This invention relates to valuable derivatives of sulphonamides and a method of making the same.

As particularly valuable therapeutic agents in combating bacterial infections such as streptococce, staphyloccoe, pneumococce, and septicemic conditions, have proved compounds of the type of the sulphonamides such as are described, for example, in German Patents Nos. 607,537, 610,220, 658,101, French Patents Nos. 212,053, 229,546, British Patents Nos. 462,576 and 462,765, Swiss Patents Nos. 192,699 and 192,700, U. S. Patents Nos. 2,111,768 and 2,111,913 and others; compare also the work of Fourneau, Tréfouel, Nitti and Bovet, Comptes Rendus Soc. Biol. 1936, vol. 125, pages 258-259; Tréfouel, Nitti and Bovet, Annales de l’Institut Pasteur, vol. 58, pages 30-47 (1937); Buttle, Gray and Stephenson, Lancet of 6.5.36, pages 1286-1288; Mayer, Oechslin, Comptes Rendus, vol. 205, pages 181-182 (1937); Goissedet, Despois and Mayer, Comptes Rendus Soc. Biol. 1936, vol. 121, pages 1082-1084 and all others. These compounds contain a sulphonamide group —SO₂NH₂ connected to an aromatic, heterocyclic or aromatic-heterocyclic residue. Very active compounds of this class of substances contain in p-position to the sulphonamide group an amino group of a group convertible thereinto. As the best known compounds of this type may be mentioned the p-sulphanilic acid amide NH₂.CH₂.SO₂.NH₂ and the azodyestuffs derived therefrom of the type of 4-sulphonamido-2,4-diaminoazobenzene (NH₄)₂.C₂H₅.N=N.C₂H₅.SO₂.NH₂

In compounds of this type also the amino bound amino groups can be substituted by suitable substituents, for example, by acyl residues, in particular by those containing acid groups, or by carboxy-alkyl residues, by carbohydrate residues by benzyl residues and the like. A whole series of compounds of this type is difficultly soluble or insoluble in water so that the administration thereof presents difficulty.

In accordance with the present invention particularly valuable derivatives of compounds of this type are produced when in them a hydrogen atom of the sulphonamide group is replaced by an acyl residue. The compounds thus obtained according to the invention correspond to the following formula:

\[ R.SO₂.NH.X \]

In this formula R indicates an aromatic, heterocyclic or aromatic-heterocyclic residue containing at least one nuclear bound amino group or a group convertible thereinto, while X indicates an acyl residue of a carboxylic acid.

In accordance with the invention by the introduction of such an acyl residue into the sulphonamide group the hydrogen atom still present in the sulphonamide group becomes replaceable by metal. By replacement of this hydrogen atom by alkali metal it is possible to convert otherwise insoluble compounds of the above mentioned class of substances into compounds easily soluble in water with neutral reaction. By this means the possibility is provided of employing all the compounds according to the invention not only as such but in the form of their water-soluble salts in aqueous solution and to administer them, for example, by intravenous or subcutaneous injection whereby a more rapid effect is promoted.

In addition there is the fact that the therapeutic activity of these substances is not reduced by the reaction specified but in many cases even increased.

Even if a few of the already known compounds of the sulphonamide type are capable of forming water-soluble salts as, for example, the p-aminobenzene-sulphonamide hydrochloride, the salts obtained according to the present invention are distinguished from these known salts by the fact that the latter do not pass into solution with neutral reaction and on this account can find no application for injection purposes.

For the manufacture of the compounds according to the present invention certain types of reaction may be followed which in themselves are known to the expert. Essentially two main groups of methods of production can be distinguished, namely:

1. Such in which the residue R.SO₂NH₂ is previously formed and the acyl group introduced,
2. Such in which the residue —NLX is previously formed and the residue R.SO₂ introduced.

To the first mentioned group of methods of manufacture belongs the simplest method, namely the acylation methods known per se, for instance, by means of acid anhydrides, acyl chlorides, ketenes and the like. If the residue R of the above formula in addition contains an amino group, the acylation must naturally be carried out in such a manner that together with the acylation of the amino group the acylation of the sulphonamide group simultaneously takes place, that is to say in general an excess of acylating agent will be employed. If necessary then by partial hydrolysis the acyl group of the nuclear bound amino group may be split off again.
Obviously also such acylation methods can be employed in which from the commencement only an acylation of the sulphonamide group takes place and the nuclear bound amino group remains unchanged, as, for example, by causing the acylating agent to react on the silver compound of the sulphonamide.

This group of manufacturing processes includes also all the processes in which such acylated sulphonamides are employed as starting materials in which the nuclear bound amino group is first protected after the production of the acylated sulphonamide group. It comprises therefore essentially two stage processes in which in fact sulphonamides which contain a group convertible into the amino group are first acylated whereupon the nuclear bound amino group is produced.

