AMENDED SPECIFICATION

Reprinted as amended in accordance with the Decision of the Superintending Examiner, acting for the Comptroller-General, dated the twenty-eighth day of December, 1944, under Section 26, of the Patents and Designs Acts, 1907 to 1942.

PATENT SPECIFICATION

555,865



Convention Dates (United States of America)

March 1, 1940:
Oct. 15, 1940:

Corresponding Applications in United Kingdom

No. 3174/41
No. 3175/41 } *dated March 8, 1941.*

(One Complete Specification Left under Section 91 (2) of the Patents and Designs Acts, 1907 to 1939.)

Specification Accepted: Sept. 10, 1943.

(Samples have been furnished in this case under Section 2, sub-section 5, of the Patents and Designs Acts, 1907 to 1942).

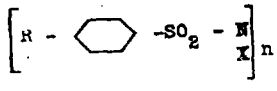
COMPLETE SPECIFICATION

Sulphonamido Pyrimidines

We, AMERICAN CYANAMID COMPANY, a corporation organized under the laws of the State of Maine, United States of America, and having its principal place of business at 30, Rockefeller Plaza, New York, State of New York, United States of America, (Assignees of PHILIP STANLEY WINNEK and RICHARD OWEN ROBLIN, Jr., both citizens of the United States of America, and residing respectively at R.F.D. #1 Box 167b, Field Road, Riverside, Connecticut, United States of America, and 15, Shore Acre Drive, Old Greenwich, Connecticut, United States of America), 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 a new class of chemical compounds, the sulphonamido pyrimidines.

The compounds of the present invention may be represented by the following type formula:—



where R is a halogen, nitro, azo, amino or substituted amino group such as alkylamino, arylamino, aralkylamino, acylamino, or mono-aldose amino, X represents hydrogen, an alkyl group or a metal, Py is a pyrimidine substituted or unsubstituted, and n is a small whole number. Numbering of the pyridimine ring normally proceeds from one or the other of the nitrogen atoms. There are therefore 3 isomeric sulphonamido pyrimidines where the ring is unsubstituted, namely the 2, 4 and 5 derivatives. The other carbon atoms may be linked to hydrogen or may carry other substituent groups.

The compounds of the present invention are useful in a number of fields. Many of them show extraordinary high activity against certain bacteria such as for example beta-hemolytic streptococci and penumococci. Others, where R is amino are useful as intermediates for the production of azo dyes and other compounds.

Since there are four carbon atoms in the pyrimidine ring capable of carrying amino groups as substituents, more than one sulphonamido compound can be prepared and the present invention includes polysulphonamido pyrimidines as well as the monosulphonamido pyrimidines.

In general the compounds of the present invention are prepared by reacting a *p*-substituted benzene sulphonyl halide with the amino-pyrimidine desired. The para-substituent is one of four types of groups as hereinafter defined, which are capable of being converted to an amino group. For example, it is possible to start with an N-acylsulphanilyl halide producing first the corresponding acylamino compound which can be transformed into the amino compound by hydrolysis of the acyl group. A second method is to start with a *p*-nitro-

benzene sulphonyl halide and produce in the first step the corresponding *p*-nitrobenzene sulphonamido pyrimidine, followed by reduction of the nitro group if the amino group is desired. Another possibility is from a *p*-halogen benzene sulphonyl halide for example, *p*-chlorobenzene sulphonyl chloride. The *p*-chlorobenzene sulphonamido pyrimidine may then be converted to the corresponding sulphanilamidopyrimidine by treatment with aqueous ammonia under pressure. Still another possibility is to start with a *p*-azobenzene sulphonyl halide and an aminopyrimidine followed by reduction of the azo group to an amino group.

The mono-aldose amino compounds are prepared from the corresponding amino compounds by a reaction with a monoaldose sugar such as glucose or galactose. In the production of the sugar derivatives it is preferable, although not essential to carry out the reaction in an organic solvent such as ethanol.

The invention consists in a method of preparing *p*-substituted benzene-sulphonamido-pyrimidines which comprises reacting a benzene-sulphonyl halide such as a chloride substituted in the para position by a group transformable into an amino group by hydrolysis, or by reduction or by reaction with ammonia or an amine such as acylamino, nitro, halogen, or azo group, with an amino-pyrimidine.

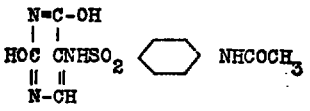
The first step in producing any of the compounds of the present invention usually involves a reaction of a sulphonyl halide with an amino compound. This sets free a hydrogen halide and it is therefore desirable where a good yield is to be obtained, to provide a basic substance which will unite with the hydrogen halide evolved. This can be effected simply by carrying out the reaction in aqueous solution and adding a suitable amount of sodium hydroxide, or the reaction may be effected in an organic liquid such as dioxane, acetone or benzene. Some organic solvents such as triethyl amine and pyridine are themselves basic, and may be used. In such cases, however, the compound of the organic base with the halogen acid is somewhat acidic and if desired a more neutral reaction mixture may be obtained by the addition of a stronger base such as caustic alkali.

