PATENT SPECIFICATION

665,339

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COMPLETE SPECIFICATION

Process for Manufacturing Dicarboxylic Acid Derivatives of Sulfonamides

We, SHARP & DOHME (CANADA) LTD., a corporation of Canada, of 865, Bay Street, Toronto, Ontario, Dominion of Canada, 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:—

The present invention relates to a process for the preparation of dicarboxylic acid derivatives of sulfonamides.

PRIOR ART.

Acylated sulfonamides have been known since Gelmo first synthesized sulfanilamide in 1908. In his synthesis one of the intermediates was para-acetyl amino benzene sulfonamide.

After the attractive therapeutic properties of sulfanilamide had been discovered efforts continued to develop derivatives with better or more special therapeutical properties. By substituting the N^1-group there followed sulfapyridine, sulfathiazole, sulfadiazine, sulfamerazine, sulfaguanidine, only to mention the few of those derivatives which, out of thousands, have achieved wide applications.

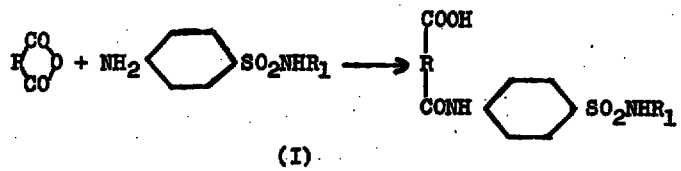
Efforts to vary or substitute the N^4-group were also numerous. A great number of organic acids have been for instance attached to the N^4-group. As a new N^1-substituted sulfanilamide appeared, derivatives substituted at the N^4-group followed right away. In this way there appeared, described in the literature, the various acylated sulfapyridines, sulfathiazoles, etc.

Of the N^4-acylated sulfanilamides a particular interest was shown for those derivatives which carried on the N^4-group a dicarboxylic acid as a substituent. In these derivatives, one of the carboxyl groups was free to form water soluble sodium or potassium salts. Since most sulfanilamides are poorly soluble in water and their sodium salts yield strongly alkaline solutions it was hoped that the dicarboxylic acid derivatives would result in neutral aqueous solutions when neutralized with alkali carbonates or hydroxides and that such products would still have the attractive therapeutical properties of the unsubstituted sulfanilamide.

While this hope was not fulfilled it was found that at least some of the dicarboxylic acid substituted sulfanilamides possess valuable therapeutic properties in some special therapeutic applications. Among these products phthalylsulfathiazole and succinylsulfathiazole achieved a particular popularity.

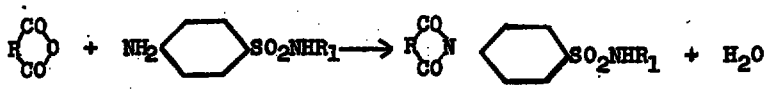
Phthalyl- and succinyl- derivatives of sulfanilamide have been prepared since 1939 (J.A.C.S. Vol. 61 (1939) p. 1198 and J.A.C.S. Vol. 64 (1942) page 1572). Such derivatives can be prepared by heating together the dicarboxylic acid with the sulfanilamide. A better method is to react in the same way the dicarboxylic acid anhydride with the sulfanilamide. This reaction may be carried out also in the presence of a solvent. If a solvent is used other derivatives of the dicarboxylic acid such for instance as the chlorides or esters, may be used.

It seems that of all the above processes the use of the dicarboxylic acid anhydride gives the best yield and the smoothest processes (I).



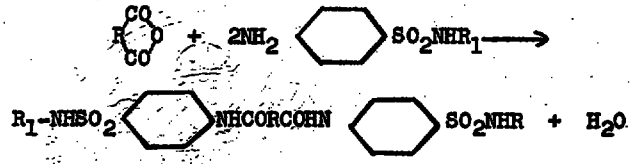
(I)

It has been shown, however that the conditions under which the dicarboxylic acid anhydride is reacted with the sulfonamide has a big influence on the yields obtained. For instance, melting together the dicarboxylic acid anhydride with the sulfonamide without any solvent present yields almost exclusively an anil (II).



(II)

or a diamide (III).



(III)

with many of the dicarboxylic acid anhydrides. If pyridine is being used as a solvent, again mostly the anil will be formed and the desired dicarboxylated sulfonamide can be produced only by subjecting this anil to a further hydrolysis. Absolute alcohol has found wide use for this process and yielded a high proportion of the desired compounds. However, even with the use of alcohol a certain amount of anil has been formed. Acetone has also been recommended as a medium for this reaction based on the idea that its low boiling point will not allow the formation of anils since this by-product seems to form only at high temperatures.

APPLICANT'S DEVELOPMENT.

According to the present invention, it has been found that N^4-dicarboxylic benzene sulfonamide derivatives can be prepared by reacting *p*-amino benzene sulfonamide alkali salts in aqueous solution with the corresponding dicarboxylic acid anhydride.