The various methods for converting nitrogen-containing and non-nitrogen-containing groups into an amino group are well known and are described, for example, in Houben "Die Methoden der organischen Chemie," second edition, 1923-1925, vol. 3, page 315 et seq., vol. 4, page 247 et seq., page 337 et seq., page 339, et seq., and page 354 et seq. As example may be mentioned the acylation of p-nitrobenzene-sulphonamide with subsequent reduction of the nitro group to the amino group. Instead of the nitro group also any other of the groups convertible into the amino group can be present, for example, the nitroso, azo, azoxy, hydrazo and the like groups which by reduction are converted into the amino group, halogen, which by treatment with amine or ammonia sulphur, suitably in the presence of catalysts, gives the amino group, the acylamino and azo-methylene groups, which can be hydrolysed to the amino group, or an acid amide or hydrazide group which can be converted into the amino group by Hoffmann, Curtius or the like degradation reactions, and others.

To this group of manufacturing processes belongs also the process in which the nuclear bound amino group before the acylation is converted into such an acylamino group as can more easily be split off to the amino group of the sulphonamide group. Such groups are, for example, the carboxethoxy, the carbobenzyloxy group and others as are mentioned, for example, in German Patent 556,796. These can easily by reduction treatment or by hydrolysis be split off again without affecting the acylated sulphonamide group being influenced. Also the method of benzylation the amine group can be used with advantage for this type of reaction.

To this group of manufacturing processes belong finally also the methods in which at first aromatic, heterocyclic or aromatic-heterocyclic amino-sulphonamide compounds are acylated in the sulphonamide group, and then the free or again liberated nuclear bound amino group is diazotized and the diazo compound obtained coupled in the manner known per se, corresponding, for example, to the directions of German Patents Nos. 609,537, 610,520 and others with aromatic, heterocyclic or aromatic-heterocyclic bases which are capable of coupling. There are obtained in this manner azo compounds acylated in the sulphonamide group which on the one hand contain a nuclear bound amino group and on the other an acylated sulphonamide group and which likewise constitute valuable therapeutic agents. Obviously such compounds can be employed for the manufacture of such azo compounds also other manufacturing methods known per se as are mentioned in the above specified patents. Thus, for example, an aromatic, heterocyclic or aromatic-heterocyclic nitro compound which contains a nuclear bound basic nitrogen atom can be condensed in customary manner to the azo compound. It is also possible to reduce corresponding azoxy compounds to the azo compounds or to dehydrogenate correspondingly constituted hydrazone-compounds to the azo compounds.

The formation of the nuclear-bound amino group by splitting of substituents or by conversion of another group convertible thereof (nitro-, azo-, halogen- and similar groups) is necessary in certain instances to render the compound therapeutically active. Thus, such conversion is necessary in the case of the p-halogeno-sulphonamides, such as p-chloro- or p-bromobenzensulphonamide, since such compounds, as tests have shown, are inactive, and active compounds are produced therefrom only by conversion into the corresponding p-aminobenzensulphonamides.

To the second group of manufacturing processes belong all the processes in which such sulphonic acids or their derivatives as contain a nuclear bound amino group or a group convertible thereinto (nitro-, azo- sulphonamido- and similar groups) is necessary in certain instances to render the compound therapeutically active. Thus, such conversion is necessary in the case of the p-halogeno-sulphonamides, such as p-chloro- or p-bromobenzensulphonamide, since such compounds, as tests have shown, are inactive, and active compounds are produced therefrom only by conversion into the corresponding p-aminobenzensulphonamides.

As particularly valuable starting materials for the reaction of the present invention have proved the following substances:

- p-Aminobenzene-sulphonamide
- p-Benzylaminobenzene-sulphonamide
- p-Aminobenzensulphonamido-benzene-m-sulphonamide
- p-Amino-benzene-sulphonamido-p-sulphonamide

and their acylamine derivatives or sulphonchlorides,azo-dyes of the type of the 4-sulphonamido-2,4'-diamino-1,1'-azonobenzene, the glucosides of p-aminobenzensulphonamides and others as are described in the patents and literature references set forth above and in the pending patent applications Ser. No. 147,478, filed on June 10, 1937, and Ser. No. 210,746 of May 28, 1938.

By interaction of the compounds according to the invention acylated on the sulphonamide group, with metal oxides, hydroxides or carbon-
ates or the like there are obtained the corresponding metal compounds. Thus it is easy to manufacture the alkali compounds by treating the new compounds with the calculated quantity of alkali hydroxide solution or sodium carbonate to a neutral reaction and, if necessary, salting out the alkal salt or precipitating it by the addition of organic solvents miscible with water. Of course, the salts can be isolated from their solutions by simply evaporating the latter to dryness.

It is also possible, however, to produce other metal compounds, such as the alkaline earth, gold, copper, mercury, silver, aluminium, magnesium and the like compounds which are likewise of practical importance. For the manufacture of these salts there is especially suitable the known method of double decomposition, according to which, for instance, the alkaline earth metal salts of the acetylated sulphonamides (that is, of alkaline earth metals whose sulphates are insoluble) are reacted with soluble sulphates of heavy metals. Thereby the insoluble alkaline earth metal sulphate precipitates while the soluble heavy metal salt of the acetylated sulphonamide remains in solution and is isolated therefrom. Also organic bases, as, for example, alkylamines, alkanol amines such as ethanolamines, pyridine, aniline, 1-phenyl-2,3-dimethyl-4-dimethylamino-5-pyrazolone, quinine and others are suitable for salt formation.

