PATENT SPECIFICATION

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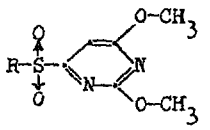
COMPLETE SPECIFICATION

Process for the manufacture of a Sulphonamide

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:—

This invention relates to a process for the manufacture of a sulphonamide, namely 4-sulphanilamido - 2,6 - dimethoxy - pyrimidine.

According to the process provided by the invention, the sulphonamide aforesaid is manufactured by reacting an alkali-metal salt of sulphanilamide with a pyrimidine derivative of the general formula



(I)

wherein R represents an alkyl, aralkyl, aryl, acylamino-aryl or a hydroxy group of the —O—Me group in which Me stands for a metal atom.

The substituent R in the foregoing formula may be, for example, a lower-alkyl group such as methyl, ethyl, propyl, *iso*propyl, butyl or hexyl or a phenyl-(lower alkyl) group such as benzyl or phenethyl or a monocyclic or bicyclic aryl group such as phenyl or naphthyl, or a lower alkanoylamino-phenyl group such as acetylamino-phenyl. R may also represent a hydroxy group. In the latter instance the reaction may be carried out using a pyrimidine derivative in which the hydroxy group is in the form of a metallo derivative e.g. an alkali-metal derivative such as —O—Na or O—K.

The reaction of the sulphanilamide salt with the pyrimidine compound is advantageously carried out by dry heating a mixture of the reactants at a temperature between about 100°C. and about 150°C. The sulphanilamido radical thereupon replaces the sulphur-containing substituent in the pyrimidine molecule. When 2,6 - dimethoxy-pyrimidine - (4) - sulphonic acid is used as starting material, it is preferable to heat that starting material with sodium sulphanilamide in molten acetamide.

The pyrimidine derivatives of formula I may be produced by several methods. One preferred method comprises reacting a sulphide of the general formula

$$R^1—S—Me$$

(wherein R^1 represents an alkyl, aralkyl, aryl or acylamino-aryl group and Me represents a metal atom) with a 2,6 - dimethoxy - 4-halogeno - pyrimidine and oxidising the resulting thioether. Any halogen may be present in the halogeno-pyrimidine but preferably it is chlorine or bromine. The reaction of the pyrimidine with the sulphide is best effected in an alcohol (e.g. a lower-alkanol) at an elevated temperature; for example, by heating in ethyl alcohol under reflux. The oxidation of the resulting thioether is preferably effected by means of peracetic acid.

According to another modification, the pyrimidine derivative of general formula I may be obtained by the reaction of a metal salt of an appropriately substituted aliphatic or aromatic sulphinic acid with a 2,6 - dimethoxy - 4 - halogeno - pyrimidine. According to an especially preferred method, the sulphinic acid (in the form of a dry alkali-metal salt) is heated with 2,6 - dimethoxy-4 - chloro - pyrimidine for several hours in ethyleneglycol at about 120°C. to 160°C. By using a salt of *p* - acetamino - benzene-sulphinic acid as the sulphinic acid salt, the chemical requirements are reduced since both this type of salt and the alkali-metal salt of the sulphanilamide used in the subsequent step are derived from *p* - acetamino - benzene-sulphonyl chloride.

The process of this invention allows of very good yields (in most instances more than 80% of theory) and the 2,6 - dimethoxy - 4-sulphanilamido - pyrimidine obtained is so

pure that wasteful purification operations are minimized.

The following examples are given by way of illustration of the process:—

EXAMPLE 1.

A. 4 - Phenylsulphonyl - 2,6 - dimethoxy-pyrimidine.

1) 1.15 g of of sodium were dissolved in 30 ml of absolute alcohol and the solution was treated with 5.2 ml of thiophenol. After the addition of 8.7 g of 4 - chloro - 2,6 - dimethoxy - pyrimidine, the mixture was heated at the boil for two hours while excluding moisture. After cooling, sodium chloride was separated from the reaction mixture by filtration (2.7 g) and the alcohol solution was concentrated *in vacuo*. Upon the addition of water to the oily residue, crystallization ensued. The crude 4 - phenylmercapto - 2,6-dimethoxy - pyrimidine was dried; it melted at 45°—55°C. The product was dissolved and precipitated from alcohol; it then melted at 65°—69°C. [yield of pure compound 9.5 g (76% of theory)].