The hydrogen of the sulphonamido group is an acidic hydrogen and is capable of reacting with bases to form salts. The alkali metal salts can be produced directly by a reaction of the compounds with an alkali metal hydroxide in concentrated aqueous solution. Warming on a steam bath is advantageous in bringing about salt formation. The salt can then be crystallized out on cooling, or if desired, crystallization from absolute alcohol can be effected. Salts of the heavy metals can be obtained by a reaction of an aqueous solution of the alkali metal salts with a solution of the desired heavy metal salt. The salts of the heavy metals are either insoluble or have such a low degree of solubility that they readily precipitate out of solution.

The invention will be described in greater detail in conjunction with the following specific examples which set forth the preparation of typical compounds falling under the present invention. The parts in the examples refer to grams except in the case of liquids where parts refer to cubic centimetres.

Example 1.

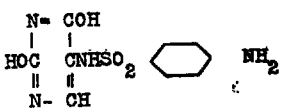
5-(N^4-acetylsulphanilamido)-2,4-dihydroxy-pyrimidine.



6 parts of 5-amino-2,4-dihydroxy-pyrimidine were suspended in 200 parts of water by stirring and the mixture warmed to 60° C. 15 parts (assuming 73% purity of the acid chloride) of *p*-acetylamino-benzene sulphonyl chloride were added gradually. The pH of the reaction mixture was maintained as close as possible to 7 by adding sodium hydroxide solution from time to time. The temperature was finally raised to 80° C. and maintained there for one-half hour. The reaction mixture was allowed to stand over night. The 5-(*p*-acetyl-aminobenzene-sulphonamido)-2,4-dihydroxypyrimidine which had precipitated was filtered off and washed with water.

Example 2.

5-(sulphanilamido)-2,4-dihydroxy-pyrimidine.

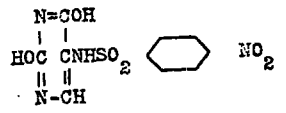


12 parts of 5-(*p*-acetylaminobenzene-sulphonamido)-2,4-dihydroxy-pyrimidine were dissolved in 80 parts of water containing 14 parts of sodium hydroxide and the solution was boiled gently for 20 minutes. A small amount of decolorizing charcoal was then added and the boiling was continued for 5 minutes. It was then filtered, cooled, diluted with 200 parts of water and neutralized with dilute hydrochloric acid. The 5-(sulphanilamido)-2,4-dihydroxy-pyrimidine separated as a light

brown precipitate. It was purified by crystallization from hot water after treatment with decolorizing charcoal. It finally crystallized as pure white needles.

EXAMPLE 3.

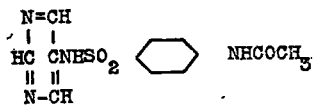
5-(*p*-NITROBENZENE SULPHONAMIDO)-2,4-DIHYDROXY-PYRIMIDINE.



16 parts of 5-amino-2,4-dihydroxy-pyrimidine were made into a thick slurry with 32 parts of dry pyridine. 35 parts of *p*-nitrobenzene sulphonyl chloride were added gradually with stirring. The temperature was maintained at 40° C. ± 5° C. The reaction mixture was then heated on a steam bath with stirring for 2 hours. 7.5 parts of sodium hydroxide dissolved in 100 parts of water were then added slowly. Stirring and heating on the steam bath was continued for 3 hours, hot water being added from time to time to maintain the volume. The reaction mixture was then cooled and the pH adjusted to 7 by addition of a few drops of dilute hydrochloric acid. The yellow precipitate of 5-(*p*-nitrobenzenesulphonamido) - 2,4 - dihydroxy-pyrimidine was filtered off and washed with water. It was purified by dissolving in cold dilute alkali, stirring the solution in the cold for 1 hour with decolorizing charcoal, filtering and neutralizing with dilute hydrochloric acid. The 5-(*p*-nitrobenzene - sulphonamido) - 2,4-dihydroxy-pyrimidine precipitated as a light yellow coloured solid. It was filtered off and washed with water. It may be reduced in very dilute alcoholic hydrochloric acid with iron dust to give 5-(sulphanilamido)-2,4-dihydroxy-pyrimidine identical with the product obtained in Example 2.

EXAMPLE 4.

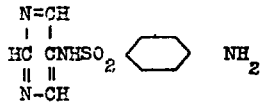
5-(N^4-ACETYLSULPHANILAMIDO)-PYRIMIDINE.



20 parts of 5-aminopyrimidine were made into a slurry with 45 parts of anhydrous pyridine. 47 parts of N^4-acetylsulphanilyl chloride were added gradually with vigorous stirring. The reaction mixture was heated on a steam bath 1 hour. It was then cooled and diluted with 75 parts of water containing 0.9 part of sodium hydroxide. The crude 5-(N^4-acetylsulphanilamido) - pyrimidine separated out as a brown solid. It was washed with water.

EXAMPLE 5.

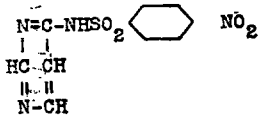
5-SULPHANILAMIDO-PYRIMIDINE.



2.5 parts of 5-(N^4-acetylsulphanilamido)-pyrimidine were dissolved in 25 parts of water containing 3 parts of sodium hydroxide and the solution boiled gently for one-half hour. It was then filtered, cooled and neutralized with dilute hydrochloric acid. The crude 5-sulphanilamido-pyrimidine separated as a brown solid. It was purified by crystallization from water using decolorizing charcoal to remove colour and impurities. The hydrolysis of the 5-(N^4-acetylsulphanilamido)-pyrimidine to give 5-sulphanilamido-pyrimidine also can be carried out using 10% hydrochloric acid as hydrolyzing agent.