Both the acetylated sulphonamide compounds of the formula R₂SO₃.NH₂X and also their metal and other derivatives are intended to find application not only as therapeutic agents but also as intermediate products for the manufacture of other pharmaceutical and technically valuable substances, for example, for the manufacture of plant protecting agents and the like.

The following examples illustrate the invention without, however, limiting the same to them:

**Example 1**

**4-aminobenzene-sulphonacetyl-amide**

17.2 grams of 4-aminobenzene-sulphonamide are heated to boiling with 75 cc. of acetic anhydride for one hour and thereupon the diacetyl product caused to separate by stirring into ice water. After recrystallisation from alcohol the 4-acetylamino-benzene-sulphonacetyl-amide forms colorless prisms of melting point 253° C. with decomposition. The product is easily soluble in alkalies and forms neutral salts. The acetylation can also take place with acetyl chloride. Instead of the 4-aminobenzene-sulphonamide also 4-acetylamino-sulphonamide can be employed. The action of 4-acetylamino-benzene-sulphonamic acid chloride on acetylamide yields the same product.

By heating the diacetyl compound with sodium hydroxide solution partial saponification of the acetyl groups takes place. 25.6 grams of diacetyl compound are heated to boiling for some hours with 100 cc. of 2 N sodium hydroxide solution. The precipitate produced by acetylation of the solution with acetic acid is filtered off and treated with dilute sodium carbonate solution. The 4-aminobenzene-sulphonacetylamide passes into solution while the simultaneously formed 4-acetylamino-benzene-sulphonamide remains undissolved. It is filtered with suction and the filtrate again acidified with acetic acid. The 4-aminobenzene-sulphonacetylamide separates out and is recrystallised from water. It forms colorless lustrious rhombic crystals of M. P. 181° C. It is easily soluble in alcohol and acetone, more difficultly in water, insoluble in benzene and chloroform.

**Example 2**

**4-propionylaminobenzene-sulphon-propionyl-amide**

17.2 grams of 4-aminobenzene-sulphonamide are heated to boiling for one hour with 20 cc. of propionic acid anhydride. The working up according to example 1 yields the dipropionyl-amino-benzene - sulphonamide. Recrystallised from alcohol it forms colorless microscopic needles of M. P. 232° C. The product is soluble in sodium carbonate solution and can be partially saponified by heating with sodium hydroxide solution as in Example 1, yielding 4-aminobenzene-sulphon-propionyl-amide of M. P. 130-131° C.

**Example 3**

**4-acetilaminobenzene-sulphonbenzoylamide**

21.4 grams of 4-acetilaminobenzene-sulphonamide are dissolved with 200 cc. of N sodium hydroxide solution and shaken with 28.2 grams of benzoyl chloride until the benzoyl derivative separates. The latter is filtered with suction and for purification taken up in dilute sodium carbonate solution. It is filtered and precipitated with acetic acid. The precipitate is recrystallised from dilute alcohol. The 4-acetilaminobenzene-sulphonbenzoyl-amide forms needles which on heating decompose at 245-246° C. By heating with sodium hydroxide solution, as in Example 1, partial saponification takes place. The 4-amino-benzene-sulphonbenzoyl-amide obtained has the melting point of 179-186° C.

**Example 4**

**4-benzylaminobenzene-sulphonacetamide**

26.2 grams of 4-benzylaminobenzene-sulphonamide are heated for some hours with 250 cc. of acetic anhydride. The working up according to Example 1 yields the 4-benzylaminobenzene-sulphonacetamide. It is purified by recrystallisation from alcohol and then forms microscopic needles of melting point of 143-144° C.

**Example 5**

**4'-acetilaminobenzene-sulphonamidobenzene-sulphonacetamide**

32.7 grams of 4'-aminobenzene-sulphonamidobenzene-sulphonamide are heated to boiling with 200 cc. of acetic anhydride. After solution has taken place the whole is boiled for a further hour and then the diacetyl compound caused to separate by pouring the solution into ice water. The precipitate is purified by dissolving in sodium carbonate solution and precipitation of the filtrate with acetic acid. Recrystallized from dilute alcohol the product forms colorless needles which melt at 187° C. By partial saponification with normal sodium hydroxide solution the corresponding amino product of M. P. 187° C is obtained.

**Example 6**

**4-acetilaminobenzene-sulphonamido-3'-benzene-sulphonacetamide**

32.7 grams of 4-acetilaminobenzene-sulphonamido-3'-benzene-sulphonacetamide of M. P. 156° C. (produced by the action of 4-acetilaminobenzene-sulphonamic acid chloride on 3-aminobenzene-sulphonamide and subsequent saponification of the acetyl group of the condensation product) are
heated with 200 cc. of acetic anhydride for one hour to boiling and thereupon the diacetyl product isolated as described in Example 5. After recrystallisation from dilute alcohol the product melts at 145-146°. By partial saponification the corresponding amino compound is obtained.