2.5 g of 4 - phenylmercapto - 2,6 - dimethoxy - pyrimidine were dissolved in 4 ml of glacial acetic acid and treated at 20°C. with 16 ml of peracetic acid (13%). When the exothermic reaction died down, the mixture was heated for 30 minutes on a boiling-water bath. After distilling off the acetic acid *in vacuo*, the residual oil was dissolved in 10 to 15 ml of methanol and placed in the refrigerator. The crystalline 4 - phenylsulphonyl-2,6 - dimethoxy - pyrimidine was isolated and weighed 2.4 g (85% of theory); m.p. = 100°—104°C. The product was dissolved and recrystallised from alcohol; it then melted at 104°—106°C.

2) 2 g of the dry potassium salt of benzenesulphinic acid, 1.7 g of 4 - chloro - 2,6-dimethoxy - pyrimidine and 5 ml of ethylene glycol were maintained for 5 hours in an oil bath at 140°—145°C. (inside temperature). After cooling, 30 ml of water were added and the mixture was extracted with ether. 2.5 g of an oil remained which crystallised upon trituration with 10 ml of alcohol. The 4-phenylsulphonyl - 2,6 - dimethoxy - pyrimidine melted at 102°—104°C.

B. 4 - sulphanilamido - 2,6 - dimethoxy-pyrimidine.

1.4 g of 4 - phenylsulphonyl - 2,6 - dimethoxy - pyrimidine and 4 g of sodium sulphanilamide (both dried over potassium hydroxide) were very finely ground and heated in oil bath for 10 hours at 120°C. (inside temperature). The reaction mixture was taken up in 30 ml of water and treated with 3 ml of 2-*N* sodium hydroxide solution. After standing for 1 hour at 0°C. the turbid solution was filtered and the filtrate was made alkaline with sodium carbonate. After again standing for 1 hour at 0°C., the precipitate was filtered off (1.9 g. of regenerated sulphanilamide) and the filtrate was neutralized with acetic acid, whereupon crystallisation resulted. The isolated crystals of 4 - sulphanilamido - 2,6-dimethoxy - pyrimidine weighed 1.3 g (84% of theory); m.p. 190°—196°C.

EXAMPLE 2.

A. 4 - Ethylmercapto - 2,6 - dimethoxy-pyrimidine.

5.22 g of 4 - chloro - 2,6 - dimethoxy-pyrimidine were dissolved in 15 ml of absolute alcohol and treated at 20°C. with 2.52 g of sodium ethyl mercaptide in 17 ml of alcohol. The mixture was heated under reflux for two hours with the exclusion of moisture. After cooling, the precipitated sodium chloride (1.6 g) was filtered off and the alcoholic filtrate was evaporated to dryness *in vacuo*. 10 ml of water were added and the mixture was twice extracted with ether. 5.5 g of 4 - ethyl-mercapto-2,6 - dimethoxy - pyrimidine remained as a residual oil (92% of theory); b.p. = 145°C./12 mm.

B. 4 - Ethylsulphonyl - 2,6 - dimethoxy-pyrimidine.

2 g of 4 - ethylmercapto - 2,6 - dimethoxy-pyrimidine were treated with 17 ml of 13% peracetic acid while cooling with ice. When the exothermic reaction died out and after standing for an additional 10 minutes, the mixture was briefly heated to 80°C. (2 to 3 minutes). The acetic acid was distilled off *in vacuo*. The oil obtained then crystallised upon trituration with water. Upon dissolving and recrystallising from dilute methanol (1 : 1), the product melted at 108°—111°C. (1.2 g, 52% of theory).

C. 4 - Sulphanilamido - 2,6 - dimethoxy-pyrimidine.

1 g of 4 - ethylsulphonyl - 2,6 - dimethoxy-pyrimidine and 2 g of sodium sulphanilamide (both well dried) were finely powdered and heated for 2.5 hours in an oil bath at 120°C. (inside temperature). After cooling, 20 ml of water were added and the precipitated sulphanilamide was brought into solution by the addition of a few drops of sodium hydroxide solution. After filtration of 10 mg of an unidentified compound, the mixture was made alkaline with sodium carbonate and allowed to stand at 0°C. for one hour. In this manner 0.95 g of regenerated sulphanilamide were obtained. The filtrate was neutralized with acetic acid and the precipitated crystals were isolated (1.0 g, m.p. = 180°—190°C.). The product was dissolved and recrystallized from alcohol-water and then melted at 195°—197°C.

EXAMPLE 3.

A. 4 - (*p* - acetamino - phenylsulphonyl)-2,6 - dimethoxy - pyrimidine.

2.7 g of the sodium salt of *p* - acetamino-benzenesulphinic acid were heated with 1.74 g of 4 - chloro - 2,6 - dimethoxy-pyrimidine and 5 ml of ethyleneglycol for 3.5 hours in an oil bath at 140°C. (inside temperature).

