PATENT SPECIFICATION

NO DRAWINGS

826,924

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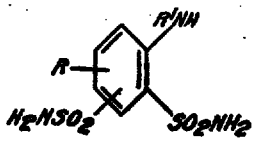
COMPLETE SPECIFICATION

Sulphonamides

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:—

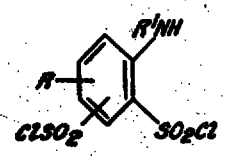
This invention is concerned with novel compounds having diuretic, including natriuretic, properties.

In short, this invention provides substituted disulphamoyl aniline compound having the general formula:



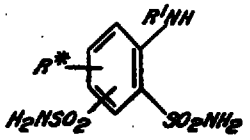
in which R is a halogen, such as chlorine, bromine, or fluorine, or a C_{1-5} alkoxy, nitro or amino group, and R^1 is a hydrogen atom, a C_{1-5} alkyl radical or a C_{1-8} carboxylic acyl radical such as C_{1-8} alkanoyl.

In accordance with the invention, the novel compounds are produced by the reaction of an aniline disulphonyl chloride having the general formula:

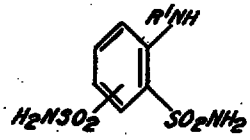


with ammonia. The starting aniline disulphonyl chlorides are claimed in and may be prepared by methods described and claimed in the specification of our copending application No. 21905/58 (Serial No. 826,922). They may be treated with any convenient form of ammonia including aqueous ammonium hydroxide, alcoholic ammonia, and liquid ammonia, or by bubbling gaseous ammonia through a solution of the disulphonyl chloride compound in an organic solvent.

Also in accordance with the present invention those of the novel compounds having the formula



in which R^1 is a hydrogen atom or C_{1-5} alkyl radical and R* is a halogen atom, may be hydrogenated in the presence of a base to produce a compound of formula



This hydrogenation step is preferably carried out in the presence of a palladium-on-charcoal catalyst.

The new compounds are also useful as starting materials in the process described and claimed in the Specification of our copending application No. 13921/57 (Serial No. 826,921), which is directed to the preparation of certain substituted benzothiadiazine-1,1-dioxide compounds that also have diuretic properties.

The following examples illustrate more fully the preparation of the new compounds.

EXAMPLE 1.

5-chloroaniline - 2,4 - disulphonyl chloride, obtained by the process of Example 1 of Specification No. 21905/58 (Serial No. 826,922), 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.

EXAMPLE 2.

6 - chloroacetanilide - 2,4 - disulphonyl chloride, obtained by the process of Example 2, of Specification No. 21905/58 (Serial No. 826,922), was cooled in an ice bath and treated with 50 ml. of 28% ammonium hydroxide. The ammoniacal solution was heated on the steam bath for 1 hour and cooled, and the product was collected on the filter. Crystallization from the dilute alcohol gave 6-chloro-2,4-disulphamoylaniline as colourless needles, m.p. 242—244° C.

EXAMPLE 3.

m-Bromoaniline (86 g., 0.5 mole) was added dropwise over a period of 1 hour to 375 ml. of chlorosulphonic 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 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, viz., 5 bromoaniline - 2,4 - disulphonyl chloride, 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 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. It should be noted that the preparation of the 5-bromoaniline-2,4-disulphonyl chloride is the same as that set forth in Example 3 of Specification No. 21905/58 (Serial No. 826,922).

EXAMPLE 4.

5 - methoxyaniline - 2,4 - disulphonyl chloride, obtained by the process of Example 4 of Specification No. 21905/58 (Serial No. 826,922), 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-disulphamoyl-5-methoxyaniline as colourless needles, m.p. 252—253° C.

EXAMPLE 5.

By replacing the 5 - chloroaniline - 2,4-disulphonyl chloride used in Example 1 with an equimolecular quantity of N-methyl-5-chloroaniline-2,4-disulphonyl chloride, obtained by the process of Example 5 of Specification No. 21905/58 (Serial No. 826,922), and carrying out substantially the same procedure as that described in Example 1, there was obtained 2,4-disulphamoyl-N-methyl-5-chloroaniline.

EXAMPLE 6.