**Example 7**

4-acetyl sulphamidobenzene-2',4'-diamino-1',1'-azo-benzene

21.4 grams of 4-aminobenzene-sulphonacetamide are diazotized in hydrochloric acid solution with 6.9 grams of sodium nitrite and the cold diazonium chloride solution treated with a hydrochloric acid solution of 11 grams of m-phenylenediamine. The coupling product immediately separates as a dark red precipitate. It is filtered with suction, taken up with dilute sodium carbonate solution, filtered and acidified in the hot with acetic acid. The dyestuff separates in the form of blue-red leaflets of metallic lustre. On heating decomposition takes place at 180° C.

The same product is obtained when the 4-sulphonamido-4',6-diamino-1',1'-azo-benzene is acetylated and partially saponified. The dyestuff is easily soluble in dilute sodium carbonate solution.

**Example 8**

4-aminobenzene-sulphonacetamidine

172 grams of sulphanilic acid amide are dissolved in 2000 cc. of N sodium hydroxide solution and to the solution at 0° C. with stirring and cooling 340 grams of benzyl-chloroboronic acid ester added. After several hours the precipitated 4-N-carbonyl acid benzyl esteraminobenzene-sulphonamidone is separated, washed with dilute hydrochloric acid and water and recrystallized from methyl alcohol. Melting point 192-192.5° C. The yield amounts to 250 grams.

By one hour's boiling of this product with five times the quantity of acetic anhydride and pouring of the solution into water the acetyl derivative is precipitated. It is filtered with suction, taken up in dilute sodium carbonate solution, filtered from any unchanged starting material and in the filtrate precipitated again by hydrochloric acid. The 4-N-carbonyl acid benzyl esteraminobenzene-sulphonyacetamidine melts after recrystallisation from methyl alcohol at 167-168° C. The yield amounts to 200 grams.

To split off the carbobenzylxy group, 200 grams of the 4-N-carbonyl acid benzyl esteraminobenzene-sulphacylamidone are dissolved in 3 litres of alcohol and with the addition of 5 grams of palladium black shaken with hydrogen so long as the latter is still taken up. For this purpose 7.6 litres of hydrogen are employed. The solution is filtered off from catalyst, concentrated and the residue recrystallised from water. The yield amounts to 196 grams of 4-aminobenzene-sulphonacetamidine of melting point of 181° C. The same yield is obtained when the catalytic hydrogenation is carried out in aqueous alkaline instead of alcoholic solution.

The splitting off of the benzyl-carbonyl acid residue can also take place by several hours treatment with three times the molar quantity of normal sodium hydroxide solution at 60° C.

**Example 9**

40 grams of carboxylic acid ethyl ester (Hentschel, Berichte, vol. 18, page 978) are introduced at 0° C. into 160 grams of chlorosulphonic acid. The mixture is heated for an hour to 55-60° C. and then introduced into ice water. The precipitated carboxy-benzyl-sulphonic acid chloride is for purification dissolved in cold methyl alcohol and precipitated by the addition of water. The melting point is 104-105° C. By introduction of ammonia into the ethereal solution of the carboxy-benzyl-sulphonic acid chloride there is produced in good yield the 4-carboxy-benzyl-sulphonic amide of melting point of 238° C.

244 grams of 4-carboxy-aminobenzene-sulphonamide, 1.25 litres of glacial acetic acid and 80 grams of acetyl chloride are heated to boiling for 2 hours. The acetylated product is introduced into water, filtered with suction and reprecipitated. It melts after recrystallisation from dilute acetone at 244° C.

For splitting off the carboxy group the 4-carboxy amino-benzene-sulphonamidone is dissolved in 2.5 N sodium hydroxide solution and the solution heated for 10 minutes to 60° C. By acidification with acetic acid the 4-aminobenzene-sulphonacetamidine is precipitated and is purified by recrystallisation from water. Melting point 181° C. The yields according to this process correspond to those given in Example 8.

Instead of 4-carboxy-aminobenzene-sulphonamide there can also be employed as starting material the carbethoxy compound; it is obtained in the following manner:

82.3 grams of the sodium salt of carbethoxy-sulphanilic acid (Nölling, Berichte 21, 3155) are added to 70 grams of phosphorus pentachloride. The solid mass is introduced into ice water, the undissolved portions filtered with suction and washed free from acid. The amide is obtained by introduction of ammonia into the ethereal solution of the sulphonchloride (melting point 117-118° C). The carbethoxy-sulphanilic acid amide melts at 226-227° C.

**Example 10**

4-aminobenzene-sulphonacetamidine-glucoside

21.4 grams of 4-aminobenzene-sulphonacetamidine are heated to boiling with 17.1 grams of glucose and 200 cc. of absolute ethyl alcohol until a clear solution is produced. From the solution on long standing the glucose compound crystallises in colorless needles. The crystals are separated and recrystallised from ethyl alcohol. The melting point is 191° C. The compound is easily soluble in water, more difficulty in ethyl alcohol. The alkali salts are easily soluble in water with neutral reaction.