After this time, 30 ml of water were added to the cooled mixture. The addition of a small amount of ether to the resulting oily precipitate initiated crystallisation. There was thus obtained 2.0 g of sulphone melting at 200°—210°C. (60% of theory). Upon dissolving and recrystallising from alcohol (50%), the melting point rose to 215°—218°C.

B. 4 - Sulphanilamido - 2,6 - dimethoxy-pyrimidine.

1 g of 4 - (*p* - acetamino - phenylsulphonyl) - 2,6 - dimethoxy - pyrimidine was finely powdered with 2 g of sodium sulphanilamide, then, after the addition of 1 ml of dimethyl - formamide, the mixture was heated in an oil bath for six hours at 125°C. (bath temperature). The nearly homogenous fused mass was cooled and dissolved in 20 ml of water, then made alkaline with sodium carbonate solution and maintained at 0°C. for one hour. 1.1 g of sulphanilamide were recovered. The filtrate, upon neutralisation, gave 0.6 g of crystalline 4 - sulphanilamido - 2,6-dimethoxy - pyrimidine having a melting point of 175°—192°C. (65% of theory). By dissolving and recrystallising from 80% alcohol, the melting point rose to 196°—200°C.

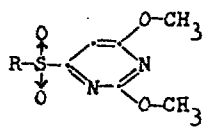
EXAMPLE 4.

4 - Sulphanilamido - 2,6 - dimethoxy - pyrimidine.

2 g of sodium sulphanilamide, 0.5 g of 2,6 - dimethoxy - pyrimidine - (4) - sulphonic acid and 2 g of acetamide were heated for five hours in an oil bath at 120°C. (inside temperature). The melt was taken up in 30 ml of water and made alkaline with sodium carbonate. After standing for one hour at 0°C., 1.5 g of sulphanilamide were filtered off and the filtrate neutralised with acetic acid. There were thus obtained 0.2 g of crystalline 4 - sulphanilamido - 2,6 - dimethoxy-pyrimidine which melts at 195°C. Upon dissolving and recrystallising from alcohol, the compound melted at 202°C.

WHAT WE CLAIM IS:—

1) A process for the manufacture of 4-sulphanilamido - 2,6 - dimethoxy - pyrimidine, which process comprises reacting an alkali-metal salt of sulphanilamide with a pyrimidine derivative of the general formula



wherein R represents an alkyl, aralkyl, aryl, acylamino-aryl or a hydroxy group or the —O—Me group in which Me stands for a metal atom.

2) A process in accordance with claim 1, wherein the reaction is carried out by dry heating a mixture of the reactants at a temperature between 100°C. and 150°C.

3) A process in accordance with claim 1, wherein the alkali-metal salt of the sulphanilamide used is the sodium salt, wherein the pyrimidine derivative used is 2,6 - dimethoxy-pyrimidine - (4) - sulphonic acid and wherein the reaction is carried out by heating in molten acetamide.

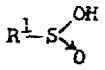
4) A process in accordance with any one of claims 1 to 3 inclusive, wherein the pyrimidine derivative used is obtained by reacting a sulphide of the general formula

$$R^1—S—Me,$$

in which R^1 represents an alkyl, aralkyl, aryl or acylamino-aryl group and Me represents a metal atom, with a 2,6 - dimethoxy - 4-halogeno - pyrimidine and oxidising the resulting thioether.

5) A process in accordance with claim 4, wherein said oxidation is carried out using peracetic acid.

6) A process in accordance with any one of claims 1 to 3 inclusive, wherein the pyrimidine derivative used is obtained by reacting a metal salt of a sulphinic acid of the general formula



in which R^1 represents an alkyl, aralkyl, aryl or acylamino-aryl group, with a 2,6 - dimethoxy - 4 - halogeno - pyrimidine.

7) A process in accordance with claim 6, wherein the metal salt used is a dry alkali-metal salt, wherein the 2,6 - dimethoxy - 4-halogeno - pyrimidine used is a 2,6 - dimethoxy - chloro - pyrimidine and wherein the reaction is carried out in ethyleneglycol at a temperature of about 120°C. to 160°C.

8) A process in accordance with claim 7, wherein said dry alkali-metal salt is the sodium salt of *p* - acetamino - benzenesulphinic acid.

