[Second Edition.]

AMENDED SPECIFICATION

Reprinted as amended in accordance with the Decision of the Superintending Examiner, acting for the Comptroller-General, dated the twenty-ninth day of April, 1946, under Section 11, of the Patents and Designs Acts, 1907 to 1946.

PATENT SPECIFICATION. 533,495



Convention Dates (Switzerland)	*Corresponding Applications in United Kingdom*	
Jan. 31, 1938:	*No. 3109/39*	*dated Jan. 30, 1939.*
Sept. 16, 1938:	*No. 3110/39*	
Nov. 24, 1938:	*No. 3111/39*	
Dec. 22, 1938.	*No. 3112/39*	

(One Complete Specification Left under Section 91 (2) of the Patents and Designs Acts, 1907 to 1938.)

Specification Accepted: Feb. 14, 1941.

COMPLETE SPECIFICATION

Manufacture of New Benzenesulphonamido-Derivatives

We, SOCIETY OF CHEMICAL INDUSTRY IN BASLE (also known as GESELLSCHAFT FUR CHEMISCHE INDUSTRIE IN BASEL), a body corporate organised according to the Laws of Switzerland, of Basle, Switzerland, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention consists in a manufacture of new benzene sulphonamido-thiazole derivatives, wherein a benzene sulphonic acid containing as a nuclear substituent in the para-position an amino-group or substituent capable of conversion into an amino-group is converted in the form of a reactive acid derivative (other than a benzene sulphonic acid halide having a free amino-group in para-position) into a benzene sulphonamido-compound containing as a substituent in the sulphonamido-group the radical of a thiazole by a method known to be capable of converting reactive acid derivatives of benzene sulphonic acids into benzene sulphonamides containing a hydrocarbon radical as a substituent in the sulphonamido-group. The word "known" is to be understood as designating methods described in the literature.

The expression "substituent capable of conversion into an amino-group" is used herein to denote an acylamino-, nitro-, nitroso-, azo- or hydrazo-group or a halogen atom.

The process may consist in causing the nuclear substituted benzene sulphonic acid in the form, for instance, of its halide or ester to react with a thiazole containing an amino-group. Alternatively, the nuclear substituted benzene sulphonic acid may be caused to react in the form of its amide with a thiazole containing a halogen atom.

When there is used a benzene sulphonic acid derivative of which the nuclear substituent is capable of conversion into an amino-group, the invention also includes the subsequent treatment of the resulting sulphonamido-derivative to convert into an amino-group the substituent so convertible.

The amino-group in the benzene sulphonic acid derivative may be a substituted amino-group, for instance, an alkylamino-, N-acyl-N-alkylamino- or aralkylamino-group; and the benzene sulphonic acid derivative may contain still further substituents, for instance, an alkyl-group.

As thiazoles there may be named, for instance, amino-thiazoles and amino-alkylthiazoles.

The new para-aminobenzene-sulphonamido-thiazoles find application in therapeutics. They have chemotherapeutic activity in streptococci infections and similar illnesses. The especially favourable activity of the products will be gathered from the following experimental data. The named compounds were tested as to their remedial effect on mice infected with highly virulent streptococci and also as to their toxicity. From the subjoined table it will be seen that the compounds obtainable as described in Example 1 herein have about

5 times the effectiveness exhibited by the already known sulphanilic acid amide. Especially to be noted is the considerably smaller toxicity of the 2-(para-amino-benzenesulphonamido)-thiazole made as described in Example 1.

TABLE.

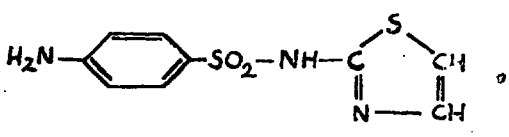
Compound	Remedial effect produced by grams of substance per kilo of mouse 100%	50%	Smallest fatal dose in grams per kilo of mouse
2-(para-amino-benzene-sulphonamido)-thiazole as described in Example 1	0.05	0.025	>15
2-(para-amino-benzene-sulphonamido)-4-methyl-thiazole described in Example 1	0.05	0.02	>15
Sulphanilic acid amide (known)	>0.25	0.1	7.5—10

The following Examples illustrate the invention, the parts being by weight:

EXAMPLE 1.