EXAMPLE 6.

4-(*p*-NITROBENZENESULPHONAMIDO)-PYRIMIDINE.

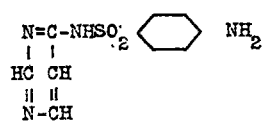


Four parts of 4-amino-pyrimidine were covered with 10 parts of anhydrous pyridine and treated with 9 parts of *p*-nitrobenzenesulphonyl chloride. The mixture was stirred well and warmed on the steam. When the mixture had cooled it was added to 100 parts of water containing 1.7 parts of sodium hydroxide and 50 parts of the liquor distilled off *in vacuo*. To the residue in the distilling flask was added 2 parts of sodium hydroxide dissolved in 100 parts of water and 20 parts of distillate collected.

The residual liquor was filtered, cooled and acidified. The 4-(*p*-nitrobenzenesulphonamido)-pyrimidine which separated was recrystallized from a hot mixture of acetic acid and water.

EXAMPLE 7.

4-(SULPHANILAMIDO)-PYRIMIDINE.

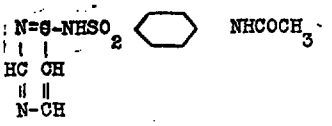


Four and one half parts of 4-(*p*-nitrobenzenesulphonamido)-pyrimidine were

suspended in 75 parts of 95% alcohol and to this was added 1 part of concentrated hydrochloric acid. The mixture was heated to reflux with stirring and 17 parts of iron powder were added. After refluxing for 14 hours the mixture was made slightly basic and filtered hot. The iron was leached with several portions of boiling alcohol and the combined filtrate and leachings were evaporated on the steam bath.

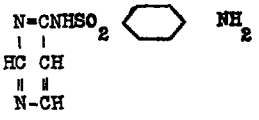
The 4-(sulphanilamido)-pyrimidine was recrystallized from boiling water with the addition of decolorizing charcoal.

EXAMPLE 8.
4-(N^4-ACETYLSULPHANILAMIDO)-PYRIMIDINE.



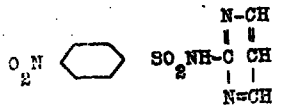
Thirty parts of 4-amino-pyrimidine were made into a slurry by adding 70 parts of anhydrous pyridine. 70 parts of N^4-acetylsulphanilyl chloride were added gradually with vigorous stirring. The reaction mixture was heated on a steam bath for 1 hour. It was then cooled and diluted with 1000 parts of water containing 13 parts of sodium hydroxide. The crude 4-(N^4-acetylsulphanilamido)-pyrimidine separated as a brown solid. It was filtered off and washed with water.

EXAMPLE 9.
4-SULPHANILAMIDO-PYRIMIDINE.



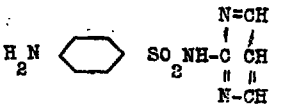
Four parts of 4-(N^4-acetylsulphanilamido)-pyrimidine were dissolved in 40 parts of water containing 5 parts of sodium hydroxide and the solution boiled gently for one-half hour. It was then filtered, cooled and neutralized with dilute hydrochloric acid. The crude 4-sulphanilamido-pyrimidine separated as a light brown solid. It was purified by crystallization from water using decolorizing charcoal to remove colour and impurities. The pure 4-sulphanilamido-pyrimidine was identical with that obtained in Example 7. The hydrolysis of the 4-(N^4-acetylsulphanilamido)-pyrimidine to yield 4-sulphanilamido-pyrimidine can also be carried out using 10% hydrochloric acid as hydrolyzing agent.

EXAMPLE 10.
2-(*p*-NITROBENZENESULPHONAMIDO-PYRIMIDINE.



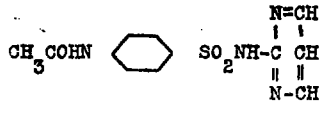
5.4 parts of 2-amino-pyrimidine were covered with 15 parts of anhydrous pyridine. The reaction mixture was treated with 14 parts of *p*-nitro-benzenesulphony chloride and the whole heated briefly on the steam bath and let stand 45 minutes at room temperature. To the reaction mixture were added 80 parts of hot alcohol and the precipitate was filtered off and washed with water. The solid was dissolved in dilute caustic solution and the solution was filtered, cooled and acidified. The 2-(nitrobenzenesulphonamido)-pyrimidine precipitated and was collected.

EXAMPLE 11.
2-(SULPHANILAMIDO)-PYRIMIDINE.



The crude 2-(*p*-nitrobenzenesulphonamido)-pyrimidine from the preceding example was suspended in 130 parts alcohol and 1.5 parts of concentrated hydrochloric acid were added. The suspension was then heated to reflux and 30 parts of iron powder were added with mechanical stirring. The mixture was refluxed and stirred for 24 hours with occasional addition of concentrated hydrochloric acid. The reaction mixture was then made slightly basic and filtered hot and the residues were extracted with several portions of boiling alcohol. The filtrate and wash solutions were combined and evaporated. The 2-(sulphanilamido)-pyrimidine was recrystallized from boiling water with decolorizing charcoal added.

EXAMPLE 12.
2-(N^4-ACETYLSULPHANILAMIDO)-PYRIMIDINE.

