927,699

PATENT SPECIFICATION

NO DRAWINGS

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International Classification:—C07d.

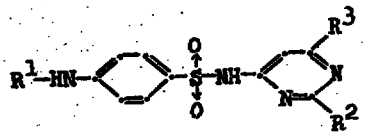
COMPLETE SPECIFICATION

A process for the manufacture of Sulphapyrimidine Compounds

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:—

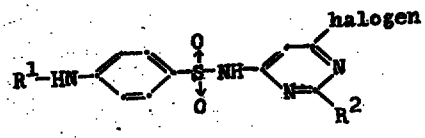
The present invention is concerned with a process for the manufacture of useful sulphapyrimidine compounds, some of which are novel. The invention is also concerned with said novel compounds themselves.

The sulphapyrimidine compounds may be formulated thus:



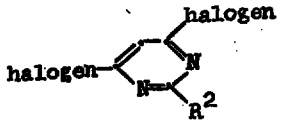
I

wherein R^1 is a hydrogen atom or an acyl group, R^2 is an alkylthio group containing up to six carbon atoms (preferably the methylthio or ethylthio group) or an alkoxy group (preferably the methoxy or ethoxy group) and R^3 is a halogen atom (preferably a chlorine or bromine atom) or, when R^2 is an alkoxy group, an alkoxy group (preferably the methoxy or ethoxy group). These products of the process to be described hereinafter are new except for those which contain two alkoxy substituents in the pyrimidine nucleus. The novel compounds may be formulated thus:



wherein R^1 and R^2 have the significance given earlier. Those in which R^1 is a hydrogen atom exhibit a high activity against pathogenic bacteria; they are useful as medicinal antibacterial agents in the same manner generally speaking as sulphadimethoxine and similar sulpha drugs. Some are also useful as intermediates for the preparation of the known and valuable 2,6-dimethoxy - 4 - sulphanilamido-pyrimidine.

According to the process provided by the invention, the compounds of formula I are manufactured by reacting a halogeno compound of the general formula



III

wherein R^2 has the significance given earlier, with an alkali-metal salt of sulphanilamide or an N-acyl derivative thereof and, if desired, hydrolysing the N^4-acyl group if present in the product and, if desired, replacing the remaining halogeno substituent and any alkylthio group by alkoxy.

The dihalogeno compounds of formula III used as starting materials may be obtained by reacting the appropriate 2 - alkoxy - 4,6 - dihydroxy - pyrimidine or 2 - alkylthio - 4,6-dihydroxy - pyrimidine with a phosphorus oxyhalide (e.g. phosphorus oxychloride) in the presence of a basic material—giving the corresponding 2 - alkoxy - 4,6 - dihalogeno - pyrimidine or 2 - alkylthio - 4,6 - dihalogeno-pyrimidine.

The reaction of the halogeno compound of formula III with an alkali-metal salt of sulphanilamide or an N-acyl derivative thereof is advantageously effected in a solvent which dissolves or partially dissolves the alkali-metal

salt but which, however, does not itself participate in the reaction. Suitable inert organic solvents of this kind are, for example, dimethyl-formamide, acetamide and dioxan.

In order to obtain good yields and also to facilitate isolation of pure reaction products, it is advantageous to employ the reactants in the relationship of one molar proportion of halogeno compound of formula III to substantially two molar proportions of alkali - metal salt of sulphanilamide or N-acyl derivative thereof. When the reactants are employed in molar ratios differing from those indicated hereinbefore, both the yield of the reaction product and its purity are adversely affected.