116 parts of acetylsulphanilic acid chloride made from acetanilide and chlorosulphonic acid are introduced into an ice-cold solution of 100 parts of 2-aminothiazole in 1000 parts of water and the mixture is stirred well for several hours. The amide which has separated is filtered with suction and recrystallised from alcohol of 50 per cent. strength. There is thus obtained in good yield (bis-para - acetaminobenzene - sulpho) - 2 - amino-thiazole of melting point 129° C.

10 parts of (bis-para-acetaminobenzene-sulpho)-2-amino-thiazole are heated together with 100 parts of caustic soda lye of 10 per cent. strength for ½ hour on the water bath. After filtration the alkaline solution is neutralised with acetic acid. The precipitated amide may be purified be recrystallisation from water or by reprecipitation from alkaline solution by means of ammonium chloride. There is thus obtained 2-(para-aminobenzene-sulphonamido)-thiazole in good yield and of melting point 202—203° C. It is soluble in alkalies and in acids and shows the diazo-reaction. Its formula may be supposed to be



In an analogous manner there is obtained, for example, from 2-amino-4-methyl-thiazole, (bis-para-acetamino-benzenesulpho) - 2 - amino - 4 - methyl - thiazole of melting point 194° C. and 2-(para - amino - benzenesulphonamido) - 4 - methyl-thiazole of melting point 241—242° C.

EXAMPLE 2.

A mixture of 22 parts of para-acetamino - benzene - sulphonamide, 14 parts of dry potassium carbonate, 17 parts of 2-brom-thiazole and 0.5 part of copper powder is heated in an oil bath within 1 hour from 150° C.—200° C. After cooling the melt is dissolved in water, filtered and 2-(para-acetamino-benzene-sulphonamido)-thiazole is precipitated by the addition of acid. 2-(Para - aminobenzene - sulphonamido) - thiazole may be obtained in the usual manner by acid or alkaline saponification.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A manufacture of benzene-sulphon-amido-thiazole derivatives, wherein a benzene sulphonic acid containing as a nuclear substituent in the para-position an amino-group or a substituent capable of conversion into an amino-group of the kind hereinbefore defined is converted in the form of a reactive acid derivative (other than a benzene sulphonic acid halide having a free amino-group in para-position) into a benzene sulphonamido-compound containing as a substituent in the sulphonamido-group the radical of a thiazole by a method known to be capable of converting reactive acid derivatives of

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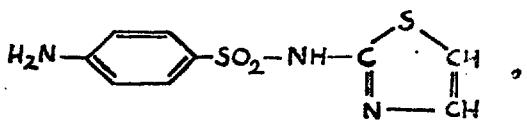

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benzene sulphonic acids into benzene sulphonamides containing a hydrocarbon radical as a substituent in the sulphonamido-group.

2. A manufacture of benzene-sulphonamido-thiazole derivatives by causing a benzene sulphonic acid halide or ester containing as a nuclear substituent in the para-position an amino-group or a substituent capable of conversion into an amino-group of the kind hereinbefore defined (other than a benzene sulphonic acid halide having a free amino-group in para-position) to react with a thiazole containing an amino-group.

3. A manufacture of benzene-sulphonamido-thiazole derivatives by causing a benzene sulphonamide containing as a nuclear substituent in the para-position an amino-group or a substituent capable of conversion into an amino-group of the kind hereinbefore defined to react with a thiazole containing a halogen atom.

4. A manufacture as claimed in any one of the preceding Claims, wherein the benzene sulphonic acid derivative contains in the para-position a substituent capable of conversion into an amino-group of the kind hereinbefore defined and the resulting product is subsequently treated to convert into an amino-group the substituent so convertible.

5. Benzene - sulphonamido - thiazole - derivatives whenever prepared or produced by the manufacture particularly described and ascertained herein or by any process which is an obvious chemical equivalent thereof.

Dated the 30th day of January, 1939.

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