AMENDED SPECIFICATION

Reprinted as amended under Section 8 of the Patents and Designs Acts, 1907 to 1946.

PATENT SPECIFICATION

568,850

Application Date: Jan. 18, 1943. No. 881/43.

Complete Specification Left: Jan. 17, 1944.

Complete Specification Accepted: April 24, 1945.

PROVISIONAL SPECIFICATION

Guanidine Derivatives

We, STANLEY BIRTWELL and CHARLES HENRY VASEY, both of Hexagon House, Blackley, Manchester, both British Subjects, and IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a Company incorporated under the laws of Great Britain, do hereby declare the nature of this invention to be as follows:—

This invention relates to the manufacture of guanidine derivatives, and more particularly to the manufacture of sulphonyl guanidines of the formula

(*p*) $X—C_6H_4—SO_2—NH—C(NH)—NH_2$

wherein X stands for amino or acylamino, for example, formylamino or acetylamino.

According to the invention we make the said sulphonyl guanidines by causing the corresponding sulphonamide (*p*) $X—C_6H_4—SO_2—NH_2$ to interact with guanidine or guanidine hydrate or a salt of guanidine with a weak acid (e.g. guanidine carbonate), or by causing an alkali metal salt of the said sulphonamide to react with a guanidine salt.

In this latter case, the guanidine salt need not be that of a weak acid. For instance, guanidine sulphate or guanidine hydrochloride will serve.

The reaction is preferably, but not necessarily, carried out in the presence of a solvent or diluent.

Guanidine salts of weak acids suitable for use in that embodiment of the invention first described above are the carbonate, the acetate, the phenate or the cresylate. In the latter two cases the phenol or cresol may serve both as the weak acid and also as solvent or diluent. Phenol and cresol are, in fact, particularly suitable solvents since the reaction is conveniently carried out at temperatures of the order of 160° C.

The starting materials need not be used in stoichiometric proportions since the reaction will go in presence of an excess of either of them. In practice it is preferred to use equimolecular proportions or a slight excess of the guanidine component.

When guanidine hydrate is used it is conveniently generated from a guanidine salt and a caustic alkali, as illustrated in Example 4 below. Guanidine itself may be similarly generated from a guanidine salt and an alkali metal alkoxide, as in Example 5.

The following Examples illustrate, but do not limit the invention. The parts are by weight.

EXAMPLE 1.

43 parts of sulphanilamide are heated to 160°—165° C. The mass fuses and 31 parts of guanidine carbonate are gradually added during half an hour. Ammonia and carbon dioxide are evolved. The mixture is maintained at 160° C. for a further hour and is then worked up as follows:

The melt is cooled to ~~150°~~ 120° C. Then 150 parts of water are added and cooling is continued. When the temperature has reached 40° C., 100 parts of hydrochloric acid (Sp. gr. 1.18) are added and the mixture is stirred until all has dissolved. Then sodium hydroxide solution is added until the mixture is strongly alkaline (pH 11). This precipitates the sulphanilyl guanidine and dissolves any unchanged sulphanilamide. After cooling to room temperature the precipitate is filtered off, washed well with water and finally dried at 70°—80° C. There is thus obtained sulphanilyl-guanidine. This may be purified, if desired, by recrystallisation from water. It then has m.p. 189°—190° C.

EXAMPLE 2.

43 parts of sulphanilamide are dissolved in 50 parts of phenol and the mixture is heated to 160° C. 22 parts of guanidine carbonate are added during three quarters of an hour. Ammonia and carbon dioxide are evolved. The mixture is maintained at 150°—160° C. for 1 hour and is then poured into 150 parts of water. 100 parts of hydrochloric acid (Sp. gr. 1.18) are

[*Price* 1/-]

added and the mixture is stirred until all has dissolved. This solution is extracted with 100 parts of toluene, whereby the phenol is removed. The aqueous layer is made strongly alkaline (pH 11) by the addition of caustic soda solution. A solid is precipitated, which is filtered off and dried. This is sulphanilyl guanidine. After recrystallisation from water it has m.p. 189—190° C.

EXAMPLE 3.

A mixture of 86 parts of sulphanilamide, 44 parts of guanidine carbonate and 100 parts of water is boiled under a reflux condenser. The reagents dissolve up rapidly. At the end of the heating period the solution is worked up as described in Example 1.

EXAMPLE 4.