By replacing the 5 - chloroaniline - 2,4-disulphonyl chloride used in Example 1 with an equimolar quantity of 5-fluoroaniline-2,4-disulphonyl chloride, and carrying out substantially the same procedure as that described in Example 1, there was obtained 5-chloro-2,4-disulphamoylaniline.

EXAMPLE 7.

A solution of 5.72 g. (0.02 mole) of 6-chloro-2,4-disulphamoylaniline, obtained as in Example 2 above, 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-disulphamoylaniline as colourless needles, m.p. 230—231.5° C.

EXAMPLE 8.

A solution of 6.6 g. of 5-chloroaniline-2,4-disulphonyl chloride, prepared as described in Example 1 of Specification No. 21905/58 (Serial No. 826,922), 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 - disulphonyl chloride as colourless needles, m.p. 171—173° C. (dec.).

7.4 g. of N - benzoyl - 5 - chloroaniline-2,4-disulphonyl chloride was added to an excess of liquid ammonia (50—75 ml.) and allowed to evaporate to dryness at room temperature. The residue was crystallized from dilute alcohol to afford N-benzoyl-5-chloro-2,4-disulphamoylaniline, m.p. 266° C. (dec.).

EXAMPLE 9.

By replacing the *m*-bromoaniline used in Example 3 by an equimolecular quantity of 5-amino-2-chlorobenzenesulphonic acid, and following substantially the same procedure described in Example 3, 4-chloro-2,5-disulphamoylaniline was obtained as colourless needles, m.p. 289—290° C.

EXAMPLE 10.

5.72 g. (0.02 mole) of 4-chloro-2,5-disulphamoylaniline, prepared by the method described in Example 9, was hydrogenated in the presence of 5% palladium-on-charcoal catalyst by substantially the same procedure as that described in Example 7 to give 2,5-disulphamoylaniline as colourless needles, m.p. 216—217° C.

WHAT WE CLAIM IS:—

1. Compounds having the general formula:

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.

EXAMPLE 2.

6 - chloroacetanilide - 2,4 - disulphonyl chloride, obtained by the process of Example 2, of Specification No. 21905/58 (Serial No. 826,922), was cooled in an ice bath and treated with 50 ml. of 28% ammonium hydroxide. The ammoniacal solution was heated on the steam bath for 1 hour and cooled, and the product was collected on the filter. Crystallization from the dilute alcohol gave 6-chloro-2,4-disulphamoylaniline as colourless needles, m.p. 242—244° C.

EXAMPLE 3.

m-Bromoaniline (86 g., 0.5 mole) was added dropwise over a period of 1 hour to 375 ml. of chlorosulphonic 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 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, viz., 5 bromoaniline - 2,4 - disulphonyl chloride, 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 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. It should be noted that the preparation of the 5-bromoaniline-2,4-disulphonyl chloride is the same as that set forth in Example 3 of Specification No. 21905/58 (Serial No. 826,922).

EXAMPLE 4.

5 - methoxyaniline - 2,4 - disulphonyl chloride, obtained by the process of Example 4 of Specification No. 21905/58 (Serial No. 826,922), 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-disulphamoyl-5-methoxyaniline as colourless needles, m.p. 252—253° C.

EXAMPLE 5.

By replacing the 5 - chloroaniline - 2,4-disulphonyl chloride used in Example 1 with an equimolecular quantity of N-methyl-5-chloroaniline-2,4-disulphonyl chloride, obtained by the process of Example 5 of Specification No. 21905/58 (Serial No. 826,922), and carrying out substantially the same procedure as that described in Example 1, there was obtained 2,4-disulphamoyl-N-methyl-5-chloroaniline.

EXAMPLE 6.

By replacing the 5 - chloroaniline - 2,4-disulphonyl chloride used in Example 1 with an equimolar quantity of 5-fluoroaniline-2,4-disulphonyl chloride, and carrying out substantially the same procedure as that described in Example 1, there was obtained 5-chloro-2,4-disulphamoylaniline.

EXAMPLE 7.

A solution of 5.72 g. (0.02 mole) of 6-chloro-2,4-disulphamoylaniline, obtained as in Example 2 above, 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-disulphamoylaniline as colourless needles, m.p. 230—231.5° C.

EXAMPLE 8.