**Example 11**

4,4'-disulphonacetamidine-diphenyl-urea

Into a solution of 21.4 grams of 4-aminobenzene-sulphonacetamidine in 200 cc. of 2 N sodium hydroxide solution is introduced at 50° C a strong stream of phosgene. When the reaction is complete the precipitate produced is filtered with suction and for purification precipitated from an alkaline solution in the hot with acetic acid. The product forms colorless microscopic needles which decompose at 253° C. The yield is quantitative. The product is very difficultly soluble in organic solvents. The water-solubility of its alkali salts is considerable.

**Example 12**

4-aminobenzene-sulphon-nicotoylamide

24.4 grams of 4-carboxy-benzyl-sulphonic acid amide are dissolved in 250 cc. of pyridine and
with stirring and cooling 14.2 grams of nicotinic acid chloride introduced drop by drop. The clear solution is introduced into ice water and treated with hydrochloric acid to an acid reaction to Congo red. The precipitate is isolated and recrystallised from dilute alcohol. The product forms needles of M. P. 241° C.

For saponification of the carboxylic group 30 grams of 4-carboxyaminobenzene-sulphon-nicotoylamide are allowed to stand for 24 hours in 210 cc. of 2 N sodium hydroxide solution. The solution is then acidified with acetic acid, the precipitate filtered with suction washed with water and recrystallised from dilute alcohol. The 4-amino-benzene-sulphon-nicotoylamide forms colorless needles and melts at 246° C.

**Example 13**

4-amino-benzene-sulphonbutyryl-amide

24.5 grams of 4-carboxyphthalamic acid amide and 150 cc. of butyric acid anhydride are stirred into water after heating for 1 hour. Thereby the acylated product precipitates in the form of an oil. By recrystallisation of the solified oil from dilute alcohol the 4-carboxyaminobenzene-sulphon-butyryl-amide is obtained in the form of needles of melting point 217-218°.

The saponification is carried out as described above by treatment with 2 N sodium hydroxide solution. The 4-amino-benzene-sulphonbutyryl-amide obtained thereby yields on recrystallisation from alcohol a product having a melting point of 125°.

**Example 14**

4-amino-benzene-sulphoncrotonyl-amide

24.5 grams of 4-carboxy-sulphanillic acid amide are heated for 2 hours to 145° C. with 125 grams of crotonic acid and 11 grams of crotonic acid chloride. After cooling the reaction mixture is stirred into 2 liters of water. The undissolved portion is separated, taken up in sodium carbonate solution and precipitated after filtration with acetic acid. The crotonylic derivative redissolved from alcohol melts at 224° C.

Saponification yields the 4-amino-nbensene-sulphoncrotonyl-amide which on recrystallisation from water melts at 175° C.

**Example 15**

4-acetylamino-benzene-sulphon-p-nitrobenzoyl-amide

21.4 grams of 4-acetylamino-benzene-sulphonamide are dissolved in 200 cc. N sodium hydroxide solution and are shaken with 18.6 grams of 4-nitrobenzoyl chloride for several hours. The filtered solution is acidified, the precipitate is dissolved in sodium carbonate solution, again filtered, and the filtrate precipitated by means of acid. On recrystallisation from alcohol the 4-acetylamino-benzene-sulphon-p-nitrobenzoylamide of M. P. 256° C. is obtained.

**Example 16**

4-benzylaminobenzene-sulphon-acetyl-amide

21.4 grams of 4-aminobenzene-sulphon-acetyl-amide obtained, for instance, according to Example 1 and having a melting point of 181° C. are heated with 12.6 grams of benzylchloride, 24 grams of calcium carbonate, and 500 cc. of water for several hours while stirring, to boiling. After adding 6 grams of calcium carbonate the mixture is again heated to boiling, filtered while hot, and the filtrate is precipitated with hydrochloric acid. The precipitate consists of 4-benzylamino-benzene-sulphonacetamide which on recrystallisation from alcohol melts at 143-144° C. The yield amounts to 15 grams.

**Example 17**

4-acetilsulphamidophenyl-azo-1' (napthol-6.8'-disulphonic acid)

21.4 grams of 4-aminobenzene-sulphon-acetyl-amide obtained, for instance, according to Example 1 are diazotised and in sodium carbonate solution coupled with a solution of 35 grams of 2-naphthol-6.8'-disulphonic acid sodium salt. In order to isolate the reaction product the solution is slightly acidified and the dyestuff is salted out by addition of sodium chloride. The disodium salt obtained thereby is recrystallised from dilute alcohol and forms vermilion-redish colored prismatic needles which decompose on heating at 333° C.

**Example 18**

4-aminobenzene-sulphonpropionyl-amide

24.5 grams of 4-carboxyaminobenzene-sulphon-amide are heated with 150 cc. of propionic acid anhydride for one hour to boiling. On stirring the mass into ice-water an oil precipitates that soon solidifies. After recrystallisation the 4-carboxyaminobenzene-sulphon-propionyl-amide is obtained in the form of needles having a melting point of 209° C. The yield amounts to 24 grams.

