PATENT SPECIFICATION

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COMPLETE SPECIFICATION

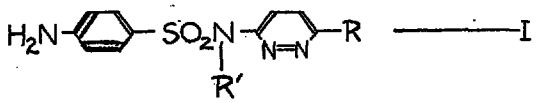
Acylated Sulfapyridazines

We, AMERICAN CYANAMID COMPANY, a corporation organised under the laws of the State of Maine, United States of America, of 30, Rockefeller Plaza, New York, State of New York, United States of America, 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 N^1 - acylated sulfapyridazines which are new compounds and the preparation thereof.

The N^4 - acyl sulfapyridazines are well known as intermediates for the preparation of such sulfa drugs as sulfapyridazine, 3 - sulfanilamido - 6 - chloropyridazine, and the like and do not in themselves possess useful antibacterial activity. On the other hand, the N^1-acylated sulfapyridazines of the present invention are used as such, and one of their principal properties is the fact that they retain their antibacterial activity while being comparatively tasteless. These properties are highly desirable, since drugs such as sulfapyridazine, when fed to animals or human beings, have a tendency to impart a bitter taste to food or water in which they are given. Because of the bitter taste, the animals will consume the medicated food or water sparingly or not at all.

The N^1-acylated sulfapyridazines of the present invention have the following general formula:



in which R is hydrogen, halogen, or a lower alkyl or lower alkoxy radical having up to 6 carbon atoms in each of said radicals, and R^1 is an alkanoyl radical. The radical R^1 can be for example an acetyl, propionyl, butyryl, valeryl, or caproyl, radical. The atom or radical R can be chloro, bromo, or iodo; or a methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, or isopropoxy radical.

The N^1 - acylated sulfapyridazines of the present invention are useful as antibacterial agents for combatting gram-positive and gram-negative bacterial. The following table shows a comparison of the activity of compounds such as N^1 - acetyl - 3 - sulfanilamido - 6-methoxypyridazine and 3 - sulfanilamido - 6-methoxypyridazine when treating infections of *Pasteurella multocida.*

PATENT OFFICE

bacteria

TABLE

Comparison of Kynex and N^1-Acetyl Kynex in the Pasteurella Multocida No. 310 Infection in CF1 Mice

Drug Intake (a) mg/kg/day	Survival (b) Ratio	% Effect
3-Sulfanilamido-6-methoxypyridazine (Kynex)		
200	39/40	97.5
100	39/40	97.5
48	23/40	57.5
27	6/40	15
17	2/40	5
Median Effective Dose = 41 (35—48) mg./kg./day		
N^1-Acetyl-3-sulfanilamido-6-methoxypyridazine (N^1-Acetyl Kynex)		
400	20/20	100.0
190	39/40	97.5
96	37/40	92.5
49	22/40	55.0
25	3/40	7.5
14	2/20	10.0
Median Effective Dose = 52 (40—68) mg./kg./day		

(a) Each drug intake value is an average based on 2 to 4 tests; in each test there were ten mice per drug-diet level.

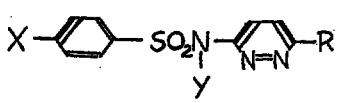
(b) Survival Ratio = Number of mice alive/total mice tested, as of the 21st day after infection.

Figures in parentheses indicate 95% confidence limits for each median.

The above table shows that the N^1 - acylated compounds have comparable antibacterial activity to the non-acylated compounds. In addition, the N^1 - acylated compounds are tasteless, while non-acylated compounds are bitter. A bitter taste in a liquid or solid oral drug is highly undesirable.

In preparing the N^1 - acylsulfapyridazines of the present invention, two different classes of intermediates are therefore used. The choice of intermediate is determined by the process used. Representative of the first group are those intermediates containing in the 4 - position an amino group wherein acylation is carried out directly. Representative of the second group are those having a group convertible to an amino group, such as a carbobenzyloxyamino, or a nitro group, convertible to amine by non-hydrolytic means.

One method according to the invention comprises reacting a compound having the general formula:

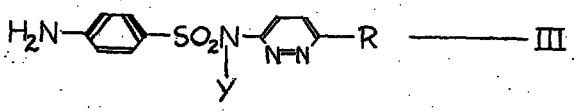


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in which X is a nitro or carbobenzyloxyamino radical, Y is hydrogen or an alkali metal and

R is as defined above, with an alkanoic acid anhydride or alkanoyl chloride and subsequently hydrogenating the reaction product.

