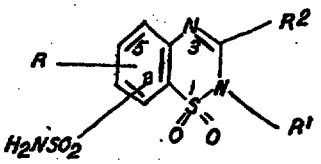


in which R is a hydrogen or halogen atom or a $C_{1-5}$ alkyl or $C_{1-5}$ alkoxy, nitro or amino radical; $R^1$ is a hydrogen atom or $C_{1-5}$ alkyl radical; and $R^2$ is a hydrogen atom, a $C_{1-5}$ alkyl group, or a phenyl, benzyl or styryl radical.

2. Thiadiazine compounds having one of the general structural formulae

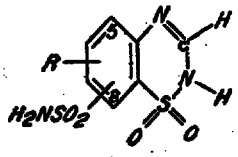


and

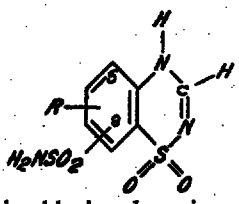


in which R and $R^1$ are as defined in Claim 1 and $R^2$ is an aryl, aralkyl, or aralkenyl group containing one benzene ring that is substituted by a $C_{1-5}$ alkyl or $C_{1-5}$ alkoxy group or halogen atom, or is an unsubstituted aralkyl or aralkenyl group containing one benzene ring.

3. Thiadiazine compounds having the general structural formulae



and



in which R is chlorine, bromine or fluorine.

4. 6 - Chloro - 3 - methyl - 7 - sulfamyl-1,2,4 - benzothiadiazine - 1,1 - dioxide.

5. 6 - Chloro - 3 - propyl - 7 - sulfamyl-1,2,4 - benzothiadiazine - 1,1 - dioxide.

6. 7 - sulfamyl - 1,2,4 - benzothiadiazine-1,1 - dioxide.

7. 7 - chloro - 6 - sulfamyl - 1,2,4 -benzothiadiazine - 1,1 - dioxide.

8. 6 - sulfamyl - 1,2;4 - benzothiadiazine-1,1-dioxide.

9. 6 - methoxy - 7 - sulfamyl - 1,2,4-benzothiadiazine- 1,1 - dioxide.

10. 6 - chloro - 3 - phenyl - 7 - sulfamyl-1,2,4 - benzothiadiazine - 1,1 - dioxide.

11. 6 - chloro - 3 - amyl - 7 - sulfamyl-1,2,4 - benzothiadiazine - 1,1 - dioxide.

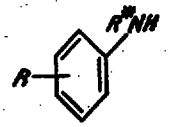
12. 6 - chloro - 4 - methyl - 7 - sulfamyl-1,2,4 - benzothiadiazine - 1,1 - dioxide.

13. 6 - amino - 7 - sulfamyl - 1,2,4-benzothiadiazine - 1,1 - dioxide.

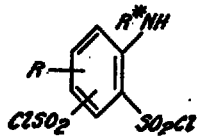
14. 6 - fluoro - 3 - benzyl - 7 - sulfamyl-1,2,4 - benzothiadiazine - 1,1 - dioxide.

15. 2 - methyl - 7 - sulfamyl - 1,2,4-benzothiadiazine-1,1-dioxide.

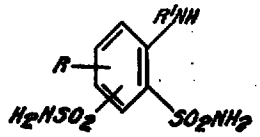
16. The process that comprises reacting an aniline derivative having the general formula



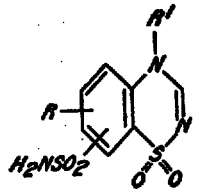
in which R is as defined in Claim 1 and R* is a hydrogen atom, a $C_{1-5}$ alkyl group, or an acetyl group, with chlorosulfonic acid in the presence of an alkali-metal halide to produce a disulfonyl chloride having the general formula



reacting the latter with ammonia to produce a diamide having the general formula



and heating this diamide with formic acid or ethyl orthoformate to produce a benzothiadiazine-1,1-dioxide compound having the general formula



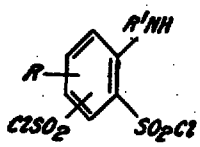
R and $R^1$ being as defined in Claim 1.

17. A process as claimed in Claim 16, in which the alkali-metal halide is sodium chloride.

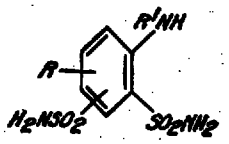
18. A process as claimed in Claim 16 or 17, in which the chlorosulfonation step is carried out by adding the aniline derivative to chlorosulfonic acid dropwise and subsequently adding the alkali-metal halide in small portions and then heating the mixture at 100—200° C.