40 parts of sodium hydroxide are dissolved in 300 parts of methanol and the solution is refluxed for ¼ hour with 122 parts of guanidine nitrate. The suspension as obtained is cooled to 20° C. and the sodium nitrate which separates out is filtered off. The solution now contains guanidine hydrate. 172 parts of sulphanilamide are added. The methanol is now distilled off. The residue is then heated to 160° C. and maintained at that temperature for 2¾ hours, after which the reaction mixture is worked up as described in Example 1.

EXAMPLE 5.

11.5 parts of sodium are dissolved in 250 parts of methanol, 61 parts of guanidine nitrate are added and the mixture is refluxed for half an hour. The suspension so obtained is cooled to 20° C. and the sodium nitrate is filtered off. The solution then contains free guanidine base.

To this solution 86 parts of sulphanilamide are added and the methanol is distilled off. The residue is heated at 160° C. for one hour and the reaction mixture is then worked up as described in Example 1.

EXAMPLE 6.

20 parts of *p*-acetylaminobenzenesulphonamide are heated with 5 parts of phenol and 10 parts of guanidine carbonate at 160—180° C. for one hour. The reaction mixture is poured into 200 parts of water and then made strongly alkaline (pH 11) by addition of sodium hydroxide solution. This dissolves up in unchanged acetylaminobenzenesulphonamide and phenol and leaves the acetylsulphanilylguanidine which has been formed undissolved. The latter is filtered off and can be converted into sulphanilylguanidine as follows.

The acetylsulphanilylguanidine is heated for 5 minutes at 100° C. with a solution of 5 parts of concentrated hydrochloric acid in 10 parts of water. The solution is cooled to 40° C., then made strongly alkaline (pH 11) by addition of sodium hydroxide and cooled to 20° C. Sulphanilylguanidine separates out and is filtered off. It is then recrystallised from boiling water whereby it is obtained in crystalline form with m.p. ~~180~~—190° C.

Dated the 18th day of January, 1943.

E. A. BINGEN,
Solicitor for the Applicants.

COMPLETE SPECIFICATION

Guanidine Derivatives

We, STANLEY BIRTWELL and CHARLES HENRY VASEY, both of Hexagon House, Blackley, Manchester, both British Subjects, and IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a Company incorporated under the laws of Great Britain, 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 relates to the manufacture of guanidine derivatives, and more particularly to the manufacture of *p*-substituted benzene sulphonyl guanidines of the formula

(*p*) $X—C_6H_4—SO_2—NH—C(NH)—NH_2$

wherein X stands for amino or acylamino, for example, formylamino or acetylamino.

According to the invention we make the said sulphonyl guanidines by heating the corresponding sulphonamide (*p*) $X—C_6H_4—SO_2—NH_2$ with a guanidine compound or its hydrate.

By the term "guanidine compound" as used in this Specification we mean guanidine itself and also those derivatives wherein one or both of the hydrogen atoms of one of the amino groups have been substituted by a lower alkyl radical such as methyl, ethyl or propyl.

Instead of supplying the guanidine compound and the sulphonamide separately, a preformed salt of the sulphonamide with the guanidine compound may be used. These salts are readily formed by bringing the components together in presence of a solvent; heating is unnecessary. It is probable, indeed, that when the starting materials are introduced separately, the first reaction is the formation of such a salt, which is subsequently decomposed by the heating with formation of the sul-

phonyl guanidine and ammonia or a primary or secondary amine.

The reaction is preferably, but not necessarily, carried out in presence of a solvent or diluent.

The starting materials need not be used in stoichiometric proportions since the reaction will go in presence of an excess of either of them. In practice it is preferred to use equimolecular proportions or a slight excess of the guanidine component.

When a guanidine hydrate is used it is conveniently generated from a guanidine salt and a caustic alkali, as illustrated in Example 1 below. The guanidine base itself may be similarly generated from a guanidine salt and an alkali metal alkoxide, as in Example 2.

As is known, sulphanilyl guanidine is of value as an intestinal antibacterial agent and also as an intermediate for the manufacture of other chemotherapeutic agents. The acyl derivatives are readily hydrolysed by known methods to sulphanilyl guanidine.

The following Examples illustrate, but do not limit, the invention. The parts are by weight.

EXAMPLE 1.

