PATENT SPECIFICATION

NO DRAWINGS

826,922

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International Classification:—C07c.

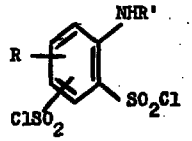
COMPLETE SPECIFICATION

Aromatic Sulphonyl Chlorides

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:—

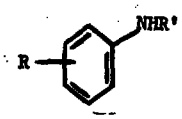
This invention is concerned with aromatic sulphonyl chlorides that are intermediates in a synthesis of certain new benzothiadiazine derivatives. These derivatives, which have valuable diuretic (including natriuretic) properties, together with a method of synthesizing them, are claimed in the specification of our co-pending application No. 13921/57 (Serial No. 826,921), and certain particularly preferred derivatives are claimed in the specification of our co-pending application No. 37102/58 (Serial No. 826,923).

The present invention provides compounds having the general formula:



in which R is a halogen atom such as chlorine, bromine, or fluorine, ~~of~~ a C_{1-5} alkoxy or nitro group, and R^1 is a hydrogen atom, a C_{1-5} alkyl group, or a C_{1-6} carboxylic acyl group such as a C_{1-6} alkanoyl group, or a phenylacetyl group.

In accordance with the present invention, the new compounds are prepared by chlorosulphonating a compound of the general formula:



such as *m*-chloroaniline, *m*-bromoaniline, *o*-chloroacetanilide, *m*-anisidine, N-methyl-*m*-chloroaniline, or *m*-fluoroaniline, in the presence of an alkali metal halide, for example, sodium, potassium or lithium chloride. For all practical purposes sodium chloride can be used as it is readily available and cheap, and the reaction proceeds quite smoothly in its presence. As the reaction between these ingredients is quite vigorous, it is preferred to carry it out by adding the aniline derivative to chlorosulphonic acid dropwise, preferably 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 from about 100° to 200° C., preferably in an oil-bath.

The disulphonyl chloride may then be converted in accordance with the invention claimed in Application 13921/57 (Serial No. 826,921), to benzothiadiazine derivatives having natriuretic and/or diuretic properties.

The preparation of the new disulphonyl chlorides in accordance with the present invention is more fully described in the following examples:

EXAMPLE 1

64 g. (0.5 mole) of *m*-chloroaniline was added dropwise with stirring to 375 ml. of chlorosulphonic acid in a 3-liter round-bottom, 3-necked flask cooled in an ice bath. 350 g. of sodium chloride was added portionwise over a period of 1—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 removal of ether on the steam bath, the residual 5-chloroaniline-2,4-disulphonyl chloride was crystallized from benzene-hexane; it melted at 130—132° C.

[Price 3s. 6d.]

EXAMPLE 2

15.2 g. of *o*-chloroacetanilide was added portionwise to 120 ml. chlorosulphonic acid at room temperature followed by portionwise addition of 100 g. of sodium choride 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-disulphonyl chloride, taken up in ether and washed with water and dried over sodium sulphate.

EXAMPLE 3

86 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. 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, viz., 5-bromoaniline-2,4-disulphonyl chloride, was taken up in ether, washed with water, and dried.

EXAMPLE 4

150 ml. of chlorosulphonic acid 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 chlorosulphonic 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 product, viz., 5-methoxyaniline-2,4-disulphonyl chloride, was taken up in ether, washed with water and dried, and the solvent evaporated on steam bath.

EXAMPLE 5

By replacing the *m*-chloroaniline used in Example 1 by an equimolecular quantity of N-methyl-*m*-chloroaniline and then following the same procedure as that described in Example 1, there was obtained N-methyl-5-chloroaniline-2,4-disulphonyl chloride.

EXAMPLE 6

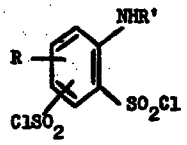
By replacing the *m*-chloroaniline used in Example 1 by an equimolecular quantity of *m*-fluoroaniline and following substantially the same procedure as that described in Example 1 for the preparation of 5-chloroaniline-2,4-disulphonyl chloride, 5-fluoroaniline-2,4-disulphonyl chloride was prepared.

EXAMPLE 7

5-Fluoroaniline-2,4-disulphonyl 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-disulphonyl chloride.

WHAT WE CLAIM IS:—

1. An aminobenzene disulphonyl chloride compound having the formula:



where 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 an acetyl or phenylacetyl group.

2. A compound having the general formula set forth in Claim 1, but in which R^1 is a C_{1-6} carboxylic acyl group.

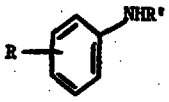
3. 5-Choloroaniline-2,4-disulphonyl chloride.