A preferred embodiment of the process of the invention comprises reacting a 2 - alkoxy-4,6 - dihalogeno - pyrimidine or a 2 - alkylthio - 4,6 - dihalogeno - pyrimidine with the alkali-metal salt referred to hereinbefore for a period of several hours at 80° C. to 120° C. in dimethylformamide or acetamide, digesting this reaction mixture with water, filtering off the excess sulphanilamide or N - acyl - sulphanilamide which separates and isolating from the filtrate the 2 - alkoxy - 4 - (N^4 - acyl - sulphanilamido) - 6 - halogeno - pyrimidine or 2 - alkoxy - 4 - sulphanilamido - 6 - halogeno - pyrimidine or 2 - alkylthio - 4 - (N^4-acyl - sulphanilamido) - 6 - halogeno - pyrimidine or 2 - alkylthio - 4 - sulphanilamido-6 - halogeno - pyrimidine as the case may be by acidification. When, for example, 2 - methoxy - 4,6 - dichloro - pyrimidine is reacted with the sodium salt of N - acetyl - sulphanilamide, the product obtained—2 - methoxy-4 - (N^4 - acetyl - sulphanilamido) - 6 - chloro-pyrimidine—can be treated with an excess of an alkali-metal methoxide in methanol at a temperature above 100° C. under pressure and then, after distilling off the methanol, heated with dilute sodium hydroxide solution in order to replace the 6-chloro substituent by methoxy and split off the N^4-acetyl group and so form on acidifying the known 2,6-dimethoxy - 4 - sulphanilamido - pyrimidine. The acetyl group can be removed from the foregoing 2 - methoxy - 4 - (N^4 - acetyl - sulphanilamido) - 6 - chloro - pyrimidine by treatment with approximately 0.5-*N* sodium hydroxide solution at *ca* 95°—100° C. for a period of *ca* 1 to 4 hours. The resulting 2-methoxy - 4 - sulphanilamido - 6 - chloro - pyrimidine is a novel compound. This compound also occurs in the embodiment of the process wherein 2 - methoxy - 4,6 - dichloro-pyrimidine is reacted with the sodium salt of sulphanilamide to form 2 - methoxy - 4 - sulphanilamido - 6 - chloro - pyrimidine which is heated under pressure with an alkali-metal methoxide in methanol to form 2,6 - dimethoxy - 4 - sulphanilamido - pyrimidine.

When, for example, a 2 - alkylthio - 4,6 - dihalogeno - pyrimidine is treated with an alkali-metal salt of sulphanilamide or an N-acyl derivative thereof to form a 2 - alkylthio-4 - sulphanilamido - 6 - halogeno - pyrimidine or its N-acyl derivative, the product can then be heated under pressure with an alkali-metal methoxide in methanol to form 2,6 - dimethoxy - 4 - sulphanilamido - pyrimidine or its N-acyl derivative and the latter compound hydrolysed to form 2,6 - dimethoxy - 4 - sulphanilamido - pyrimidine. In this embodiment the 2 - alkylthio - 4,6 - dihalogeno - pyrimidine used is preferably 2-methylthio - 4,6 - dichloro - pyrimidine and this is preferably treated with the sodium salt of sulphanilamide or the N - acetyl derivative thereof.

The following examples are illustrative of the process:

Example 1

1(a) 2 - Methoxy - 4,6 - dichloro - pyrimidine

A solution of 33 g of *O* - methyl - urea chloride in 100 ml of absolute methanol is cooled to —8° C. (bath temperature). A solution of 13.8 g of sodium in 140 ml of absolute methanol is added slowly, dropwise, while stirring. Immediately thereafter, 39.6 g of malonic acid dimethyl ester is quickly added to the reaction mixture. The mixture is allowed to stand for an additional period of 4 hours in the ice bath and is then kept for 3 days at room temperature with precautions to exclude moisture. The crystalline mass is filtered off. The filtrate is neutralized with dilute hydrochloric acid and evaporated to dryness *in vacuo*. The two portions of crystalline material are combined and mixed with 100 ml of water and, where necessary, the mixture is again adjusted to pH 4—5 with dilute hydrochloric acid. The precipitation which takes place is completed by cooling and the precipitate is filtered off and washed with 35 ml of ice-water. The resulting crystalline slurry of 2 - methoxy - 4,6 - dihydroxy - pyrimidine is filtered off under suction, dried *in vacuo* on a water bath and completely freed from water in a desiccator at 105° C. Yield, over 80%; decomposition point, 190° C. (with bubble formation).