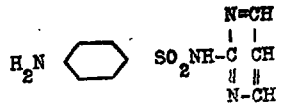


20 parts of 2-aminopyrimidine were partially dissolved and partially suspended in 45 parts of anhydrous pyridine.

47 parts of N^4-acetylsulphanilyl chloride were added gradually with vigorous stirring. The reaction mixture was heated on a steam bath 1 hour. It was then cooled and diluted with 750 parts of water containing 9 parts of sodium hydroxide. The crude 2 - (N^4 - acetylsulphanilamido)-pyrimidine separated as a brown solid. It was filtered off and washed with water.

EXAMPLE 13.

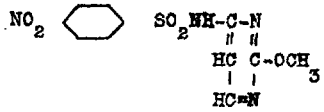
2-SULPHANILAMIDO-PYRIMIDINE.



15 parts of 2-(N^4-acetylsulphanilamido)-pyrimidine were dissolved in 150 parts of water containing 17.5 parts of sodium hydroxide and the solution boiled gently for 25 minutes. A small amount of decolorizing charcoal was added and the boiling was continued for 5 minutes. The solution was then filtered, cooled and neutralized with dilute hydrochloric acid. The crude 2-sulphanilamido-pyrimidine separated as a light brown solid. It was purified by crystallization from water using decolorizing charcoal to remove colour. The pure 2-sulphanilamido-pyrimidine was identical with that prepared in Example 11. The hydrolysis of the 2-(N^4-acetylsulphanilamido)-pyrimidine also can be carried out using 10% hydrochloric acid as hydrolyzing agent.

EXAMPLE 14.

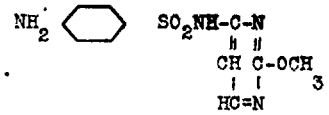
4-*p*-NITROBENZENESULPHONAMIDO-2-METHOXYPYRIMIDINE.



15 parts of 4-amino-2-methoxypyrimidine were dissolved in 30 parts of anhydrous pyridine by warming. The solution was cooled with vigorous shaking and 30 parts of *p*-nitrobenzenesulphonyl chloride were added. The mixture was then stirred and warmed on the steam bath. After cooling to room temperature, 250 parts of warm alcohol were added. The mixture was cooled, and the solid which had separated was removed by filtration. A further precipitate was obtained by the addition of water to the filtrate. This precipitate was washed with cold water and combined with the previously obtained solid. The combined products were dissolved in cold base and clarified with decolorizing charcoal. The 4-*p*-nitrobenzenesulphonamido-2-methoxypyrimidine was then precipitated from the clarified filtrate by acidification, and recrystallized from acetic acid.

EXAMPLE 15.

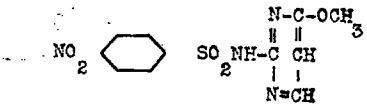
4-SULPHANILAMIDO-2-METHOXYPYRIMIDINE.



7 parts of 4-*p*-nitrobenzenesulphonamido-2-methoxypyrimidine were suspended in 100 parts of 95% ethanol containing 1.5 parts of concentrated hydrochloric acid. The mixture was heated and stirred and 25 parts of iron powder were added gradually. After refluxing for 16 hours the mixture was made slightly basic and filtered hot. The residue was extracted with several portions of hot alcohol and the filtrates combined and evaporated on the steam bath. The 4-sulphanilamido - 2 - methoxy - pyrimidine was recrystallized from dilute alcohol, using decolorizing charcoal to decolorize it.

EXAMPLE 16.

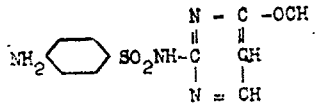
2-(*p*-NITROBENZENESULPHONAMIDO)-4-METHOXYPYRIMIDINE.



Ten parts of 2-amino-4-methoxypyrimidine were dissolved by warming in 20 parts of anhydrous pyridine. The solution was cooled and treated with 20 parts of *p*-nitrobenzene sulphonyl chloride. The mixture was then stirred and warmed on the steam bath. After cooling to room temperature, 250 parts of warm alcohol were added. The mixture was cooled, and the solid which had separated was removed by filtration. A further precipitate was obtained by the addition of water to the filtrate. This precipitate was washed with cold water and combined with the previously obtained solid. The combined products were dissolved in cold base and clarified with decolorizing charcoal. The 2 - (*p*-nitrobenzene - sulphonamido) - 4-methoxypyrimidine was then precipitated from the clarified filtrate by acidification, and recrystallized from acetic acid.

EXAMPLE 17.

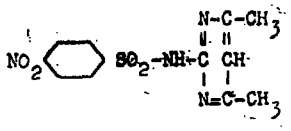
2-SULPHANILAMIDO-4-METHOXYPYRIMIDINE.



4.5 parts of 2-(*p*-nitrobenzenesulphonamido)-4-methoxypyrimidine were suspended in 75 parts of 95% ethanol containing 1 part of concentrated hydrochloric acid. The mixture was heated and stirred and 17 parts of iron powder were added gradually. After refluxing for 16 hours the mixture was made slightly basic and filtered hot. The residue was extracted with several portions of hot alcohol and the filtrates combined and evaporated on the steam bath. The 2-sulphanilamido-4-methoxypyrimidine was recrystallized from dilute alcohol, using decolorizing charcoal to decolorize it.

EXAMPLE 18.