The saponification of the carboxy residue is carried out in the same manner as described in Example 9, i. e. by heating with 2 N sodium hydroxide solution. The 4-aminobenzene-sulphonpropionyl-amide obtained thereafter is acidified with acetic acid solidifies after a short time and forms crystals that on recrystallisation from dilute alcohol melt at 130-131° C.

**Example 19**

4-aminobenzene-sulphon-phenacetyl-amide

24.4 grams of 4-carboxy-sulphanillic acid amide are heated with 16 grams of phenacetyl chloride for several hours to 160-170° C. The cooled reaction mixture is dissolved in dilute sodium carbonate solution and is acidified after filtration, with hydrochloric acid. The 4-carboxy-sulphanillic acid phenacetyl amide precipitated thereby is recrystallised from alcohol and melts at 209° C.

The saponification of this compound is carried out by treating the same with 2 N sodium hydroxide solution. The 4-aminobenzene-sulphon-phenacetyl-amide obtained thereby melts after recrystallisation from dilute alcohol at 182° C.

**Example 20**

4-carboxy-aminobenzene-sulphonaminocetic acid amide

24.4 grams of 4-carboxy-sulphanillic acid amide and 50 grams of chloro acetic acid anhydride are heated for one hour to 120-125° C. The reaction mixture is then triturated with water, the undissolved is removed by filtration, and is recrystallised from dilute alcohol. It melts at 229° C. The 4-carboxy-aminobenzene-sulphon-chloro-acetic acid amide yields on treatment with concentrated ammonia solution at ordinary room temperature 4-carboxy-aminobenzene-sulphonaminocetic acid amide which on recrystallisation from water melts at 223° C.
EXAMPLE 21
4-aminobenzene-sulphonesalicylic acid amide
24.4 grams of 4-carbethoxy-sulphanilic acid amide and 15.7 grams of salicylic acid chloride are heated for several hours to 170-180° C. The reaction mixture is then dissolved in dilute sodium carbonate solution. The solution is filtered and precipitated with hydrochloric acid. By recrystallisation from glacial acetic acid the reaction product is obtained in a pure state and melting at 242° C. The saponification with 2 N sodium hydroxide solution yields 4-aminobenzene-sulphonesalicylic acid amide which on recrystallisation from water melts at 200-201° C.

EXAMPLE 22
4-aminobenzene-sulphonfuroyl amide
48.8 grams of 4-carbethoxy-sulphanilic acid amide are dissolved in 250 cc. of pyridine and mixed while cooling and stirring, slowly and gradually with 26.5 grams of pyromucic acid chloride. After standing for some time the solution is poured into ice-water, filtered and the condensation product precipitated by acidifying with hydrochloric acid. The product purified by re-precipitation, melts at 255° C., with decomposition. The yield is almost quantitative. By treating this product with 2 N sodium hydroxide solution the carboxhy group is split off and the 4-aminobenzene-sulphonfuroyl-amide is obtained on acidification. It forms a crystalline mass that on recrystallisation from water melts at 188-189° C.

EXAMPLE 23
4-aminobenzene-sulphon-hydrochaullie-acid amide
24.4 grams of 4-carbethoxy-sulphanillic acid amide are slowly heated with 29.6 grams of hydrochaullie (chaumooricer) acid chloride (Wagner-Jauregg und Volet, Berichte der Deutschen Chemischen Gesellschaft, vol. 71, page 1976) to 145° C. The reaction product is poured into water and is brought into solution with an amount of sodium carbonate sufficient to dissolve the product. After filtration hydrochloric acid is added and the precipitate is recrystallised from dilute alcohol in the presence of charcoal. The product forms colorless globular crystals having a melting point of 131° C.

EXAMPLE 24
4,4'-diaminodiphenyl-disulphonadipic acid diamide
48.8 grams of 4-carbethoxy-sulphanillic acid amide are heated with 18.3 grams of adipic acid dichloride for several hours to 150° C. The solid mixture is then dissolved and is dissolved with sodium carbonate solution. After acidifying the filtered solution, the precipitate is recrystallised from a large quantity of dilute alcohol. The product melts at 229° C. with decomposition. The splitting off of the carboxhy group is carried out in customary manner by means of 2 N sodium hydroxide solution. Thereby the 4,4'-diaminodiphenyl-disulphon-adipic acid diamide is obtained that after decrystallisation from dilute alcohol melts at 212° C.

EXAMPLE 25
4,4'-diamino-diphenyl-disulphon-mucic acid diamide
48.8 grams of 4-carbethoxy-sulphanillic acid amide are mixed with 24.7 grams of mucic acid chloride and the mixture is heated for one hour to 190° C. The pulviserised reaction mixture is dissolved in dilute sodium carbonate solution, filtered, the filtrate acidified by means of hydrochloric acid, the precipitate filtered off by suction, and recrystallised from dilute alcohol. The dicarbethoxy compound melts at 201° C. By treating the same with 2 N sodium hydroxide solution the two carbethoxy groups are split off and the 4,4'-diamino-diphenyl-disulphon-mucic acid diamide having a melting point of 233° C. is obtained.