19. A modification of the process claimed in any one of Claims 16—18, in which R* represents a $C_{2-6}$ alkanoyl group.

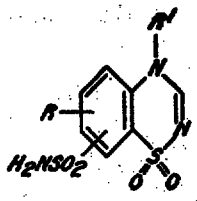
20. The process that comprises reacting an aniline disulfonyl chloride having the general formula



with ammonia to produce a diamide having the general formula



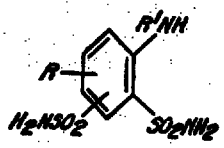
and heating this diamide with formic acid or ethyl orthoformate to produce a benzothiadiazine-1,1-dioxide compound having the general formula



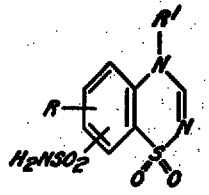
R and $R^1$ being as defined in Claim 1.

21. A process as claimed in any one of Claims 16—20, in which the reaction of the aniline disulfonyl chloride with ammonia is carried out using aqueous or alcoholic ammonium hydroxide.

22. The process that comprises heating a disulfamyl aniline having the general formula



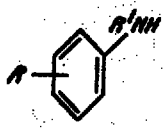
with formic acid or ethyl orthoformate to produce a benzothiadiazine-1,1-dioxide compound having the general formula



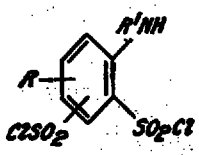
R and $R^1$ being as defined in Claim 1.

23. A process as claimed in any one of Claims 16—22, in which the reaction with formic acid or ethyl orthoformate is carried out at a temperature of 100 to 150° C.

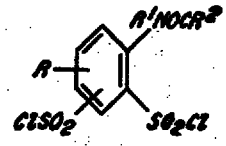
24. The process that comprises reacting an aniline derivative having the general formula



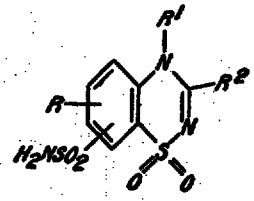
in which R and $R^1$ are as defined in Claim 1 with chlorosulfonic acid in the presence of an alkali-metal halide to produce a disulfonyl chloride having the general formula



reacting the latter with an acid chloride or acid anhydride derived from an alkanoic acid containing not more than six carbon atoms or from a mononuclear aryl carboxylic acid to produce an N-acyl derivative having the general formula



reacting this N-acyl derivative with ammonia, and heating the resulting N-acyldisulfamyl compound to form a benzothiadiazine-1,1-dioxide having the general formula



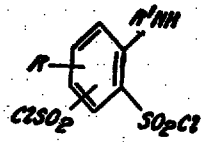
in which R and $R^1$ are as defined in Claim 1 and $R^2$ is a hydrogen atom or a $C_{1-5}$ alkyl or a mononuclear aryl group.

25. A process as claimed in Claim 24, in which the alkali-metal halide is sodium chloride.

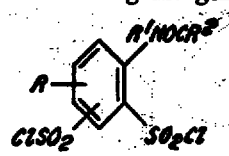
26. A process as claimed in Claim 24 or 25, in which the chlorosulphonation step is carried out by adding the aniline derivative to chlorosulfonic acid dropwise and subsequently adding the alkali-metal halide in small portions and then heating the mixture at 100—200° C.

27. A modification of the process claimed in any one of Claims 24—26 in which the acid chloride or anhydride has the general formula $R^2COCl$ or $(R^2CO)_2O$, where $R^2$ is an aralkyl or aralkenyl group containing one benzene ring which may or may not have a $C_{1-5}$ alkyl, $C_{1-5}$ alkoxy, or halogen substituent, or is a mononuclear aryl group containing a $C_{1-5}$ alkyl, $C_{1-5}$ alkoxy, or halogen substituent in the benzene ring.

28. The process that comprises reacting an aniline disulfonyl chloride having the general formula

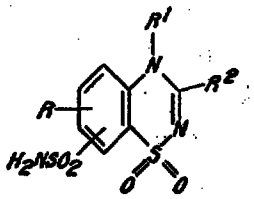


with an acid chloride or acid anhydride derived from an alkanoic acid containing not more than six carbon atoms or from a mononuclear aryl carboxylic acid to produce an N-acyl derivative having the general formula



reacting this N-acyl derivative with ammonia, and heating the resulting N-acyldisulfamyl compound to form a benzothiadiazine-1,1-dioxide having the general formula

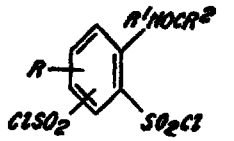
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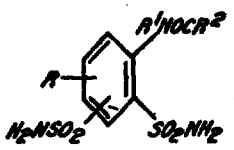
in which R and $R^1$ are as defined in Claim 1 and $R^2$ is as defined in Claim 24.