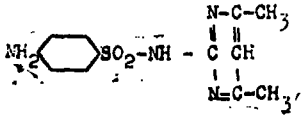
2-(*p*-NITROBENZENE-SULPHONAMIDO)-4,6-DIMETHYLPYRIMIDINE.



Six parts of 2-amino-4,6-dimethylpyrimidine were dissolved by warming in 10 cc. of anhydrous pyridine. The solution was cooled and to it were added 12 parts of *p*-nitrobenzenesulphonyl chloride. The mixture was then stirred and warmed on the steam bath. After cooling to room temperature, 250 parts of warm alcohol were added. The mixture was cooled, and the solid which had separated was removed by filtration. A further precipitate was obtained by the addition of water to the filtrate. This precipitate was washed with cold water and combined with the previously obtained solid. The combined products were dissolved in cold base and clarified with decolorizing charcoal. The 2-(*p*-nitrobenzene-sulphonamido)-4,6-dimethylpyrimidine was then precipitated from the clarified filtrate by acidification and recrystallized from acetic acid.

EXAMPLE 19.

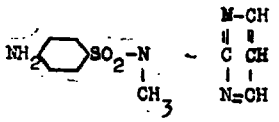
2-SULPHANILAMIDO-4,6-DIMETHYL-PYRIMIDINE.



Three parts of 2-*p*-nitrobenzenesulphonamido-4,6-dimethlypyrimidine were suspended in 40 parts of 95% ethanol containing 1 part of concentrated hydrochloric acid. The mixture was heated to reflux with stirring and 14 parts of iron powder were added gradually. After refluxing for 16 hours the mixture was made slightly basic and filtered hot. The residue was extracted with several portions of hot alcohol and the filtrates combined and evaporated on the steam bath. The 2-sulphanilamido-4,6-dimethylpyrimidine was recrystallized from dilute alcohol, using decolorizing charcoal to decolorize it.

EXAMPLE 20.

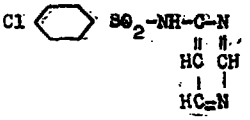
2-N^1-METHYL-SULPHANILAMIDOPYRIMIDINE.



Four parts of 2-methylaminopyrimidine were added to 10 parts of anhydrous pyridine. To this were added 9 parts of *p*-nitrobenzenesulphonyl chloride. The resulting mixture was stirred well and warmed on the steam bath. When the reaction mixture had cooled, it was added to 150 parts of water. The precipitate of 2-*p*-nitrobenzenesulphonmethylamidopyrimidine was separated and recrystallized from glacial acetic acid. The 2-N^1-methyl sulphanilamidopyrimidine was obtained by reduction of the nitro group as described in Example 7. It was recrystallized from ethanol with the addition of decolorizing charcoal.

EXAMPLE 21.

4-*p*-CHLOROBENZENE-SULPHONAMIDO-PYRIMIDINE.



16 parts of *p*-chlorobenzenesulphonyl chloride were added to 7 parts of 4-aminopyrimidine in 16 parts of dry pyridine. The reaction mixture was then heated on the steam bath for a short time. After cooling, water was added and the precipitated 4-*p*-chlorobenzene-sulphonamidopyrimidine removed by filtration. It was then recrystallized from acetic acid.

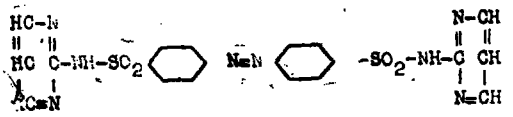
For conversion to 4-sulphanilamidopyrimidine, 5 parts of 4-*p*-chlorobenzenesulphonamidopyrimidine were heated with 20 parts of concentrated aqueous ammonia containing ¼ part of cuprous chloride. The reaction was carried out in a closed tube at 150—175° C. for 14 hours. On evaporation of the excess ammonia 4-sulphanilamido-pyrimidine was obtained.

By the substitution of amines such as methylamine, aniline and benzylamine for ammonia in the above process, substituted aminobenzene sulphonamido-

pyrimidines such as 4-N⁴-methylsulphanilamidopyrimidine, 4-N⁴-phenylsulphanilamidopyrimidine, and 4-N⁴-benzylsulphanilamidopyrimidine may be obtained.

EXAMPLE 22.

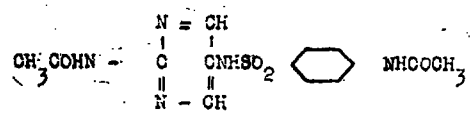
AZOBENZENE-*p*,*p*¹-(DI-2-SULPHONAMIDOPYRIMIDINE.



To 9.5 parts of 2-aminopyrimidine in 65 parts of dry pyridine was added 20 parts of azobenzene-*p*,*p*¹-disulphonyl chloride. When the reaction was completed, the reaction mixture was added to 300 parts of water. The precipitated azobenzene-*p*,*p*¹-(di-2-sulphonamidopyrimidine) was removed by filtration and washed with water. For purification it was dissolved in alkali and reprecipitated with acid. By reduction with sodium hydrosulphite in alkaline solution 2-sulphanilamidopyrimidine was obtained

EXAMPLE 23.

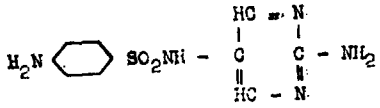
5-(N⁴-ACETYLSULPHANILAMIDO)-2-ACETYLAMINOPYRIMIDINE.