Another method according to the invention comprises reacting a compound having the general formula:



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in which Y is hydrogen or an alkali metal and R is as defined above, with an alkanoic acid anhydride.

The compounds of the present invention can be used in the form of tablets, pills, powders, etc., which may also contain starch, excipients, and other ingredients necessary to the compounding of such dosage forms. They may also be used singly or in combination with other sulfa drugs or with antibiotics in liquid preparations to which they are especially suited because of their comparative tastelessness. For use in animals they can be mixed in food or drinking water.

In order that the preparation of the N^1-acylated sulfapyridazines in accordance with the invention may be fully understood, it will now be described with reference to the following specific examples.

EXAMPLE 1

N^1 - Acetyl - 3 - Sulfanilamido - 6 - Methoxypyridazine

56 g. (0.2 mole) 3 - sulfanilamido - 6 - methoxypyridazine is dissolved in 100 cc. H_2O and 21.5 cc. of 10 N sodium hydroxide. 47.25 g. (0.25 real equivalents) of carbobenzyloxychloride (95%) and 52 cc. of 5N sodium hydroxide are then added dropwise and simultaneously over a period of twenty minutes. The temperature is kept at 35°—40° C. Stirring of the mixture is vigorous throughout the addition and is continued for one hour, during which time a solid is formed. The solid is dissolved with alkali and warm water, and the resulting clear solution is added to dilute hydrochloric acid solution at below 20° C. to precipitate the product. The product is a fine white powder; melting point 186°—187° C. (with decomposition; corr.) after a second precipitation.

The N^4 - carbobenzyloxy - 3 - sulfanilamido - 6 - methoxy - pyridazine prepared above (75.6 g.; 0.132 mole) is dissolved in 52.2 cc. acetic anhydride and 133 cc. dry pyridine. The solution is heated to 90°—95° C. for 45 minutes. The reaction mixture is cooled and water and 80 cc. of 5N sodium hydroxide are added with stirring to precipitate the product. The product is filtered, washed with 1M ammonium hydroxide, then with water, and dried. Recrystallization from methanol gives material melting at 195°—196° C. corr.

The N^4 - carbobenzyloxy - N^1 - acetyl - 3 - sulfanilamido - 6 - methoxypyridazine prepared immediately above (9 g., 0.02 mole) is dissolved in 100 cc. dioxane. 3.0 g. of 10% palladium on carbon catalyst is added and the mixture is reduced under low pressure hydrogen for 40 minutes. The mixture is filtered and the clear filtrate is treated with 200 cc. water and seeded to crystallize the product as fine white crystals, melting point 178°—179° C. dec. (melting point varies considerably with rate of heating).

EXAMPLE 2

N^1 - Acetyl - 3 - Sulfanilamido - 6-Chloropyridazine

5.0 g. (0.0175 mole) 3 - sulfanilamido - 6-chloropyridazine are dissolved in 35 cc. acetone and 1.35 cc. (0.0175 mole) dry pyridine at room temperature. 1.62 cc. (0.0175 mole) acetic anhydride are added slowly with stirring. The solution is stirred for one hour, during which time some solid formed. The reaction slurry is treated with 50 cc. of water and evaporated in the air to leave a yellow solid. This is washed with 1M ammonium hydroxide, and the insoluble solid is filtered, washed, and dried. The product is in the form of white crystals, melting at 221°—223° C. (corr.) after recrystallization from cold acetone-water.

EXAMPLE 3

N^1 - Acetyl - 3 - Sulfanilamido - 6 - Methylpyridazine

1.0 g. (0.0035 mole) sodium - 3 - sulfanilamido - 6 - methylpyridazine is slurried with 7.0 cc. of N,N - dimethyl-acetamide. 0.33 cc. (0.0035 mole) acetic anhydride is added dropwise with stirring at 25° C. The bright yellow solution is stirred for one hour. The mixture is then chilled in an ice-alcohol bath and water is added to crystallize out a pale yellow solid. This solid is filtered, washed with 1M ammonium hydroxide, then with water and dried. The product is a colorless crystalline solid, melting at 121°—122° C. (corr.) after recrystallization from cold acetone-water.