4. 5-Fluoroaniline-2,4-disulphonyl chloride.

5. N-methyl-5-chloroaniline-2,4-disulphonyl chloride.

6. N-phenylacetyl-5-fluoroaniline-2,4-disulphonyl chloride.

7. The process that comprises chlorosulphonating, in the presence of an alkali-metal halide, an aniline derivative of the general formula

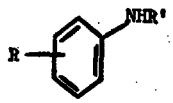


in which R and R^1 are as defined in Claim 1, to produce a compound as claimed in Claim 1.

8. A process as claimed in Claim 7, in which the alkali-metal halide is sodium chloride.

9. A process as claimed in Claim 7 or 8, carried out by adding the aniline derivative to chlorosulphonic acid dropwise and subsequently adding the alkali-metal halide in small portions and then heating the mixture at 100—200° C.

10. A modification of the process claimed in any one of claims 7—9, in which the aniline derivative has the general formula



in which R is as defined in Claim 1 and R^1 is a C_{1-6} carboxylic acyl group.

11. A process as claimed in any one of Claims 7—9, in which the aniline derivative is *m*-chloroaniline.

12. A process as claimed in any one of Claims 7—9, in which the aniline derivative

EXAMPLE 2

15.2 g. of *o*-chloroacetanilide was added portionwise to 120 ml. chlorosulphonic acid at room temperature followed by portionwise addition of 100 g. of sodium choride 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-disulphonyl chloride, taken up in ether and washed with water and dried over sodium sulphate.

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86 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. 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, viz., 5-bromoaniline-2,4-disulphonyl chloride, was taken up in ether, washed with water, and dried.

EXAMPLE 4

150 ml. of chlorosulphonic acid 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 chlorosulphonic 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 product, viz., 5-methoxyaniline-2,4-disulphonyl chloride, was taken up in ether, washed with water and dried, and the solvent evaporated on steam bath.

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EXAMPLE 6

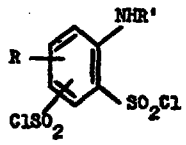
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EXAMPLE 7

5-Fluoroaniline-2,4-disulphonyl 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-disulphonyl chloride.

WHAT WE CLAIM IS:—

1. An aminobenzene disulphonyl chloride compound having the formula:



where 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 an acetyl or phenylacetyl group.

2. A compound having the general formula set forth in Claim 1, but in which R^1 is a C_{1-6} carboxylic acyl group.

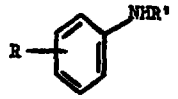
3. 5-Choloroaniline-2,4-disulphonyl chloride.

4. 5-Fluoroaniline-2,4-disulphonyl chloride.

5. N-methyl-5-chloroaniline-2,4-disulphonyl chloride.

6. N-phenylacetyl-5-fluoroaniline-2,4-disulphonyl chloride.

7. The process that comprises chlorosulphonating, in the presence of an alkali-metal halide, an aniline derivative of the general formula

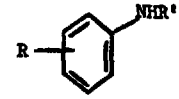


in which R and R^1 are as defined in Claim 1, to produce a compound as claimed in Claim 1.

8. A process as claimed in Claim 7, in which the alkali-metal halide is sodium chloride.

9. A process as claimed in Claim 7 or 8, carried out by adding the aniline derivative to chlorosulphonic acid dropwise and subsequently adding the alkali-metal halide in small portions and then heating the mixture at 100—200° C.

10. A modification of the process claimed in any one of claims 7—9, in which the aniline derivative has the general formula



in which R is as defined in Claim 1 and R^1 is a C_{1-6} carboxylic acyl group.

11. A process as claimed in any one of Claims 7—9, in which the aniline derivative is *m*-chloroaniline.

12. A process as claimed in any one of Claims 7—9, in which the aniline derivative

* C L M S *

is *o*-chloroacetanilide.

13. A process as claimed in any one of Claims 7—9, in which the aniline derivative is *m*-bromoaniline.

14. A process as claimed in any one of Claims 7—9, in which the aniline derivative is *m*-anisidine.

15. A process as claimed in any one of Claims 7—9, in which the aniline derivative is N-methyl-*m*-chloroaniline.

16. A process as claimed in any one of Claims 7—9, in which the aniline derivative is *m*-fluoroaniline.

17. A process as claimed in Claim 7, substantially as described in any one of the foregoing examples.

18. A compound as claimed in Claim 1, whenever prepared by a process as claimed in any one of Claims 7—9 and 11—17 or an obvious chemical equivalent of such a process.

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