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COMPLETE SPECIFICATION

Process for the manufacture of 4-Sulphanilamido-2, 6-Dimethoxy-Pyrimidine

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124-184 Grenzacherstrasse, Basle, Switzerland, 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:—

The present invention relates to a novel process for the manufacture of 4-sulphanilamido-2, 6-dimethoxy-pyrimidine, a compound which is useful as an antibacterial agent for combatting pathogenic micro-organisms such as the *Streptococci* and *Staphylococci*. The invention also relates to a novel method for producing an intermediate useful for the production of said anti-bacterial agent.

Previous methods disclosed for the production of 4-sulphanilamido-2, 6-dimethoxy-pyrimidine suffer from numerous disadvantages. The yield of final product is very low, e.g. only of the order of 15% when barbituric acid is the starting material. They are costly because the starting materials and other agents are relatively expensive. In addition, certain intermediate products irritate the skin or are gaseous, requiring difficult recovery procedures. The process of the present invention gives good yields and avoids the foregoing disadvantages.

The process of the invention in ~~board~~ broad outline may be described as follows: The starting material is 4-amino-2, 6-dihydroxy-pyrimidine, a material which is readily procurable [CONRAD, Liebig's Annalen der Chemie, 1905, *340*, 312], and is converted to 4-amino-2, 6-dichloro-pyrimidine. This step avoids the use of trichloro-pyrimidine which has irritant properties and from which only low yields of the desired 4-amino-2, 6-dichloro-pyrimidine are obtained. The 4-amino-2, 6-dichloro-pyrimidine is then converted to 4-amino-2, 6-dimethoxy-pyrimidine in high yield and the latter is condensed with a benzene-sulphonyl chloride and the substituent on the benzene ring is converted to the amino group to obtain the required 4-sulphanilamido-2, 6-dimethoxy-pyrimidine. In this process, however, particular conditions must be observed at certain stages in order that high conversion efficiencies are obtained, difficult separations and recoveries as well as toxic materials are avoided and a technically valuable synthesis results. At these critical stages, discussed more fully hereinafter, even the adoption of expedients which increase the yield of similar compounds are not effective here.

The production of 4-amino-2, 6-dichloro-pyrimidine from 4-amino-2, 6-dihydroxy-pyrimidine is a critical step since very poor conversions are obtained except under particular conditions. The 4-amino-2, 6-dichloro-pyrimidine is produced by heating 4-amino-2, 6-dihydroxy-pyrimidine with excess phosphorus oxychloride ($POCl_3$) in the presence of N, N-~~de~~methyl-aniline to a temperature of about 70°C. to 130°C., preferably 80°C. to 100°C. It is essential in order to achieve good results to use the materials in the following proportions on a weight (gram) basis: 1 part 4-amino-2, 6-dihydroxy-pyrimidine; 4 to 12 parts, preferably 11 parts, phosphorus oxychloride and 0·2 to 1·5 parts, ~~perfarably~~ preferably 0·3 parts, N,N-dimethyl-aniline. The proportion of N,N-dimethyl-aniline is particularly significant. A decrease in the proportion of N,N-dimethyl-aniline from the amounts stated increases the time of reaction. An increase in the proportion of N,N-dimethyl-aniline from the amounts stated complicates the working up of the product and causes greater losses in the recovery of phosphorus oxychloride without increasing the yield of product. About 2 to 10 hours should be allowed for the reaction.

In addition, it is particularly advantageous when working up the crude 4-amino-2,

6-dichloro-pyrimidine to remove a substantial part of the excess phosphorus oxychloride. This may be effected, for example by distilling *in vacuo*. The residue should then be dissolved in water. It is important that the temperature of the water should not be too low. Water at a temperature in the range 0 °C. to 40 °C., preferably about 30 °C., should be used. Then upon adjusting the pH of the solution to 3·8 to 4·5, for example by means of aqueous ammonia solution, and heating to boiling, the 4-amino-2, 6-dichloro-pyrimidine precipitates. Under these conditions yields of about 60% to 90% of crude 4-amino-2, 6-dichloro-pyrimidine are obtained. This product need not further be purified in order to be used in the succeeding step of the synthesis.