7.2 g of the finely powdered, dry 2-methoxy - 4,6 - dihydroxy - pyrimidine are carefully introduced into a mixture of 25 ml of phosphorus oxychloride and 12.5 ml of dimethyl-aniline. The flask is cooled externally in order to avoid too sudden a reaction. When evolution of heat has ceased, the reaction mixture is heated under reflux (using boiling stones) on an oil bath and under a vertical condenser, first for one hour at 105° C. and then for 1.5 hour at 125° C. The reaction mixture is cooled, the flask provided with a descending condenser, and excess phosphorus oxychloride distilled off *in vacuo* (12 mm) at *ca* 50° C. The viscous contents of the flask are poured

on to ice and crystals separate. After 0.5 hour, a layer of ether is poured over the mixture and the mixture is extracted 3 times with ether in a separating funnel. The combined ethereal extracts are washed twice with water until neutral and dried over sodium sulphate. The ether is distilled off, and the residue distilled *in vacuo*. The product, 2 - methoxy - 4,6 - dichloro - pyrimidine, distils over at 105° C./11 mm. It solidifies in the receiver to a colourless mass of melting point 59° C. Yield, 6.4 g (70%).

(b) 2 - Methoxy - 4 - (N^4 - acetyl - sulphanilamido) - 6 - chloro - pyrimidine

16.1 g (2 mol) of sodium acetyl - sulphanilamide are introduced into 70 ml of dry dimethyl - formamide and heated to 130° C. on an oil bath with occasional shaking. The material dissolves incompletely. The mixture is cooled to 80° C. and 6.1 g (1 mol) of 2-methoxy - 4,6 - dichloro - pyrimidine are introduced while stirring. A fine suspension results. It is heated to 105° C. and kept at this temperature for 4 hours. Then the dimethyl-formamide is distilled off *in vacuo* on a water bath. The syrupy residue is digested with water (about 45 ml) whereupon excess crystalline N^4 - acetyl - sulphanilamide separates. The solution exhibits an alkaline reaction. It is allowed to stand for 0.5 hour in a refrigerator and then filtered off under suction. The filtrate is acidified with glacial acetic acid, whereupon 2 - methoxy - 4 - (N^4 - acetyl - sulphanilamido) - 6 - chloro - pyr - imidine separates. It precipitates at first in resinous form but then crystallizes to hard pieces, which are triturated with the mother liquor. The white precipitate is filtered off under suction and washed Yield of crude product 11.4; melting point 230°C. For purposes of analysis, a portion of the product is dissolved in soda solution and introduced into excess dilute hydrochloric acid. The precipitate is washed, dried and recrystallized from 80% (w/w) alcohol, avoiding unnecessarily prolonged heating; melting point 233° C.

2(i) 2,6 - Dimethoxy - 4 - sulphanilamido-pyrimidine

6 g of 2 - methoxy - 4 - (N^4 - acetyl - sulphanilamido) - 6 - chloro - pyrimidine are heated for 5 hours at 120° C. in a glass autoclave on an oil bath with a solution of 1.95 g of sodium (5 mol) in 35 ml of absolute methanol. Upon cooling, sodium chloride precipitates on the bottom of the vessel. The methanol is distilled off *in vacuo* and the residue taken up in 17 ml of 1-*N* sodium hydroxide solution and hydrolysed for one hour on a water bath at 90° C. A little carbon is added, the mixture filtered and acidified with glacial acetic acid. On filtering off the precipitate there is obtained 4.95 g of 2,6 - dimethoxy - 4 - sulphanilamido - pyrimidine of melting point 194°—196° C. This product is heated under reflux with a quantity of 96% (w/w) alcohol which is insufficient for solution, and then the mixture is diluted with water to an alcohol content of about 80% (w/w). The mixture is allowed to stand for 12 hours in ice, to yield 4.6 g of purified product of melting point 202° C.

(ii) 2 - Methoxy - 4 - sulphanilamido - 6 - chloro-pyrimidine

3 g of 2 - methoxy - 4 - (N^4 - acetyl - sulphanilamido) - 6 - chloro - pyrimidine are dissolved in 67.2 ml of 0.5-*N* sodium hydroxide solution (4 mol) and heated on a water bath for 3 hours at 98° C. (bath temperature). At the end of this time the clear solution is cooled externally with ice-water and added dropwise, while stirring, to a solution of 12 ml of concentrated hydrochloric acid in 21 ml of water. White flocks precipitate. The mixture is allowed to stand in a refrigerator for one hour and filtered off under suction. While cooling with ice and stirring, the filtrate is adjusted to pH 4—5 by dropwise addition of concentrated ammonia. Thereupon 2 - methoxy - 4 - sulphanilamido - 6 - chloro - pyrimidine precipitates in flocks. The mixture is allowed to stand for 16 hours in a refrigerator, whereupon the precipitate crystallizes. Crude yield, 2.1 g; melting point 160°—166° C. Upon recrystallization from methanol/water, there is obtained 1.85 g of purified product of melting point 174° C.