A solution of 6.6 g. of 5-chloroaniline-2,4-disulphonyl chloride, prepared as described in Example 1 of Specification No. 21905/58 (Serial No. 826,922), 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 - disulphonyl chloride as colourless needles, m.p. 171—173° C. (dec.).

7.4 g. of N - benzoyl - 5 - chloroaniline-2,4-disulphonyl chloride was added to an excess of liquid ammonia (50—75 ml.) and allowed to evaporate to dryness at room temperature. The residue was crystallized from dilute alcohol to afford N-benzoyl-5-chloro-2,4-disulphamoylaniline, m.p. 266° C. (dec.).

EXAMPLE 9.

By replacing the *m*-bromoaniline used in Example 3 by an equimolecular quantity of 5-amino-2-chlorobenzenesulphonic acid, and following substantially the same procedure described in Example 3, 4-chloro-2,5-disulphamoylaniline was obtained as colourless needles, m.p. 289—290° C.

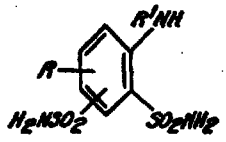
EXAMPLE 10.

5.72 g. (0.02 mole) of 4-chloro-2,5-disulphamoylaniline, prepared by the method described in Example 9, was hydrogenated in the presence of 5% palladium-on-charcoal catalyst by substantially the same procedure as that described in Example 7 to give 2,5-disulphamoylaniline as colourless needles, m.p. 216—217° C.

WHAT WE CLAIM IS:—

1. Compounds having the general formula:

* C L M S *



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 radical, or a C_{1-8} carboxylic acyl radical.

2. 5-chloro-2,4-disulphamoylaniline.

3. 6-chloro-2,4-disulphamoylaniline.

4. 5-bromo-2,4-disulphamoylaniline.

5. 5-methoxy-2,4-disulphamoylaniline.

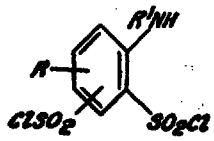
6. N-methyl-5-chloro-2,4-disulphamoylaniline.

7. 5-fluoro-2,4-disulphamoylaniline.

8. N-benzoyl-5-chloro-2,4-disulphamoylaniline.

9. 4-chloro-2,5-disulphamoylaniline.

10. The process which comprises reacting a compound having the general formula:



in which R and R^1 are as defined in Claim 1, with ammonia to produce a compound as claimed in Claim 1.

11. A process as claimed in Claim 10, in which the ammonia is used in aqueous solution.

12. A process as claimed in Claim 10, in which the ammonia is used in alcoholic solution.

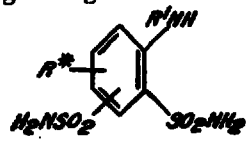
13. A process as claimed in Claim 10, in which liquid ammonia is used.

14. A process as claimed in Claim 10, substantially as described in any one of Examples 1—6, 8 and 9 hereinbefore.

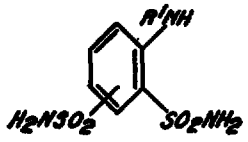
15. A process as claimed in any one of Claims 10—14 including the step of preparing the starting material by a process described and claimed in the Specification of our copending Application No. 21905/58 (Serial No. 826,922).

16. A process as claimed in any one of Claims 10—15, as applied to the preparation of any one of the compounds claimed in Claims 2—9.

17. The process that comprises hydrogenating, in the presence of a base, a compound having the general formula:



in which R^1 is a hydrogen atom or C_{1-5} alkyl radical and R* is a halogen atom, to produce a compound having the general formula:

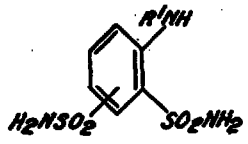


in which R^1 is as defined above.

18. A process as claimed in Claim 17, in which the hydrogenation is carried out in the presence of a palladium-on-charcoal catalyst.

19. A process as claimed in Claim 17, substantially as described in Example 7 or 10 hereinbefore.

20. A compound having the general formula:



when prepared by a process in any one of Claims 17—19, or an obvious chemical equivalent of such a process.

21. A compound as claimed in Claim 1, when prepared by a process as claimed in any one of Claims 10—16, or an obvious chemical equivalent of such a process.

D. YOUNG & CO.,
10, Staple Inn,
London, W.C.1,
Agents for the Applicants.

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* C L M S *