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

10) 4 - Sulphanilamido - 2,6 - dimethoxy-pyrimidine when manufactured in accordance with the process claimed in any one of the preceding claims.

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After this time, 30 ml of water were added to the cooled mixture. The addition of a small amount of ether to the resulting oily precipitate initiated crystallisation. There was thus obtained 2.0 g of sulphone melting at 200°—210°C. (60% of theory). Upon dissolving and recrystallising from alcohol (50%), the melting point rose to 215°—218°C.

B. 4 - Sulphanilamido - 2,6 - dimethoxy-pyrimidine.

1 g of 4 - (*p* - acetamino - phenylsulphonyl) - 2,6 - dimethoxy - pyrimidine was finely powdered with 2 g of sodium sulphanilamide, then, after the addition of 1 ml of dimethyl - formamide, the mixture was heated in an oil bath for six hours at 125°C. (bath temperature). The nearly homogenous fused mass was cooled and dissolved in 20 ml of water, then made alkaline with sodium carbonate solution and maintained at 0°C. for one hour. 1.1 g of sulphanilamide were recovered. The filtrate, upon neutralisation, gave 0.6 g of crystalline 4 - sulphanilamido - 2,6-dimethoxy - pyrimidine having a melting point of 175°—192°C. (65% of theory). By dissolving and recrystallising from 80% alcohol, the melting point rose to 196°—200°C.

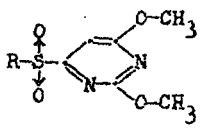
EXAMPLE 4.

4 - Sulphanilamido - 2,6 - dimethoxy - pyrimidine.

2 g of sodium sulphanilamide, 0.5 g of 2,6 - dimethoxy - pyrimidine - (4) - sulphonic acid and 2 g of acetamide were heated for five hours in an oil bath at 120°C. (inside temperature). The melt was taken up in 30 ml of water and made alkaline with sodium carbonate. After standing for one hour at 0°C., 1.5 g of sulphanilamide were filtered off and the filtrate neutralised with acetic acid. There were thus obtained 0.2 g of crystalline 4 - sulphanilamido - 2,6 - dimethoxy-pyrimidine which melts at 195°C. Upon dissolving and recrystallising from alcohol, the compound melted at 202°C.

WHAT WE CLAIM IS:—

1) A process for the manufacture of 4-sulphanilamido - 2,6 - dimethoxy - pyrimidine, which process comprises reacting an alkali-metal salt of sulphanilamide with a pyrimidine derivative of the general formula



wherein R represents an alkyl, aralkyl, aryl, acylamino-aryl or a hydroxy group or the —O—Me group in which Me stands for a metal atom.

2) A process in accordance with claim 1, wherein the reaction is carried out by dry heating a mixture of the reactants at a temperature between 100°C. and 150°C.

3) A process in accordance with claim 1, wherein the alkali-metal salt of the sulphanilamide used is the sodium salt, wherein the pyrimidine derivative used is 2,6 - dimethoxy-pyrimidine - (4) - sulphonic acid and wherein the reaction is carried out by heating in molten acetamide.

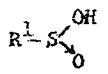
4) A process in accordance with any one of claims 1 to 3 inclusive, wherein the pyrimidine derivative used is obtained by reacting a sulphide of the general formula

$$R^1—S—Me,$$

in which R^1 represents an alkyl, aralkyl, aryl or acylamino-aryl group and Me represents a metal atom, with a 2,6 - dimethoxy - 4-halogeno - pyrimidine and oxidising the resulting thioether.

5) A process in accordance with claim 4, wherein said oxidation is carried out using peracetic acid.

6) A process in accordance with any one of claims 1 to 3 inclusive, wherein the pyrimidine derivative used is obtained by reacting a metal salt of a sulphinic acid of the general formula



in which R^1 represents an alkyl, aralkyl, aryl or acylamino-aryl group, with a 2,6 - dimethoxy - 4 - halogeno - pyrimidine.

7) A process in accordance with claim 6, wherein the metal salt used is a dry alkali-metal salt, wherein the 2,6 - dimethoxy - 4-halogeno - pyrimidine used is a 2,6 - dimethoxy - chloro - pyrimidine and wherein the reaction is carried out in ethyleneglycol at a temperature of about 120°C. to 160°C.

8) A process in accordance with claim 7, wherein said dry alkali-metal salt is the sodium salt of *p* - acetamino - benzenesulphinic acid.

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

10) 4 - Sulphanilamido - 2,6 - dimethoxy-pyrimidine when manufactured in accordance with the process claimed in any one of the preceding claims.

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