In the conversion of 4-amino-2, 6-dichloro-pyrimidine to 4-amino-2, 6-dimethoxy-pyrimidine, which is effected by means of an alkali-metal methoxide (e.g. sodium methoxide) in methanol, it is important to permit the reaction to continue for sufficient time in order to obtain substantially complete conversion and to avoid chlorinated compounds in the product. This may be accomplished by heating ~~under reflux~~ at a temperature exceeding the boiling point of the alcohol; that is to say, by heating ~~under reflux~~ under pressure.

The 4-amino-2, 6-dimethoxy-pyrimidine, may be purified by distillation or sublimation *in vacuo* at about 0·5 mm. of mercury and with a bath temperature at about 130 °C. to 140 °C.

The 4-amino-2, 6-dimethoxy-pyrimidine is then condensed with a benzene-sulphonyl halide (preferably the chloride) containing in the 4-position a substituent group which may be converted by hydrolysis or reduction to the amino group; examples of suitable substituents are acylamino groups (such as acetylamino or propionylamino) or alkoxycarbonylamino groups (such as ethoxycarbonylamino) or the nitro group. This condensation is effected in the presence of an acid-binding agent (e.g. pyridine). As a last stage in the reaction, the substituent in the 4-position of the benzene ring is converted by hydrolysis or reduction to the amino group.

An advantageous method of producing 4-sulphanilamido-2, 6-dimethoxy-pyrimidine, from the point of view of purity and yield, includes the treatment of 4-amino-2, 6-dimethoxy-pyrimidine with a slight excess of 4-acetylamino-benzenesulphonyl chloride in the presence of pyridine at a temperature not exceeding 60 °C. preferably 20 °C to 30 °C. The 4-(4¹-acetylamino-benzene-sulphonamido)-2, 6-dimethoxy-pyrimidine thus formed need not be further purified for the final step of hydrolysis.

The first step of the present process, namely the preparation of 4-amino-2, 6-dichloro-pyrimidine, is described and claimed in the specification of our copending application for Letters Patent No.: 32370/59 (now serial No.: 841239).

It will be appreciated that the second step of the process, namely that which comprises heating 4-amino-2, 6-dichloro-pyrimidine with an alkali-metal methoxide in methanol at a temperature exceeding the boiling temperature of methanol, *per se* also forms part of the invention.

The following examples are illustrative of the process:

Example 1.

3·0 g. of 4-amino-2, 6-dihydroxy-pyrimidine moistened with 1 ml. of N,N-dimethyl-aniline were heated with 20 ml. of phosphorus oxychloride over a bath at a temperature of 125 °C. to 135 °C. under reflux-cooling and with occasional agitation. After about 3 to 4 hours there resulted a clear red-brown solution. After heating for approximately 5 additional hours, there was only a very weak evolution of hydrogen chloride gas. The excess phosphorus oxychloride was substantially completely removed *in vacuo* at about 15 mm. of mercury and a temperature of 100 °C. Water was added to the evaporation residue. By stirring the water layer, the material was gradually dissolved at a temperature not exceeding 30 °C. After standing and filtering, the pH was adjusted to 3·8 with concentrated ammonia while cooling with ice. The mixture was then heated to boiling whereupon crystallisation began and was continued until a hot filtered sample produced no more precipitate upon additional heating. The mixture was cooled, the precipitate was isolated and washed with water. 2·47 g. (63·5% of theory) of 4-amino-2, 6-dichloro-pyrimidine (decomposition point 265 °C.) were obtained. Further purification by vacuum sublimation was not necessary in order to use the product in the next step of the synthesis.

6·27 g. of dry, crude 4-amino-2,6-dichloro-pyrimidine were treated with a solution of 2·3 g. of sodium in 50 ml. of absolute methanol and were heated under pressure for 12 hours at bath temperature of 120 °C. The concentrate was treated with water and extracted with hot benzene to obtain 5·05 g. (about 85% of theory) of crystallized crude product. The crude product was purified by subliming *in vacuo* (at 0·5 mm. of mercury) and a bath temperature of 120 °C. to 130 °C. whereby practically pure 4-amino-2, 6-dimethoxy-pyrimidine of m.h. 145 °C. to 150 °C. was obtained in a yield of 81%. Upon recrystallisation from ether, the product melted at ~~150°C~~ 150°C.