40 parts of sodium hydroxide are dissolved in 300 parts of methanol and the solution is refluxed for ¼ hour with 122 parts of guanidine nitrate. The suspension so obtained is cooled to 20° C. and the sodium nitrate which separates out is filtered off. The solution now contains guanidine hydrate. 172 parts of sulphanilamide are added. The methanol is now distilled off. The residue is then heated to 160° C. and maintained at that temperature for 2¾ hours.

The melt is cooled to 120° C. Then 600 parts of water are added and cooling is continued. When the temperature has reached 40° C., 400 parts of hydrochloric acid (Sp. gr. 1.18) are added and the mixture is stirred until all has dissolved. Then sodium hydroxide solution is added until the mixture is strongly alkaline (pH 11). This precipitates the sulphanilyl guanidine and dissolves any unchanged sulphanilamide. After cooling to room temperature the precipitate is filtered off, washed well with water and finally dried at 70°—80° C. There is thus obtained sulphanilyl guanidine. This may be purified, if desired, by recrystallisation from water. It then has m.p. 189°—190° C.

EXAMPLE 2.

11.5 parts of sodium are dissolved in 250 parts of methanol, 61 parts of guanidine nitrate are added and the mixture is refluxed for half an hour. The suspension so obtained is cooled to 20° C. and the sodium nitrate is filtered off. The solution then contains free guanidine base.

To this solution 86 parts of sulphanilamide are added and the methanol is distilled off. The residue is heated at 160° C. for one hour and the reaction mixture is then worked up as described in Example 1.

EXAMPLE 3.

40 parts of caustic soda are dissolved in 300 parts of methanol and the solution is refluxed for ¼ hour with 122 parts of methylguanidine sulphate. The suspension so obtained is cooled to 20° C. and the sodium sulphate which separates out is filtered off. The solution now contains methylguanidine hydrate. 172 parts of sulphanilamide are added and the methanol is distilled off. 50 parts of the mixture of isomeric methyl cyclohexanols sold under the trade name "Sextol" are added and the mixture is heated to 160° C. for 2 hours. The melt is then cooled slightly and 30 parts of water are added. The resulting solution is poured into a solution of 175 parts of hydrochloric acid in 1000 parts of water, and then crude sulphanilylguanidine is precipitated by addition of caustic soda until the mixture is quite alkaline (pH 11). The solid is filtered off and twice recrystallised from water. It then has m.p. 186°—187° C.

EXAMPLE 4.

The procedure here is exactly as in Example 3 except that instead of 122 parts of methylguanidine sulphate, 136 parts of α:α-dimethylguanidine sulphate are used. The precipitated sulphanilylguanidine after one recrystallisation from water, had m.p. 188—189° C.

We are aware that in British Specification No. 571,780 there is claimed a process for the production of para-substituted benzene sulphonylguanidines which comprises heating to the reaction temperature a guanidine salt and a compound of the formula p-R—C_6H_4—SO_2NH_2 wherein R represents an amino radical, a radical hydrolysable to an amino group, including acyl amino radicals, or a group reducible to an amino group, including a nitro group, but we make no claim herein to anything therein claimed.

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 subject to the foregoing disclaimer what we claim is:—

1. Process for the manufacture of p-substituted benzene sulphonyl guanidines of the formula

(p) X—C_6H_4—SO_2—NH—C(NH)—NH_2,

wherein X stands for amino or acylamino, which comprises heating the corresponding sulphonamide (p) X—C_6H_4—SO_2—NH_2

phonyl guanidine and ammonia or a primary or secondary amine.

The reaction is preferably, but not necessarily, carried out in presence of a solvent or diluent.

The starting materials need not be used in stoichiometric proportions since the reaction will go in presence of an excess of either of them. In practice it is preferred to use equimolecular proportions or a slight excess of the guanidine component.

When a guanidine hydrate is used it is conveniently generated from a guanidine salt and a caustic alkali, as illustrated in Example 1 below. The guanidine base itself may be similarly generated from a guanidine salt and an alkali metal alkoxide, as in Example 2.

As is known, sulphanilyl guanidine is of value as an intestinal antibacterial agent and also as an intermediate for the manufacture of other chemotherapeutic agents. The acyl derivatives are readily hydrolysed by known methods to sulphanilyl guanidine.

The following Examples illustrate, but do not limit, the invention. The parts are by weight.

EXAMPLE 1.