EXAMPLE 26
4-aminobenzene-sulphoncarbethoxy-amide
24.4 grams of 4-carbethoxy-sulphanillic acid amide are dissolved in 250 cc. of pyridine. To this solution there are added drop by drop while stirring 11 grams of chloro carbonic acid ethyl ester. The solution is heated for several hours to 60-70° C., then diluted with 8 times its amount of water and acidified with hydrochloric acid. The precipitate obtained is dissolved in dilute sodium carbonate solution in order to remove any non-reacted starting material, the solution is filtered, and the 4-carbethoxy-aminobenzene-sulphon-carbethoxy-amide is obtained. For the filtrate by means of hydrochloric acid. On recrystallisation from alcohol needles having a melting point of 162° C. are obtained.

By treating this product with 2 N sodium hydroxide solution the carboxhy group is split off from the aminomethyl group. The 4-aminobenzene-sulphoncarbethoxy-amide obtained thereby melts after recrystallisation from alcohol at 133° C. It forms alkaline salts that are readily soluble in water with neutral reaction.

EXAMPLE 27
4-carbethoxy-aminobenzene-sulphon-carbethoxyamide
26.4 grams of 4-carbethoxy-sulphanillic acid chloride are heated with 100 grams of urethane to 140-150° C. until a sample is readily and completely soluble in dilute sodium carbonate solution. The reaction mixture is then dissolved in very dilute sodium carbonate solution, filtered, and the filtrate acidified with acetic acid. The precipitate is recrystallised from alcohol and corresponds with the product obtained according to the preceding example.

EXAMPLE 28
Salts of 4-aminobenzene-sulphon-acetamide
(a) Sodium salt: 21.4 grams of 4-aminobenzene-sulphon-acetamide are dissolved in 100 cc. of N sodium hydroxide solution and the sodium salt is precipitated with alcohol after concentrating the solution. On recrystallisation from dilute alcohol the salt melts at 258° C.
(b) Barium salt: 21.4 grams of 4-aminobenzene-sulphon-acetamide are dissolved in an aqueous solution of 15.8 grams of barium hydroxide, the solution is evaporated to dryness and the residue is recrystallised from dilute alcohol. Melting point: 185° C. (with decomposition).
(c) Copper salt: The aqueous solution of 5 grams of the barium salt of 4-aminobenzene-sul-
A greenish powder is obtained.

(e) Pyridine salt: 4-aminobenzene-sulphon-acetamide is dissolved while heating in pyridine. The pyridine salt precipitated on cooling is recrystallised from alcohol. It has a melting point of 120° C.

(f) Diethanol amine salt: 21.4 grams of 4-aminobenzene-sulphon-acetamide are brought into solution by means of 10.5 grams of diethanol amine in 100 cc. of water. The residue obtained on evaporating the solution to dryness is recrystallised from dilute alcohol. Melting point of the salt: 155° C. (not sharp).

(g) Calcium salt: 21.4 grams of 4-aminobenzene-sulphon-acetamide are dissolved in 100 cc. of water while heating. To this solution there are added 5.0 g. of calcium carbonate. After boiling for a short time it is filtered and the filtrate evaporated to dryness. The residue is recrystallised from dilute alcohol.

Silver salt: The aqueous solution of 4-aminobenzene-sulphon-acetamide sodium is mixed with a silver nitrate solution. The silver salt precipitates, is filtered off by suction, and is washed with water, alcohol, and ether. The product has a melting point of 216° C.

(i) Mercury salt: From an aqueous solution of the sodium salt of 4-aminobenzene-sulphon-acetamide the mercury salt of this sulphon amide compound is obtained by precipitation by means of a mercury acetate solution. It has a melting point of 251° C. (under decomposition).

(k) Quinine salt: 31.4 grams of 4-aminobenzene-sulphon-acetamide and 32.4 grams of quinine are dissolved in 200 cc. of alcohol. After distilling off the alcohol the quinine salt remains. It is soluble in water and melts at about 73° C.

(i) Morphine salt: 21.4 grams of 4-aminobenzene-sulphon-acetamide and 30.3 grams of morphine are dissolved while heating in 200 cc. of alcohol. The salt is precipitated by adding ether and has a melting point of 160° C. (not sharp).

Example 29

4-aminobenzene-sulphonpropionyl-amide calcium salt

22.8 grams of 4-aminobenzene-sulphonpropionyl amide are dissolved while heating in 150 cc. of water. To this solution 5.0 grams of calcium carbonate are added. After heating to boiling the solution is filtered and the filtrate is evaporated to dryness. The residue is recrystallised from dilute alcohol and has a melting point of 283° C. (with decomposition).

Example 30

4-aminobenzene-sulphonfurolyl-amide magnesium salt

26.6 grams of 4-aminobenzene-sulphonfurolylamide are dissolved while heating in 200 cc. of water. The solution is heated to boiling with 4.2 grams of magnesium carbonate. The filtered solution is concentrated by evaporation and is recrystallised from dilute alcohol.
melting point 178°C, produced from 2-chloropyridine-5-sulfonamide by boiling with aniline, the 2-anilido-pyridine-5-sulfonacetamide.