4·65 g. of sublimed 4-amino-2, 6-dimethoxy-pyrimidine was dissolved in 15 ml. of absolute pyridine while warming. The

solution was cooled and treated with 8·30 g. of 4-(ethoxycarbonylamino)-benzenesulphonyl chloride. The mixture was maintained for 15 minutes at 20 °C. and 1 hour at 60 °C. (bath temperature) and the pyridine was then separated *in vacuo*. The amorphous residue was digested with sodium carbonate solution (7 g. of salt in 70 ml. of water) until dissolved. The solution was filtered and the product was precipitated in the filtrate with 20 ml. of 30% acetic acid. After digesting the precipitate at 40 °C. (bath temperature) and isolation, there were obtained upon cooling 10·1 g. (88% of theory) of 4-(4¹-ethoxycarbonylamino-benzenesulphonamido)-2, 6-dimethoxy-pyrimidine; m.p. 192 °C. to 196 °C.

10·1 g. of 4-(4¹-ethoxycarbonylamino-benzenesulphonamido)-2, 6-dimethoxy-pyrimidine were heated with 92 ml. of 1-*N* sodium hydroxide for 1 hour at an internal temperature of 88 °C. to 90 °C. (yellow colour). The clear coloured solution was dropped into cool dilute hydrochloric acid (50 ml. concentrated hydrochloric acid in 70 ml. water) while cooling. The clear, slightly coloured, solution was warmed to about 35 °C., digested with charcoal and filtered. Upon neutralisation with ammonia while cooling, there crystallised immediately from the colourless filtrate, 4-sulphanilamido-2, 6-dimethoxy-pyrimidine in pure white form; m.p. 201 °C. to 203 °C.; 7·3 g. (89% of theory).

Example 2.

72 g. of 4-amino-2, 6-dimethoxy-pyrimidine (obtained according to example 1) were suspended in 216 ml. of pyridine under exclusion of moisture. 152 g. of 4-acetylamino-benzenesulphonyl chloride were added with stirring and cooling, at such a rate that the temperature was kept between 20 °-25 °C. After stirring for 24 hours, 450 ml. of water and, 10 minutes later, 175 ml. of 80% acetic acid were added and the mixture was stirred at 0 °C. for 2 more hours. The crystals of 4-(4¹-acetylamino—benzenesulphonamido-2, 6-dimethoxy-pyrimidine formed were filtered off and washed several times with water. After drying *in vacuo* at 80 °C., there were obtained 148 g. of a material melting at ~~220 °C~~- 224 °C.

70 g. of 4-(4¹-acetylamino-benzenesulphonamido)-2, 6-dimethoxy-pyrimidine were dissolved at 40 °C. in 200 ml. of concentrated ~~sodium~~ hydroxide and 400 ml. of water. The mixture was kept at this temperature for 16 hours. Then the mixture was cooled with ice, and 140 ml. of concentrated hydrochloric acid were added. After filtration over charcoal and washing out with 300 ml. of water, carbon dioxide was introduced and 4-sulphanilamido-2, 6-dimethoxy-pyrimidine was obtained; m.p. 203 °C-204 °C., yield, 52 g.

WHAT WE CLAIM IS:

1. A process for the manufacture of 4-sulphanilamido-2, 6-dimethoxy-pyrimidine, which process comprises heating 4-amino-2, 6-~~di~~hydroxy-pyrimidine at 70 °C to 130 °C with phosphorus oxychloride and N,N-dimethyl-aniline (for each part by weight of 4-amino-2, 6-dihydroxy-pyrimidine, 4 to 12 parts by weight of phosphorus oxychloride and 0·2 to 1·5 parts by weight of N,N-dimethyl-analine being used), removing a substantial part of the excess phosphorus oxychloride from the product and treating the residue with water at a temperature within the range of 0 °C to 40 °C, heating the resulting 4-amino-2, 6-dichloro-pyrimidine ~~under reflux~~ with an alkali-metal methoxide in methanol at a temperature exceeding the boiling temperature of methanol, condensing the 4-amino-2, 6-dimethoxy-pyrimidine thus obtained with a benzene-sulphonyl halide which contains as a substituent in the 4-position a group which is convertible by hydrolysis or reduction to an amino group and converting the said group in the condensation product to an amino group.

2. A process in accordance with Claim 1, wherein for each part by weight of 4-amino-2, 6-dihydroxy-pyrimidine there are used 11 parts by weight of phosphorus oxychloride and 0·3 parts by weight of N,N-dimethyl-aniline and wherein the heating is conducted at 80 °C to 100 °C.