EXAMPLE 2

1. 2 - Methoxy - 4 - sulphanilamido - 6 - chloro - pyrimidine

11.64 g (2 mol) of dry sodium sulphanilamide is mixed with 20 ml of dimethyl-formamide and heated to 100° C. The sodium salt remains largely undissolved. While stirring, 5.37 g of 2 - methoxy - 4,6 - dichloro - pyrimidine is added slowly (in about 15 minutes) to the reaction mixture, with precautions to avoid increase of temperature above 110° C. When the reaction has slowed down (indicated by a lowering of temperature) the syrupy mixture is allowed to stand for 0.5 hour on a boiling-water bath, with exclusion of moisture. The dimethyl - formamide is distilled off *in vacuo* (12 mm). The residue is mixed with 40 ml of water, whereupon excess sulphanilamide separates. The mixture is allowed to stand for 0.5 hour in a refrigerator and is filtered off under suction. The filtrate is acidified with 50% by volume acetic acid, whereupon 2 - methoxy - 4 - sulphanilamido - 6 - chloro - pyrimidine precipitates. The precipitate is filtered off under suction, dissolved in soda and again precipitated with 50% by volume acetic acid. Crude yield 8.3 g; melting point 169°—171° C. On recrystallization from 20 ml of methanol, the melting point rises to 172°—174° C.

In the place of dimethyl-formamide, 10 g of acetamide may also be used with initial heating to 150° C. The sodium sulphanilamide forms a homogeneous melt with the acetamide. After cooling to 100° C., the pyrimidine derivative is introduced.

2. 2,6 - Dimethoxy - 4 - sulphanilamido-pyrimidine

3 g of dry 2 - methoxy - 4 - sulphanilamido-6 - chloro - pyrimidine are heated for 4 hours in a glass autoclave at 120° C. on an oil bath with a solution of 0.9 g of sodium in 17 ml of absolute methanol. Upon cooling sodium chloride precipitates on the bottom of the vessel. The methanol is distilled off *in vacuo* and the residue taken up in 25 ml of water, whereupon all passes into solution. The solution is acidified with 50% by volume acetic acid, yielding 2.7 g of crude 2,6 - dimethoxy-4 - sulphanilamido - pyrimidine of melting point 201° C. Upon recrystallization from 80% (w/w) ethanol, there is obtained 2.5 g of a purified product having a melting point of 202°—203° C.

EXAMPLE 3

2-Methylthio - 4 - sulphanilamido - 6-chloro-pyrimidine

9.6 g (2 mol) of dry sodium sulphanilamide are mixed with 20 ml of dimethyl-formamide and heated to 100° C., the sodium salt remaining largely undissolved. While stirring, 4.8 g of 2 -methyl - thio - 4,6 - dichloro - pyrimidine is added in portions. The sodium salt disappears and a homogeneous syrupy mixture results. After all the pyrimidine reactant has been introduced, the mixture is stirred for an additional period of 15 minutes at 100° C. and allowed to stand for 45 minutes on a water bath at 98° C. in order to complete the reaction. Then the dimethyl-formamide is distilled off *in vacuo* (12 mm). The residue is taken up in 35 ml of water. Initially all passes into solution, but soon thereafter, upon stirring and scratching with a glass rod, a separation of excess sulphanilamide takes place. After the reaction mixture has remained in a refrigerator for 30 minutes at 0° C., the precipitate is filtered off under suction and the filtrate acidified by dropwise addition of 50% by volume acetic acid. A resinous mass separates, which is isolated and dissolved in aqueous soda solution. Upon further acidification with acetic acid, the resin which precipitates soon changes into a hard crystalline mass which is powdered in a mortar while still in contact with the liquid from which it was deposited and is then filtered off under suction from that liquid. The powder is then recrystallized from 10 ml of methanol, then again from 40 ml of absolute benzene, in which it is heated under reflux for 20 minutes. The crystals of 2 - methyl - thio - 4 - sulphanilamido - 6 - chloro - pyrimidine obtained upon filtration melt at 156°—157° C. Yield of crude product, 7.4 g; after recrystallization, 5.5 g. The compound is slightly soluble in water, but easily soluble in methanol, ethyl acetate and acetone, and somewhat less easily soluble in ether and benzene. The compound is also soluble in sodium bicarbonate solution.