EXAMPLE 4

N^1 - Acetyl - 3 - Sulfanilamido Pyridazine

Using the procedure described in Example 2, N^1 - acetyl - 3 - sulfanilamido pyridazine is prepared from 3 - sulfanilamido - pyridazine and acetic anhydride and isolated in the same manner. This product is pale yellow crystals melting at 200°—201° C. after recrystallization from acetonitrile.

EXAMPLE 5

N^1 - Acetyl - 3 - Sulfanilamido - 6 - Methoxypyridazine

5.0 g. (0.018 mole) 3 - sulfanilamido - 6-methoxy - pyridazine is dissolved in 100 ml. (1.24 mole) pyridine. This solution is cooled to 0° and with stirring 2 ml. (0.021 mole) acetic anhydride is added dropwise. The temperature is maintained at 0°—10° C. with stirring for 1 hour. The solution is then concentrated to 1/3 its volume and the product is precipitated by addition of an equal volume of both water and

1M ammonium hydroxide. After filtering and drying, the white solid melts at 176.5°—178° C. The infrared spectrum of the product is identical with the product in Example 1 and is analytically pure.

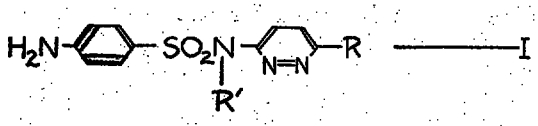
EXAMPLE 6

N^1 - Acetyl - 3 - Sulfanilamido - 6 - Methoxypyridazine

In a reaction carried out in a manner similar to Example 3, N^1 - acetyl - 3 - sulfanilamido - 6 - methoxypyridazine is prepared from the reaction of sodium 3 - sulfanilamido-6 - methoxypyridazine and acetic anhydride and isolated in the same manner.

WHAT WE CLAIM IS:—

1. New compounds comprising N^1 - acylated sulfapyridazines having the general formula:



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in which R is hydrogen, halogen, or a lower alkyl or lower alkoxy radical having up to 6 carbon atoms in each of said radicals and R^1 is an alkanoyl radical.

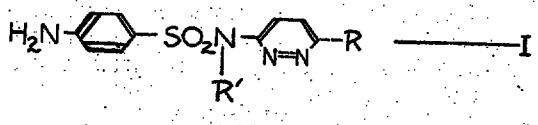
2. The compound N^1 - acetyl - 3 - sulfanilamido - 6 - methoxy - pyridazine.

3. The compound N^1 - acetyl - 3 - sulfanilamido - 6 - chloropyridazine.

4. The compound N^1 - acetyl - 3 - sulfanilamido - 6 - methyl - pyridazine.

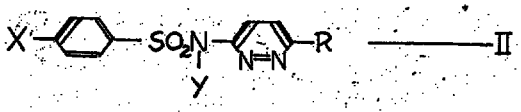
5. The compound N^1 - acetyl - 3 - sulfanilamidopyridazine.

6. A method of preparing N^1 - acylated sulfapyridazines having the general formula:



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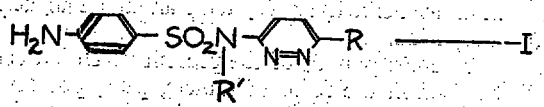
in which R is hydrogen, halogen, or a lower alkyl, or lower alkoxy radical having up to 6 carbon atoms in each of said radicals, and R^1 is an alkanoyl radical which comprises reacting a compound having the general formula:



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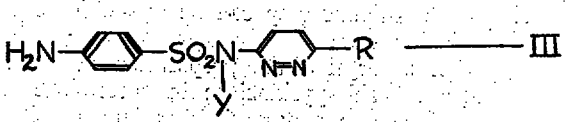
in which X is a nitro or carbobenzyloxyamino radical, Y is hydrogen or an alkali metal and R is as defined above, with an alkanoic acid anhydride or alkanoyl chloride and subsequently hydrogenating the reaction product.