14 parts of 2-acetylamino-5-aminopyrimidine were made into a slurry of 25 parts of anhydrous pyridine. 25 parts of N⁴-acetylsulphanilyl chloride were added gradually with vigorous stirring. The reaction mixture was heated on a steam bath for one hour. It was then cooled and diluted with 150 parts of water. The crude 5-(N⁴-acetylsulphanilamido)-2-acetylamino-pyrimidine separated out as a yellow solid. It was filtered off and washed with water.

EXAMPLE 24.

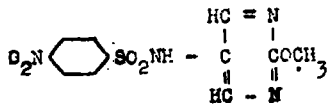
5-SULPHANILAMIDO-2-AMINOPYRIMIDINE.



15 parts of 5-(N⁴-acetylsulphanilamido)-2-acetylaminopyrimidine were dissolved in 150 parts of water containing 20 parts of sodium hydroxide and the solution was boiled gently for 25 minutes. A small amount of decolorizing charcoal was added and the boiling was continued for five minutes. The solution was then filtered, cooled and neutralized with dilute hydrochloric acid. The crude 5-sulphanilamido-2-aminopyrimidine separated as a light brown solid. It was purified by crystallization from water using decolorizing charcoal to remove the colour.

EXAMPLE 25.

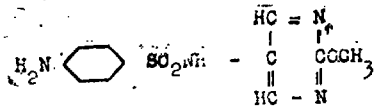
5-(*p*-NITROBENZENESULPHONAMIDO)-2-METHOXYPYRIMIDINE.



12.5 parts of 5-amino-2-methoxypyrimidine were suspended in 25 parts of anhydrous pyridine. 25 parts of *p*-nitrobenzene sulphonyl chloride were gradually added with vigorous stirring. The reaction mixture was then warmed on the steam bath for 1 hour. It was cooled and diluted with 160 parts of water. The crude 5-(*p*-nitrobenzenesulphonamido) - 2 - methoxypyrimidine separated as a yellow solid. It was purified by crystallization from acetic acid.

EXAMPLE 26.

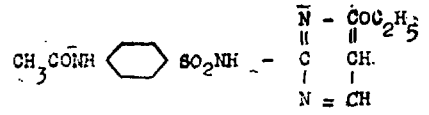
5-SULPHANILAMIDO-2-METHOXYPYRIMIDINE.



5 parts of 5-(*p*-nitrobenzenesulphonamido)-2-methoxypyrimidine were suspended in 75 parts of 95% ethanol containing 1 part of concentrated hydrochloric acid. The mixture was heated and stirred and 20 parts of iron powder were added gradually. After refluxing for 18 hours the mixture was made slightly basic and filtered hot. The residue was extracted with several portions of hot ethanol and the filtrates combined and evaporated on the steam bath. The 5-sulphanilamido-2-methoxypyrimidine was crystallized from dilute alcohol, using decolorizing charcoal to remove the colour.

EXAMPLE 27.

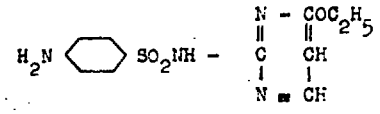
2(N⁴-ACETYLSULPHANILAMIDO)-4-ETHOXYPYRIMIDINE.



12 parts of 2-amino-4-ethoxypyrimidine were suspended in 22 parts of dry pyridine. To the stirred suspension were added 22.7 parts of N⁴-acetylsulphanilyl chloride

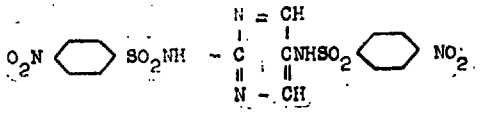
at a temperature of 55 to 60° C. The reaction mixture was then stirred for one hour at 50 to 60° C. and precipitated by the addition of 100 parts of 30% acetic acid. The precipitate was collected and dried. 14 parts of dry 2-(N^4-acetylsulphanilamido)-4-ethoxypyrimidine was obtained. It was purified by treatment of a solution of the sodium salt with decolorizing charcoal and precipitating of the clarified filtrate with dilute acid.

EXAMPLE 28.
2-SULPHANILAMIDO-4-ETHOXYPYRIMIDINE.



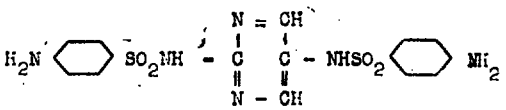
To a solution of 4.2 parts of solid caustic soda in 42 parts of water were added 14 parts of 2-(N^4-acetylsulphanilamido)-4-ethoxypyrimidine. The clear solution was boiled gently for one hour, the volume being maintained by the addition of water from time to time. The hydrolyzed solution was diluted with 150 parts of water and clarified by stirring with decolorizing charcoal. The colourless filtrate was precipitated with dilute acid and the 2-sulphanilamido - 4 - ethoxypyrimidine filtered off, and purified by recrystallization from alcohol or from the mono-ethyl ether of ethylene glycol.

EXAMPLE 29.
2,5-DI(*p*-NITROBENZENESULPHONAMIDO)-PYRIMIDINE.



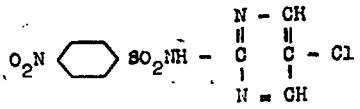
11 parts of 2,5-diamino-pyrimidine were suspended in 50 parts of anhydrous pyridine. 50 parts of *p*-nitrobenzenesulphonyl chloride were added gradually with vigorous stirring. The reaction mixwas then stirred for 1½ hours with heating. It was cooled and diluted with 250 parts of water. The crude 2,5-di(*p*-nitrobenzenesulphonamido) - pyrimidine separated as a yellow solid. It was purified by crystallization from acetic acid.