EXAMPLE 37

4-acycloxsulfamidobenzene-1.1'-azo-2.6'-diaminopyrididine

5 grams of 4-aminobenzene sulfonacetamide are diazotized in a customary manner in hydrochloric acid solution with 1.6 grams of sodium nitrite. To the diazo solution there is added a hydrochloric acid solution of 2.6 grams of 2.6-di-aminopyrididine. After adding sodium acetate to this solution a voluminous, orange-redprecipitate of the reaction product is formed which is filtered off by suction, washed with water and recrystallized from alcohol. The azo compound forms orange-red needles of melting point 191-192°C, and is soluble in sodium carbonate solution.

Instead of pyridine compounds other heterocyclic compounds may be used likewise such as those of the quinoline, pyrrole, indol, pyrazole and the like series.

Instead of the acylating agents employed in these examples obviously also others can be employed, for example, the anhydrides or halides of higher fatty acids such as those of palmitic acid, hydnocarpus acid, phenyl-cinchonic acid, pyridine carboxylic acids and others.

It is true that sulphonamides amino substituted in the nucleus have previously been acylated, compare French specification 820,546. As, however, is shown by the more detailed description of the specification in this case always 1 mol of acylating agent is employed for 1 mol of the sulphonamide. By this means, however, only the nuclear bound amino group is acylated. According to the process of the present application, however, an excess of acylating agent is employed so that both the nuclear bound amino group and also the sulphonamide group are acylated; one of these acyl groups and in fact that which has entered the nuclear bound amino group can then again easily be split off so that the free amino group is reformed.

In the subjoined claims the term "aromatic" is to be understood as embracing compounds having either a phenyl or a pyridyl radical, e.g. the benzene, pyridine and quinoline compounds disclosed hereinabove.

What we claim is:

1. A 4-aminobenzene-sulfonacetamidylamide of the general formula

\[
\text{NH}_2\text{C}_6\text{H}_4\text{SO}_2\text{N} (Y) \cdot \text{CO} \cdot \text{CH}_3
\]

wherein \( Y \) is a member of the group consisting of hydrogen and metals.

2. A process for preparing \( N' \)-acylsulfanilamides which comprises reacting sulfanilamide with at least two equivalents of a member of the group consisting of monobasic aliphatic carboxylic acid halides and anhydrides, and hydrolysing the \( N' \)-acylamino group only of the resulting product.

3. \( N' \)-acylsulfanilamides of the following formula:

\[
\text{NH} - \text{C} - \text{OS} - \text{NH} - \text{CO} - \text{alkyl}
\]

4. 4-amino-benzene-sulfanacetylamide.

5. The sodium salt of 4-amino-benzene-sulfonacetamidylamide.

6. In a process for the manufacture of \( N' \)-acyl sulphonamides, the step comprising subjecting a sulphonamide compound having directly attached to the sulphur atom a ring carbon of an aromatic residue which has an amino group linked through the nitrogen to a ring carbon in \( p \)-position to the first-mentioned carbon, to the action of at least 2 mols of an acylating agent to acylate both the amide nitrogen and the clearly bound amino group, the sulphonamide group being converted into the group \(-\text{SO}_2\cdot\text{NH} \cdot \text{OC} \cdot \text{R}, \) the group \(-\text{OC} \cdot \text{R}\) being the acyl radical of a carboxylic acid.

7. In a process for the manufacture of \( N' \)-acyl sulphonamides, the steps comprising subjecting a sulphonamide compound having directly attached to the sulphur atom a ring carbon of an aromatic residue which has an amino group linked through the nitrogen to a ring carbon in \( p \)-position to the first-mentioned carbon, to the action of at least 2 mols of an acylating agent to acylate both the amide nitrogen and the clearly bound amino group, the sulphonamide group being converted into the group

\[
\text{SO}_2\cdot\text{NH} \cdot \text{OC} \cdot \text{R}
\]

8. Process for the manufacture of 4-amino-benzensulphonamidylamines, comprising subjecting p-aminobenzensulphonamide to the action of at least 2 mols of an acylating agent to acylate both the amide nitrogen and the clearly bound amino group, the sulphonamide group being converted into the group \(-\text{SO}_2\cdot\text{NH} \cdot \text{OC} \cdot \text{R}, \) the group \(-\text{OC} \cdot \text{R}\) being the acyl radical of a carboxylic acid, and saponifying the 4-acylamino group to yield the 4-aminobenzensulphonicamidylamide.

9. In a process for the manufacture of \( N' \)-acyl sulphonamides, the steps comprising subjecting a sulphonamide compound having directly attached to the sulphur atom a ring carbon of an aromatic residue which has an amino group linked through the nitrogen to a ring carbon in \( p \)-position to the first-mentioned carbon, to the action of at least 2 mols of an acylating agent to acylate both the amide nitrogen and the clearly bound amino group, the sulphonamide group being converted into the group

\[
\text{SO}_2\cdot\text{NH} \cdot \text{OC} \cdot \text{R}
\]

the group \(-\text{OC} \cdot \text{R}\) being the acyl radical of a carboxylic acid, and converting the \( N' \)-acyl sulphonamides into salts by treatment with a member of the group consisting of organic and inorganic bases.

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