EXAMPLE 4

1. 2 - Methylthio - 4 - (N^4 - acetyl - sulphanilamido) - 6 - chloro - pyrimidine

This compound was prepared from sodium acetyl - sulphanilamide and 2 - methylthio - 4,6 - dichloro - pyrimidine in an analogous manner to that given in example 3.

2. 2,6 - Dimethoxy - 4 - (N^4 - acetyl - sulphanilamido) - pyrimidine

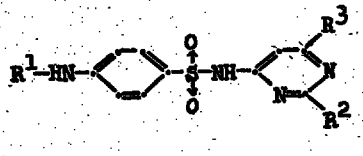
3.7 g of 2 - methyl - thio - 4 - (N^4 - acetyl-sulphanilamido) - 6 - chloro - pyrimidine are heated for 5 hours at 120° C. in a glass autoclave on an oil bath with a solution of 1.15 g of sodium in 20 ml of absolute methanol. Upon cooling, sodium chloride precipitates. The methanol is distilled off *in vacuo* and the residue dissolved in 20 ml of water. The aqueous solution is acidified with 50% by volume acetic acid, whereupon crystals of 2,6-dimethoxy - 4 - (N^4 - acetyl - sulphanil - amido) - pyrimidine precipitate. Upon recrystallization from methanol, the melting point rises to 222°—224° C. Yield, 3.2 g.

3. 2,6 - Dimethoxy - 4 - sulphanilamido - pyrimidine

1 g of 2,6 - dimethoxy - 4 - (N^4 - acetyl-sulphanilamido) - pyrimidine is dissolved in 10 ml of 1-*N* sodium hydroxide solution and heated on a water bath for 2 hours at 58° C. Upon acidification with acetic acid, there is obtained 0.75 g of crude 2,6 - dimethoxy - 4-sulphanilamido - pyrimidine of melting point 188°—192° C. Upon recrystallization from methanol, the melting point rises to 197°—199° C.

WHAT WE CLAIM IS:—

1) A process for the manufacture of sulphapyrimidine compounds of the general formula



wherein R^1 is a hydrogen atom or an acyl group, R^2 is an alkylthio group containing up to six carbon atoms or an alkoxy group and R^3 is a halogen atom or, when R^2 is an alkoxy group, an alkoxy group, which process comprises reacting a halogeno compound of the general formula

* C L M S *

In the place of dimethyl-formamide, 10 g of acetamide may also be used with initial heating to 150° C. The sodium sulphanilamide forms a homogeneous melt with the acetamide. After cooling to 100° C., the pyrimidine derivative is introduced.

2. 2,6 - Dimethoxy - 4 - sulphanilamido-pyrimidine

3 g of dry 2 - methoxy - 4 - sulphanilamido-6 - chloro - pyrimidine are heated for 4 hours in a glass autoclave at 120° C. on an oil bath with a solution of 0.9 g of sodium in 17 ml of absolute methanol. Upon cooling sodium chloride precipitates on the bottom of the vessel. The methanol is distilled off *in vacuo* and the residue taken up in 25 ml of water, whereupon all passes into solution. The solution is acidified with 50% by volume acetic acid, yielding 2.7 g of crude 2,6 - dimethoxy-4 - sulphanilamido - pyrimidine of melting point 201° C. Upon recrystallization from 80% (w/w) ethanol, there is obtained 2.5 g of a purified product having a melting point of 202°—203° C.