7. A method of preparing N^1 - acylated sulfapyridazines having the general formula:



—————I

in which R is hydrogen, halogen or a lower alkyl or lower alkoxy radical having up to 6 carbon atoms in each of said radicals, and R^1 is an alkanoyl radical, which comprises reacting a compound having the general formula:



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in which Y is hydrogen or an alkali metal and R is as defined above, with an alkanoic acid anhydride.

8. A method according to claim 6 or 7 in which said anhydride is acetic anhydride.

9. A method of preparing N^1 - acylated sulfapyridazines having the general formula I herein substantially hereinbefore described with reference to claim 6.

10. A method of preparing N^1 - acylated sulfapyridazines having the general formula I herein substantially as hereinbefore described with reference to claim 7.

11. N^1 - acylated sulfapyridazines whenever prepared by the method according to any of claims 6 to 10.

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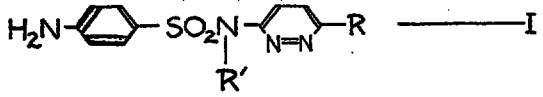
EXAMPLE 6

N^1 - Acetyl - 3 - Sulfanilamido - 6 - Methoxypyridazine

In a reaction carried out in a manner similar to Example 3, N^1 - acetyl - 3 - sulfanilamido - 6 - methoxypyridazine is prepared from the reaction of sodium 3 - sulfanilamido-6 - methoxypyridazine and acetic anhydride and isolated in the same manner.

WHAT WE CLAIM IS:—

1. New compounds comprising N^1 - acylated sulfapyridazines having the general formula:



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in which R is hydrogen, halogen, or a lower alkyl or lower alkoxy radical having up to 6 carbon atoms in each of said radicals and R^1 is an alkanoyl radical.

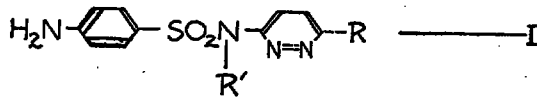
2. The compound N^1 - acetyl - 3 - sulfanilamido - 6 - methoxy - pyridazine.

3. The compound N^1 - acetyl - 3 - sulfanilamido - 6 - chloropyridazine.

4. The compound N^1 - acetyl - 3 - sulfanilamido - 6 - methyl - pyridazine.

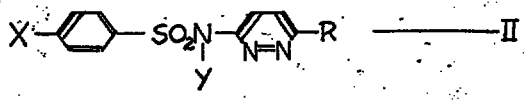
5. The compound N^1 - acetyl - 3 - sulfanilamidopyridazine.

6. A method of preparing N^1 - acylated sulfapyridazines having the general formula:



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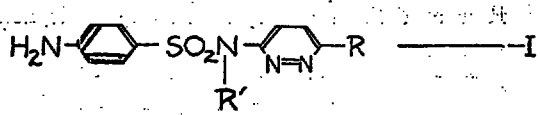
in which R is hydrogen, halogen, or a lower alkyl, or lower alkoxy radical having up to 6 carbon atoms in each of said radicals, and R^1 is an alkanoyl radical which comprises reacting a compound having the general formula:



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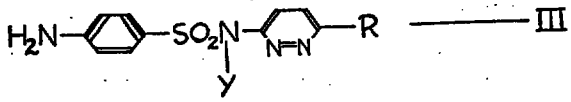
in which X is a nitro or carbobenzyloxyamino radical, Y is hydrogen or an alkali metal and R is as defined above, with an alkanoic acid anhydride or alkanoyl chloride and subsequently hydrogenating the reaction product.

7. A method of preparing N^1 - acylated sulfapyridazines having the general formula:



—————I

in which R is hydrogen, halogen or a lower alkyl or lower alkoxy radical having up to 6 carbon atoms in each of said radicals, and R^1 is an alkanoyl radical, which comprises reacting a compound having the general formula:



—————III

in which Y is hydrogen or an alkali metal and R is as defined above, with an alkanoic acid anhydride.

8. A method according to claim 6 or 7 in which said anhydride is acetic anhydride.

9. A method of preparing N^1 - acylated sulfapyridazines having the general formula I herein substantially hereinbefore described with reference to claim 6.

10. A method of preparing N^1 - acylated sulfapyridazines having the general formula I herein substantially as hereinbefore described with reference to claim 7.

11. N^1 - acylated sulfapyridazines whenever prepared by the method according to any of claims 6 to 10.

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