40 parts of sodium hydroxide are dissolved in 300 parts of methanol and the solution is refluxed for ¼ hour with 122 parts of guanidine nitrate. The suspension so obtained is cooled to 20° C. and the sodium nitrate which separates out is filtered off. The solution now contains guanidine hydrate. 172 parts of sulphanilamide are added. The methanol is now distilled off. The residue is then heated to 160° C. and maintained at that temperature for 2¾ hours.

The melt is cooled to 120° C. Then 600 parts of water are added and cooling is continued. When the temperature has reached 40° C., 400 parts of hydrochloric acid (Sp. gr. 1.18) are added and the mixture is stirred until all has dissolved. Then sodium hydroxide solution is added until the mixture is strongly alkaline (pH 11). This precipitates the sulphanilyl guanidine and dissolves any unchanged sulphanilamide. After cooling to room temperature the precipitate is filtered off, washed well with water and finally dried at 70°—80° C. There is thus obtained sulphanilyl guanidine. This may be purified, if desired, by recrystallisation from water. It then has m.p. 189°—190° C.

EXAMPLE 2.

11.5 parts of sodium are dissolved in 250 parts of methanol, 61 parts of guanidine nitrate are added and the mixture is refluxed for half an hour. The suspension so obtained is cooled to 20° C. and the sodium nitrate is filtered off. The solution then contains free guanidine base.

To this solution 86 parts of sulphanilamide are added and the methanol is distilled off. The residue is heated at 160° C. for one hour and the reaction mixture is then worked up as described in Example 1.

EXAMPLE 3.

40 parts of caustic soda are dissolved in 300 parts of methanol and the solution is refluxed for ¼ hour with 122 parts of methylguanidine sulphate. The suspension so obtained is cooled to 20° C. and the sodium sulphate which separates out is filtered off. The solution now contains methylguanidine hydrate. 172 parts of sulphanilamide are added and the methanol is distilled off. 50 parts of the mixture of isomeric methyl cyclohexanols sold under the trade name "Sextol" are added and the mixture is heated to 160° C. for 2 hours. The melt is then cooled slightly and 30 parts of water are added. The resulting solution is poured into a solution of 175 parts of hydrochloric acid in 1000 parts of water, and then crude sulphanilylguanidine is precipitated by addition of caustic soda until the mixture is quite alkaline (pH 11). The solid is filtered off and twice recrystallised from water. It then has m.p. 186°—187° C.

EXAMPLE 4.

The procedure here is exactly as in Example 3 except that instead of 122 parts of methylguanidine sulphate, 136 parts of α:α-dimethylguanidine sulphate are used. The precipitated sulphanilylguanidine after one recrystallisation from water, had m.p. 188—189° C.

We are aware that in British Specification No. 571,780 there is claimed a process for the production of para-substituted benzene sulphonylguanidines which comprises heating to the reaction temperature a guanidine salt and a compound of the formula p-R—C_6H_4—SO_2NH_2 wherein R represents an amino radical, a radical hydrolysable to an amino group, including acyl amino radicals, or a group reducible to an amino group, including a nitro group, but we make no claim herein to anything therein claimed.

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 subject to the foregoing disclaimer what we claim is:—

1. Process for the manufacture of p-substituted benzene sulphonyl guanidines of the formula

(p) X—C_6H_4—SO_2—NH—C(NH)—NH_2.

wherein X stands for amino or acylamino, which comprises heating the corresponding sulphonamide (p) X—C_6H_4—SO_2—NH_2

* C L M S *

568850/4

with a guanidine compound as hereinbefore defined or with its hydrate.

2. Modification of the process of Claim 1 wherein instead of the sulphonamide and the guanidine compound there is used the preformed salt obtained by interaction of these two components.

3. Process as claimed in either of the preceding claims wherein there is used a slight excess over the theoretical proportion of the guanidine component.

4. Process as claimed in any of the preceding claims wherein the reaction is carried out in presence of a solvent or diluent.

5. Process for the manufacture of *p*-substituted benzene sulphonyl guanidines as described with reference to each of the foregoing Examples.

6. *p*-Substituted benzene sulphonyl guanidines whenever made by the process of any of the preceding claims.

Dated the 17th day of January, 1944.

E. A. BINGEN,
Solicitor for the Applicants

Leamington Spa: Printed for His Majesty's Stationery Office, by the Courier Press.—1947.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies, price 1s. 0d. each (inland) 1s. 1d. (abroad) may be obtained.

* C L M S *

9.2.9.