EXAMPLE 3

2-Methylthio - 4 - sulphanilamido - 6-chloro-pyrimidine

9.6 g (2 mol) of dry sodium sulphanilamide are mixed with 20 ml of dimethyl-formamide and heated to 100° C., the sodium salt remaining largely undissolved. While stirring, 4.8 g of 2 -methyl - thio - 4,6 - dichloro - pyrimidine is added in portions. The sodium salt disappears and a homogeneous syrupy mixture results. After all the pyrimidine reactant has been introduced, the mixture is stirred for an additional period of 15 minutes at 100° C. and allowed to stand for 45 minutes on a water bath at 98° C. in order to complete the reaction. Then the dimethyl-formamide is distilled off *in vacuo* (12 mm). The residue is taken up in 35 ml of water. Initially all passes into solution, but soon thereafter, upon stirring and scratching with a glass rod, a separation of excess sulphanilamide takes place. After the reaction mixture has remained in a refrigerator for 30 minutes at 0° C., the precipitate is filtered off under suction and the filtrate acidified by dropwise addition of 50% by volume acetic acid. A resinous mass separates, which is isolated and dissolved in aqueous soda solution. Upon further acidification with acetic acid, the resin which precipitates soon changes into a hard crystalline mass which is powdered in a mortar while still in contact with the liquid from which it was deposited and is then filtered off under suction from that liquid. The powder is then recrystallized from 10 ml of methanol, then again from 40 ml of absolute benzene, in which it is heated under reflux for 20 minutes. The crystals of 2 - methyl - thio - 4 - sulphanilamido - 6 - chloro - pyrimidine obtained upon filtration melt at 156°—157° C. Yield of crude product, 7.4 g; after recrystallization, 5.5 g. The compound is slightly soluble in water, but easily soluble in methanol, ethyl acetate and acetone, and somewhat less easily soluble in ether and benzene. The compound is also soluble in sodium bicarbonate solution.

EXAMPLE 4

1. 2 - Methylthio - 4 - (N^4 - acetyl - sulphanilamido) - 6 - chloro - pyrimidine

This compound was prepared from sodium acetyl - sulphanilamide and 2 - methylthio - 4,6 - dichloro - pyrimidine in an analogous manner to that given in example 3.

2. 2,6 - Dimethoxy - 4 - (N^4 - acetyl - sulphanilamido) - pyrimidine

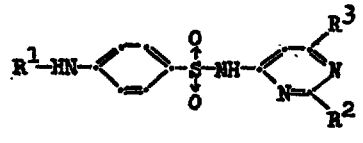
3.7 g of 2 - methyl - thio - 4 - (N^4 - acetyl-sulphanilamido) - 6 - chloro - pyrimidine are heated for 5 hours at 120° C. in a glass autoclave on an oil bath with a solution of 1.15 g of sodium in 20 ml of absolute methanol. Upon cooling, sodium chloride precipitates. The methanol is distilled off *in vacuo* and the residue dissolved in 20 ml of water. The aqueous solution is acidified with 50% by volume acetic acid, whereupon crystals of 2,6-dimethoxy - 4 - (N^4 - acetyl - sulphanil - amido) - pyrimidine precipitate. Upon recrystallization from methanol, the melting point rises to 222°—224° C. Yield, 3.2 g.

3. 2,6 - Dimethoxy - 4 - sulphanilamido - pyrimidine

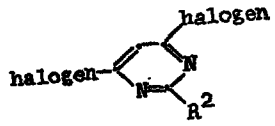
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WHAT WE CLAIM IS:—

1) A process for the manufacture of sulphapyrimidine compounds of the general formula



wherein R^1 is a hydrogen atom or an acyl group, R^2 is an alkylthio group containing up to six carbon atoms or an alkoxy group and R^3 is a halogen atom or, when R^2 is an alkoxy group, an alkoxy group, which process comprises reacting a halogeno compound of the general formula



wherein R^2 has the significance given above, with an alkali-metal salt of sulphanilamide or an N-acyl derivative thereof and, if desired, hydrolysing the N^4-acyl group if present in the product and, if desired, replacing the remaining halogeno substituent and any alkylthio group by alkoxy.

2) A process in accordance with claim 1, wherein an inert solvent which dissolves or partially dissolves the said alkali-metal salt is used in the reaction.

3) A process in accordance with claim 2, wherein N,N - dimethyl - formamide, acetamide or dioxan is used as the inert solvent.

4) A process in accordance with any one of claims 1 to 3 inclusive, wherein 2 mols of the said alkali-metal salt are used for each mol of the halogeno compound.