EXAMPLE 30.
2,5-DISULPHANILAMIDOPYRIMIDINE.



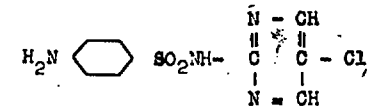
7 parts of 2,5-di(*p*-nitrobenzenesulphonamido)-pyrimidine were suspended in 150 parts of 95% ethanol containing 2 parts of concentrated hydrochloric acid. The mixture was heated and stirred and 40 parts of iron dust were added gradually. After refluxing for 18 hours the reaction mixture was made slightly basic and filtered hot. The residue was extracted with several portions of hot ethanol and the filtrates combined and evaporated under reduced pressure. The 2,5-disulphanilamidopyrimidine so obtained was crystallized from alcohol using decolorizing charcoal to remove colour.

EXAMPLE 31.
2-(*p*-NITROBENZENESULPHONAMIDO)-5-CHLOROPYRIMIDINE.



One part of 2-amino-5-chloropyrimidine and 2 parts of *p*-nitrobenzene sulphonyl chloride were mixed and suspended in 2 parts of anhydrous pyridine. The mixture was warmed slowly with stirring to 130° C. and kept at 130—140° C. for thirty minutes. The reaction was then cooled and broken up with water. The precipitated crude 2-(*p*-nitrobenzenesulphonamido)-5-chloropyrimidine was filtered off. The material was purified by treatment of its alkaline solution with decolorizing carbon, filtration and precipitation of the clarified solution by the addition of dilute acid.

EXAMPLE 32.
2-SULPHANILAMIDO-5-CHLOROPYRIMIDINE.



To the reaction mixture prepared by the addition of 24 parts of iron powder to 17 parts of 5% acetic acid was added 12 parts of 2-(*p*-nitrobenzenesulphonamido)-5-chloro pyrimidine. Water was added to permit stirring and the reaction mixture was stirred and heated at 90—95° C. for one hour. The reduction mixture was then cooled, made thoroughly alkaline and then filtered. The filtrate was clarified with decolorizing carbon and the 2-sulphanilamido-5-chloropyrimidine was precipitated by acidification. The pure white product could be further purified by recrystallization from a large volume of ethanol or isopropanol.

EXAMPLE 33.

SODIUM SALT OF 2-SULPHANILAMIDO-PYRIMIDINE.

The sodium salt is prepared by adding 2-sulphanilamidopyrimidine to the equivalent amount of sodium hydroxide dissolved in a very small volume of water. The mixture is warmed on a steam bath until solution is complete. Absolute alcohol and ether are then added and the sodium salt is precipitated as a white crystalline product. It is readily soluble in water.

Other alkali metal salts can be prepared in a similar manner by using the appropriate alkaline hydroxide.

EXAMPLE 34.

COPPER SALT OF 2-SULPHANILAMIDO-PYRIMIDINE.

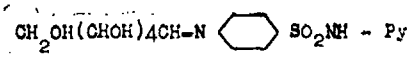
The copper salt of 2-sulphanilamidopyrimidine is prepared by adding slowly with stirring an aqueous solution of the sodium salt of 2 - sulphanilamidopyrimidine to a solution containing an equivalent amount of copper chloride. The copper salt of 2-sulphanilamidopyrimidine separates as a solid.

Salts of other heavy metals, as for example, the gold, lead and iron salts are formed by reacting the sodium salt of 2-sulphanilamidopyrimidine in aqueous solution with a suitable soluble salt of the metal desired. The desired product is obtained usually as a precipitate.

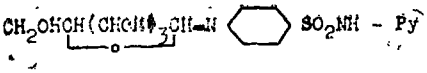
In the examples where an acylamino compound was prepared, the acetylamino derivative is described because this is the cheapest and simplest acyl compound available. The invention, however, is not limited to any particular acyl derivative.

The mono-aldose derivatives of the amino compounds of the present invention are in most instances water-soluble. These compounds may be prepared by refluxing compounds containing free amino groups with a mono-aldose sugar such as glucose or galactose in ethanol. The materials gradually go into solution and on cooling the alcoholic solutions the sugar derivatives crystallize out.

The complex resulting from the reaction of a sulphanilamidopyrimidine and glucose, for example, may be a compound of the anil or Schiff base type having the probable formula:



where Py represents a pyrimidine, or it may be a compound having the probable formula:



where Py again represents a pyrimidine, or it may be a mixture of the two types in equilibrium.

The following examples describe the preparation of the two typical samples furnished.

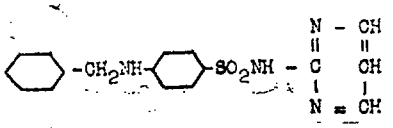
EXAMPLE 35.

GLUCOSE DERIVATIVE OF 2-SULPHANILAMIDO PYRIMIDINE.

25 parts of 2 - sulphanilamidopyrimidine, 18 parts of anhydrous glucose, and 0.2 part of ammonium chloride were suspended in 270 parts of alcohol, and the mixture heated under a reflux for a number of hours. The mixture was filtered, and on cooling the filtrate the glucose derivative of 2-sulphanilamidopyrimidine crystallized out. It was filtered off, washed with absolute alcohol and ether, and dried in a vacuum.