3. A process in accordance with Claim 1 or Claim 2, wherein the said residue is treated with water at a temperature of *ca* 30 °C and the resulting solution adjusted to pH 3·8 to 4·5, boiled and the precipitated 4-amino-2, 6-dichloro-pyrimidine separated therefrom.

4. A process in accordance with any one of the preceding claims, wherein the heating ~~under reflux~~ is carried out for a period of 10 to 15 hours.

5. A process in accordance with any one of Claims 1 to 4 inclusive, wherein the benzenesulphonyl halide used is 4-acetylamino-benzenesulphonyl chloride and the condensation is carried out in the presence of pyridine at a temperature of about 20 ° to 30 °C.

6. A process in accordance with any one of the preceding claims, wherein said conversion of the 4-substituent group into an amino group is effected by hydrolysis with dilute sodium hydroxide.

7. A process for the manufacture of 4-sulphanilamido-2, 6-dimethoxy-pyrimidine, substantially as described with reference to the examples.

8. A process for the manufacture of 4-amino-2, 6-dimethoxy-pyrimidine, which process comprises heating 4-amino-2, 6-

solution was cooled and treated with 8·30 g. of 4-(ethoxycarbonylamino)-benzenesulphonyl chloride. The mixture was maintained for 15 minutes at 20 °C. and 1 hour at 60 °C. (bath temperature) and the pyridine was then separated *in vacuo*. The amorphous residue was digested with sodium carbonate solution (7 g. of salt in 70 ml. of water) until dissolved. The solution was filtered and the product was precipitated in the filtrate with 20 ml. of 30 % acetic acid. After digesting the precipitate at 40 °C. (bath temperature) and isolation, there were obtained upon cooling 10·1 g. (88 % of theory) of 4-(4¹-ethoxycarbonylamino-benzenesulphonamido)-2, 6-dimethoxy-pyrimidine; m.p. 192 °C. to 196 °C.

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70 g. of 4-(4¹-acetylamino-benzenesulphonamido)-2, 6-dimethoxy-pyrimidine were dissolved at 40 °C. in 200 ml. of concentrated ~~soldium~~ sodium hydroxide and 400 ml. of water. The mixture was kept at this temperature for 16 hours. Then the mixture was cooled with ice, and 140 ml. of concentrated hydrochloric acid were added. After filtration over charcoal and washing out with 300 ml. of water, carbon dioxide was introduced and 4-sulphanilamido-2, 6-dimethoxy-pyrimidine was obtained; m.p. 203 °C-204 °C., yield, 52 g.

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1. A process for the manufacture of 4-sulphanilamido-2, 6-dimethoxy-pyrimidine, which process comprises heating 4-amino-2, 6-~~dihe~~dihydroxy-pyrimidine at 70 °C to 130 °C with phosphorus oxychloride and N,N-dimethyl-aniline (for each part by weight of 4-amino-2, 6-dihydroxy-pyrimidine, 4 to 12 parts by weight of phosphorus oxychloride and 0·2 to 1·5 parts by weight of N,N-dimethyl-analine being used), removing a substantial part of the excess phosphorus oxychloride from the product and treating the residue with water at a temperature within the range of 0 °C to 40 °C, heating the resulting 4-amino-2, 6-dichloro-pyrimidine ~~under reflux~~ with an alkali-metal methoxide in methanol at a temperature exceeding the boiling temperature of methanol, condensing the 4-amino-2, 6-dimethoxy-pyrimidine thus obtained with a benzene-sulphonyl halide which contains as a substituent in the 4-position a group which is convertible by hydrolysis or reduction to an amino group and converting the said group in the condensation product to an amino group.

2. A process in accordance with Claim 1, wherein for each part by weight of 4-amino-2, 6-dihydroxy-pyrimidine there are used 11 parts by weight of phosphorus oxychloride and 0·3 parts by weight of N,N-dimethyl-aniline and wherein the heating is conducted at 80 °C to 100 °C.

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7. A process for the manufacture of 4-sulphanilamido-2, 6-dimethoxy-pyrimidine, substantially as described with reference to the examples.

8. A process for the manufacture of 4-amino-2, 6-dimethoxy-pyrimidine, which process comprises heating 4-amino-2, 6-

dichloro-pyrimidine with an alkali-metal methoxide in methanol at a temperature exceeding the boiling temperature of methanol.

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