5) A process in accordance with any one of claims 1 to 4 inclusive, wherein a 2 - alkoxy-4,6 - dihalogeno - pyrimidine or 2 - alkylthio - 4,6 - dihalogeno - pyrimidine is reacted for a period of several hours at 80°—120° C. in N,N - dimethyl - formamide or acetamide with an alkali-metal salt of sulphanilamide or an N-acyl derivative thereof, the reaction mixture is then digested with water, the excess sulphanilamide starting material thus separated filtered off and the resulting 2 - alkoxy-4- sulphanilamido - 6 - halogeno - pyrimidine or 2 - alkylthio - 4 - sulphanilamido - 6 - halogeno - pyrimidine, or acyl derivative of either, isolated from the filtrate by acidification.

6) A process in accordance with claim 5 insofar as the 2 -alkoxy - 4,6 - dihalogeno - pyrimidine used is 2 - methoxy - 4,6 - di - chloro - pyrimidine and is reacted with the sodium salt of N - acetyl - sulphanilamide to form 2 - methoxy - 4 - (N^4 - acetyl - sulphanilamido) - 6 - chloro - pyrimidine, which process includes the further steps of treating the latter compound with excess alkali - metal methoxide in methanol at a temperature above 100° C. under pressure, distilling off the methanol, heating the residue with dilute sodium hydroxide solution and acidifying the alkaline solution to form 2,6 - dimethoxy - 4 - sulphanilamido - pyrimidine.

7) A process in accordance with claim 5 insofar as the 2 - alkoxy - 4,6 - dihalogeno - pyrimidine used is 2 - methoxy - 4,6 - di - chloro - pyrimidine and is reacted with the sodium salt of N - acetyl - sulphanilamide to form 2 - methoxy - 4 - (N^4 - acetyl - sulphanilamido) - 6 - chloro - pyrimidine, which process includes the further step of treating the latter compound for *ca* 1 to 4 hours at *ca* 95°—100° C. with approximately 0.5 - *N* sodium hydroxide solution to form 2 - methoxy - 4 - sulphanilamido - 6 - chloro - pyrimidine.

8) A process in accordance with claim 5, wherein the 2 - alkoxy - 4,6 - dihalogeno - pyrimidine used is 2 - methoxy - 4,6 - di - chloro - pyrimidine and this is reacted with the sodium salt of sulphanilamide to form 2-methoxy - 4 - sulphanilamido - 6 - chloro - pyrimidine which is heated under pressure with an alkali-metal methoxide in methanol to form 2,6 - dimethoxy - 4 - sulphanilamido-pyrimidine.

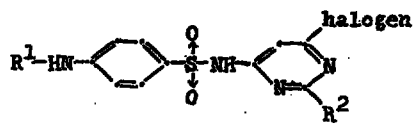
9) A process in accordance with any one of claims 1 to 4 inclusive, wherein a 2 -alkylthio - 4,6 - dihalogeno - pyrimidine is treated with an alkali-metal salt of sulphanilamide or an N-acyl derivative thereof to form a 2-alkylthio - 4 - sulphanilamido - 6 - halogeno - pyrimidine or its N-acyl derivative, the product heated under pressure with an alkali-metal methoxide in methanol to form 2,6-dimethoxy - 4 - sulphanilamido - pyrimidine or its N-acyl derivative and the latter compound hydrolysed to form 2,6 - dimethoxy-4 - sulphanilamido - pyrimidine.

10) A process in accordance with claim 9, wherein the 2 -alkylthio - 4,6 - dihalogeno - pyrimidine used is 2 - methylthio - 4,6 - dichloro - pyrimidine and this is treated with the sodium salt of sulphanilamide or the N-acetyl derivative thereof.

11) A process for the manufacture of the sulphapyrimidines formulated in claim 1, substantially as described with reference to the examples.

12) Sulphapyrimidines as formulated in claim 1, when manufactured by the process claimed in any one of claims 1 to 11 inclusive.

13) Sulphapyrimidines of the general formula



wherein R^1 and R^2 have the significance given in claim 1.

14) 2 - Methoxy - 4 - (N^4 - acetyl - sulphanilamido) - 6 - chloro - pyrimidine.

15) 2 - Methoxy - 4 - sulphanilamido - 6-chloro - pyrimidine.

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16) 2 - Methylthio - 4 - (N^4 -acetyl - sulphanilamido) - 6 - chloro - pyrimidine.
17) 2 - Methylthio - 4 - sulphanilamido - 6 - chloro - pyrimidine.

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