29. A modification of the process claimed in Claim 28, in which the acid chloride or anhydride has the general formula $R^2COCl$ or $(R^2CO)_2O$, where $R^2$ is an aralkyl or aralkenyl group containing one benzene ring which may or may not have a $C_{1-5}$ alkyl, $C_{1-5}$ alkoxy, or halogen substituent, or is a mononuclear aryl group containing a $C_{1-5}$ alkyl, $C_{1-5}$ alkoxy, or halogen substituent in the benzene ring.

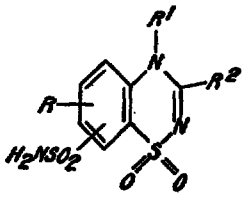
30. The process that comprises reacting a compound having the general formula



in which R and $R^1$ are as defined in Claim 1 and $R^2$ is defined as in Claim 24 or 27, with ammonia to form the corresponding compound having the general formula



and heating the latter to cyclize it and produce a compound of general formula

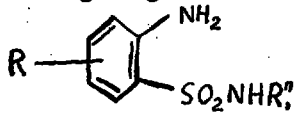


31. A modification of the process claimed in Claim 30, in which $R^2$ in the starting material is an aralkyl or aralkenyl group containing one benzene ring which may or may not have a $C_{1-5}$ alkyl, $C_{1-5}$ alkoxy, or halogen substituent, or is a mononuclear aryl group containing a $C_{1-5}$ alkyl, $C_{1-5}$ alkoxy, or halogen substituent in the benzene ring.

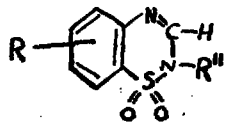
32. A process as claimed in any one of Claims 24—27, in which the reaction with ammonia is carried out using aqueous or alcoholic ammonium hydroxide.

33. A process as claimed in any one of Claims 24—32 in which the final step of heating the N-acyldisulfamyl compound to cyclize it is carried out at a temperature of 150°—250° C.

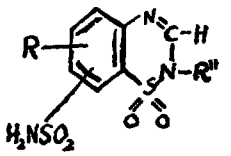
34. The process that comprises reacting a compound having the general formula



where $R^{11}$ is a $C_{1-5}$ alkyl radical and R is as defined in Claim 1, with formic acid or ethyl orthoformate to produce a benzothiadiazine-1,1-dioxide compound having the general formula



and treating the latter with chlorosulphonic acid and then ammonia to produce a benzothiadiazine-1,1-dioxide compound having the general formula



35. A process as claimed in Claim 34, which comprises heating *o*-aminobenzenesulfon-methylamide with ethyl orthoformate to produce 2 - methyl - 1,2,4 - benzothiadiazine-1,1-dioxide, converting this to 2-methyl-1,2,4-benzothiadiazine - 1,1 - dioxide 7 - sulfonyl chloride by heating it with chlorosulfonic acid, and treating the 7-sulfonyl chloride with ammonia to produce 2-methyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide.

36. The process that comprises heating 6-bromo - 7 - sulfamyl - 1,2,4 - benzothiadiazine-1,1-dioxide with an excess of ammonia under pressure to produce 6-amino-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide.

37. A process as claimed in Claim 16, substantially as described in any one of Examples 1, 2, 4 and 9 hereinbefore.

38. A process as claimed in Claim 22, substantially as described in Example 3 hereinbefore.

39. A process as claimed in Claim 28, substantially as described in any one of Examples 5, 6, 7, 8 and 11 hereinbefore.

40. A process as claimed in Claim 35, substantially as described in Example 10 hereinbefore.

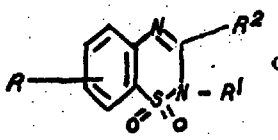
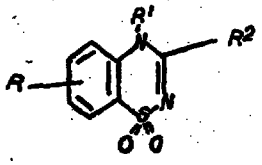
41. A process as claimed in Claim 34, substantially as described in Example 12 hereinbefore.

42. A sodium or potassium salt of a compound as claimed in any one of Claims 1 and 3—15.

43. A sodium or potassium salt of a compound as claimed in Claim 2.

44. A compound having the general formula

* C L M S *


or


in which R and $R^1$ and $R^2$ are as defined in Claim 1, when prepared by a process as claimed in any one of Claims 16—25, 27, and 29—40, or an obvious chemical equivalent or such a process.

45. A pharmaceutical composition containing, as active ingredient, a compound as claimed in any one of Claims 1, 3—15, and 42—44, together with a solid or liquid pharmaceutical diluent.

46. A composition as claimed in Claim 45, in the form of a tablet.

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