EXAMPLE 36.

2-(N^4-BENZYLSULPHANILAMIDO)-PYRIMIDINE.



25 parts of sulphanilamido-pyrimidine and 10 parts of calcium carbonate were suspended in 500 parts of 50% alcohol and the mixture boiled under a reflux with stirring. 6.4 parts of benzyl chloride were added and the reaction mixture was refluxed and stirred for a number of hours. After reaction was complete, it was filtered hot and on cooling a white precipitate separated. This was filtered off and dissolved in hot acetone. The acetone solution was then filtered and ice water added until a white precipitate separated. This precipitate was filtered off, washed with water, dissolved in dilute sodium hydroxide and again filtered. The filtrate was neutralized in the cold with dilute hydrochloric acid. A precipitate was formed which was filtered off and suspended in dilute hydrochloric acid and neutalized with 40% sodium hydroxide. N^4 - benzylsulphanilamido - pyrimidine precipitated out and was recrystallized three times from aqueous alcohol.

While the present application is not broadly limited to any particular location of the sulphonamido group or groups on the pyrimidine ring, we have found that the majority of the compounds showing outstanding therapeutic activity are sulphonamide compounds in which the sulphonamide group is attached to either the 2 or 5 carbon atom in the pyrimidine nucleus or to both.

The therapeutically active compounds

which are covered by the present invention can be administered either by mouth or in the form of their alkali metal salts parenterally. Administered by mouth they are preferably tableted with suitable diluent materials such as starch and the like, and in such form are effective against many bacterial infections. It is an advantage of the present invention that some of the compounds are not only highly effective against the bacterial infections for which sulphonamide drugs are commonly used such as those due to streptococcus, staphylococcus, gonococcus, meningococcus, pneumococcus, but are also effective against Friedlander's bacillus. Infections of this organism have hitherto not been susceptible to successful treatment by sulphonamide drugs.

The therapeutic activity of the compounds of the present invention which are active will of course vary from compound to compound and not all of them are equally effective against all diseases.

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 what we claim is:—

1. A method of preparing *p*-substituted benzene-sulphonamido-pyrimidines which comprises reacting a benzene-sulphonyl halide such as a chloride substituted in the para position by a group transformable into an amino group by hydrolysis, or by reduction or by reaction with ammonia or an amine such as acylamino, nitro, halogen, or azo group, with an amino-pyrimidine.

2. A method according to claim 1 in which the *p*-substituted group is then transformed into the amino group.

3. A method according to claims 1 and 2 in which the reaction of the benzene-sulphonyl halide and the amino-pyrimidine takes place in the presence of a compound capable of reacting with hydrogen halide to form salts, the compound being present in sufficient amounts to substantially neutralize the hydrogen halide set free by the reaction.

4. A method according to claims 1—3, in which the *p*-substituted group is an acylamino group such as acetylamino.

5. A method according to claims 1—3, in which the *p*-substituted group is a nitro group.

6. A method according to claims 1—3, in which the pyrimidine is 2-amino-pyrimidine.

7. A method according to claims 1 to 3 in which the *p*-substituted group is an acylamino group and the product is subjected to hydrolysis in the presence of caustic alkali or a mineral acid.

8. A method according to claims 2 to 7 in which the product is *p*-amino-benzene-sulphonamidopyrimidine, which is thereafter transformed into a salt by reaction with a base.

9. A method according to claims 1—7 in which the product is *p*-aminobenzene-sulphonamidopyrimidine, which is thereafter heated under a reflux condenser with a solution of a mono-aldose sugar in ethanol to form the corresponding mono-aldose-amino derivative.

Dated this 8th day of March, 1941.
CRUIKSHANK & FAIRWEATHER,
401, Bank Chambers,
29, Southampton Buildings,
Chancery Lane, London, W.C.2,
and
29, St. Vincent Place, Glasgow,
Agents for the Applicants.

Leamington Spa: Printed for His Majesty's Stationery Office, by the Courier Press.—1945.

Steven Langner Parry & Rollin

which are covered by the present invention can be administered either by mouth or in the form of their alkali metal salts parenterally. Administered by mouth they are preferably tableted with suitable diluent materials such as starch and the like, and in such form are effective against many bacterial infections. It is an advantage of the present invention that some of the compounds are not only highly effective against the bacterial infections for which sulphonamide drugs are commonly used such as those due to streptococcus, staphylococcus, gonococcus, meningococcus, pneumococcus, but are also effective against Friedlander's bacillus. Infections of this organism have hitherto not been susceptible to successful treatment by sulphonamide drugs.

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2. A method according to claim 1 in which the *p*-substituted group is then transformed into the amino group.

3. A method according to claims 1 and 2 in which the reaction of the benzene-sulphonyl halide and the aminopyrimidine takes place in the presence of a compound capable of reacting with hydrogen halide to form salts, the compound being present in sufficient amounts to substantially neutralize the hydrogen halide set free by the reaction.

4. A method according to claims 1—3, in which the *p*-substituted group is an acylamino group such as acetylamino.

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9. A method according to claims 1—7 in which the product is *p*-aminobenzene-sulphonamidopyrimidine, which is thereafter heated under a reflux condenser with a solution of a mono-aldose sugar in ethanol to form the corresponding mono-aldose-amino derivative.

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