The reactivity of the acid anhydride in an alkaline aqueous medium has been found to be unexpected in view of the fact that acid anhydrides are known to be decomposed in the presence of water. The alkaline salts of sulfonamide yield a solution having a pH between 10 and 11 and it would be normally expected that the acid anhydrides would split at this pH without any other reaction taking place.

It seems, however, that when the splitting actually occurs the *statu nascendi* dicarboxylic acid reacts with the N^4-group and the desired dicarboxylated sulfonamide results.

The preferred sulfonamide alkali salts are the sodium or potassium salts of sulfathiazole or sulfanilamide. The preferred acid anhydrides that are used in accordance with the present invention are aliphatic dicarboxylic acid anhydrides, for example, succinic, glutaric, adipic, malonic, maleic, suberic, and sebacic acids, or aromatic dicarboxylic acid anhydrides, for example, phthalic and naphthalic acid anhydrides. The anhydride of malonic acid (carbon suboxide) is obtained by removing two molecules of water from malonic acid and in the presence of water reforms malonic acid which immediately reacts with the N^4-group to form the dicarboxylic acid derivative in the manner above described.

In conducting the reaction according to the process of the present invention, the proportions of dicarboxylic acid anhydride and sulfonamide salt may be those required stoichiometrically for the reaction (equimolecular proportions), although it is preferred to use a slight excess of the dicarboxylic acid anhy-

dride, which can be readily removed from the product, to drive the reaction to completion.

The amount of water used to dissolve the sulfonamide alkali salt is not critical and depends on the equipment which is used to mix the reactants. With an efficient mixing equipment the amount of water may be reduced, though an increase in the amount of water would make no difference.

EXAMPLES.

Illustrative examples of preferred methods of producing the process of the present invention, are as follows:

EXAMPLE 1.

PHTHALYLSULFATHIAZOLE.

55.5 gm. of sodium sulfathiazole are dissolved in 250 cc. of water under strong stirring. 32.5 gm. of phthalic anhydride are added. Stirring is continued for another three hours. The mixture is made acid to Congo Red and filtered. The precipitated phthalylsulfathiazole may be purified by conventional methods.

Substituting the 55.5 gm. of sodium sulfathiazole by 58.8 gm. of potassium sulfathiazole, the same product is obtained.

EXAMPLE 2.

SUCCINYLSULFATHIAZOLE.

55.5 gm. of sodium sulfathiazole are dissolved in 250 cc. of water under strong stirring. 22 gm. of succinic anhydride are added. Stirring is continued for another three hours. The mixture is made acid to Congo Red and filtered. The precipitated succinylsulfathiazole may be purified by conventional methods.

Substituting the 55.5 gm. of sodium sulfathiazole by 58.8 gm. of potassium sulfathiazole, the same product is obtained.

EXAMPLE 3.

PHTHALYLSULFANILAMIDE.

39.0 gm. sodium sulfanilamide are dissolved in 200 cc. of water under strong stirring. 32.5 gm. of phthalic anhydride added. Stirring is continued for another three hours. The mixture is made acid to Congo Red and filtered. The precipitated phthalylsulfanilamide may be purified by conventional methods.

Substituting the 39.0 gm. sodium sulfanilamide by 42.0 gm. potassium sulfanilamide or the same product is obtained.

EXAMPLE 4.

SUCCINYLSULFANILAMIDE.

39.0 gm. sodium sulfanilamide are dissolved in 200 cc. of water under strong stirring. 22 gm. of succinic anhydride added. Stirring is continued for another three hours. The mixture is made acid to Congo Red and filtered. The precipitated succinylsulfanilamide may be purified by conventional methods.

Substituting the 39.0 gm. sodium sulfanilamide by 42.0 gm. potassium sulfanilamide, the same product is obtained.

ADVANTAGES.

The advantages of the present invention are that the reaction can be carried out in the presence of water without the formation of anil or diamide. The present invention has been found to give high yield of the desired product and also to give a product having a high purity. Furthermore, the present invention can be carried out without the application of heat and the absence of solvents other than water.

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 process for the manufacture of N^4-dicarboxylated *p*-amino benzene sulfonamide derivatives, comprising reacting the alkali salts of *p*-amino benzene sulfonamides in aqueous solution with the corresponding dicarboxylic acid anhydrides without the application of heat.

2. A process as claimed in Claim 1, wherein the sulfonamide alkali salt is that of sulfathiazole or sulfanilamide.

3. A process as claimed in Claim 2, wherein the sodium salt of sulfathiazole or sulfanilamide is reacted with phthalic anhydride.

4. A process as claimed in Claim 2, wherein the sodium salt of sulfathiazole or sulfanilamide is reacted with succinic anhydride.

5. A process for the manufacture of N^4-dicarboxylated *p*-amino benzene sulfonamide derivatives, substantially as described in any one of the specific examples herein.

6. N^4-dicarboxylated *p*-amino benzene sulfonamide derivatives whenever prepared by the process claimed in any one of the preceding claims.

Dated this 30th day of November, 1949.

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