PATENT SPECIFICATION

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COMPLETE SPECIFICATION

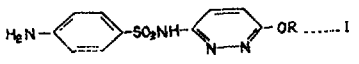
New Compounds Comprising 3-Sulfanilamido-6-Substituted Pyridazines

PATENT OFFICE

We, AMERICAN ~~CYNAMID~~ 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 the production of 3 - sulfanilamido- 6 -substituted pyridazines which are new compounds.

The new compounds of the present invention may be illustrated by the following general formula:



in which R is an alkyl, aralkyl or aryl radical. For example the alkyl radicals may be methyl, ethyl, propyl, butyl or amyl; the aralkyl radicals may be benzyl, phenethyl, phenpropyl or phenbutyl; and the aryl radicals may be phenyl or naphthyl.

The compounds of the present invention are, in general, crystalline solids having a melting point above 100° C. They can be recrystallized from water or alcohols or a mixture of water and alcohol.

In accordance with the invention these compounds can be prepared by using 3-sulfanilamido-6-chloropyridazine as an intermediate which is reacted with an alkali metal alcoholate or phenolate resulting from the reaction of an alcohol or phenol having the formula ROH and an alkali metal. Simple alcohols, phenol, benzyl alcohol, phenethyl alcohol, and the like, can be used in the reaction. It is usually desirable to heat the reaction mixture to a temperature within the range of 50° C. to 250° C. for a period of from ten minutes to fifteen hours. An alkali metal such as sodium or potassium is added to the alcohol or phenol to form the corresponding alcoholate or phenolate which is then reacted with the 3-sulfanilamido-6-chloropyridazine.

The 3 - sulfanilamido- 6 -chloropyridazine which is used as an intermediate in the reaction can be obtained by reacting 3,6-dichloropyridazine with sulfanilamide, preferably by heating at temperatures of 130° C. to 220° C. in the presence of an acid acceptor.

The preparation of the therapeutically useful compounds of the present invention is described in greater detail in the following examples. All parts are by weight unless otherwise indicated.

EXAMPLE 1.

3-SULFANILAMIDO-6-METHOXYPYRIDAZINE

2.3 Parts of clean sodium metal is dissolved in 50 parts of anhydrous methyl alcohol. 11.4 Parts of 3-sulfanilamido-6-chloropyridazine is added and the mixture heated in a sealed tube 13 hours at 130°—140° C. After the tube has cooled it is opened and the reaction mixture filtered, acidified with dilute acetic acid, then evaporated to dryness on the steam bath. The residue is dissolved in 80 parts of 5% sodium hydroxide, chilled and acidified with dilute acetic acid. The crude product is filtered and then recrystallized from water to give 3-sulfanilamido-6-methoxypyridazine of melting point 182°—183° C.

EXAMPLE 2.

3-SULFANILAMIDO-6-ETHOXYPYRIDAZINE

0.6 Parts of clean sodium metal is dissolved in 75 parts of absolute ethyl alcohol. 2.9 Parts of 3-sulfanilamido-6-chloropyridazine is added and the mixture heated in a sealed tube 13 hours at 145°—155° C. After the tube has cooled it is opened and the reaction mixture filtered, acidified with dilute acetic acid, then evaporated to dryness on the steam bath. The residue is dissolved in 20 parts of 10% sodium hydroxide, chilled and acidified with dilute acetic acid. The crude product is

filtered and then recrystallized from water-ethanol to give 3 - sulfanilamido-6-ethoxypyridazine, melting point 183°—184° C.

Example 3.
3-sulfanilamido-6-*n*-propyloxypyridazine

0.6 Parts of clean sodium metal is dissolved in 75 parts of *n*-propyl alcohol. 2.9 Parts of 3-sulfanilamido-6-chloropyridazine is added and the mixture heated in a sealed tube 13 hours at 145°—155° C. After the tube has cooled it is opened and the reaction mixture filtered, acidified with dilute acetic acid, then evaporated to dryness on the steam bath. The residue is dissolved in 10 parts of 5% sodium hydroxide, chilled and acidified with dilute acetic acid. The crude product is filtered and recrystallized from water-ethanol to give 3-sulfanilamido-6-*n*-propyloxypyridazine, melting point 184°—185° C.

Example 4.
3-sulfanilamido-6-*iso*-propyloxypyridazine

0.6 Parts of clean sodium metal is dissolved in 75 parts of *iso*-propyl alcohol. 2.9 Parts of 3-sulfanilamido-6-chloropyridazine is added and the mixture heated in a sealed tube 13 hours at 145°—155° C. After the tube has cooled it is opened and the reaction mixture filtered, acidified with dilute acetic acid, then evaporated to dryness on the steam bath. The residue is dissolved in 10 ml. of 5% sodium hydroxide, chilled and acidified with dilute acetic acid. The crude product is filtered and recrystallized from water-ethanol to give 3-sulfanilamido - 6 - *iso* - propyloxypyridazine, melting point 187°—188° C.

Example 5.
3-sulfanilamido-6-*n*-hexyloxypyridazine

0.6 Parts of clean sodium metal is dissolved in 200 parts of *n*-hexyl alcohol. 2.9 Parts of 3-sulfanilamido-6-chloropyridazine is added and the mixture refluxed 40 hours at 157° C. The excess alcohol is then vacuum distilled. The residue is suspended in ether, filtered, washed two times with ether, then dissolved in 20 parts of water and acidified with dilute acetic acid. The crude product is filtered out, then recrystallized from water-ethanol to give 3 - sulfanilamido - 6 - *n* - hexyloxypyridazine, melting point 140°—141° C.

Example 6.
3-sulfanilamido-6-phenoxypyridazine

0.6 Parts of clean sodium metal is dissolved in 50 parts of methyl alcohol. 2.9 Parts of 3 - sulfanilamido-6-chloropyridazine and 60 parts of phenol is added and this solution heated to 140° C. to drive off all traces of methyl alcohol and water. The residue is heated at 140° C. for 9 hours, then the excess phenol is distilled off. The residue is suspended in ether, filtered, washed two times with ether, then dissolved in 20 parts of water and acidified with dilute acid. The crude product is filtered out, then recrystallized from water-ethanol to give 3 - sulfanilamido - 6 - phenoxypyridazine. The compound melts at 139°—140° C., resolidifies and melts again at 160°—161° C.

Example 7.
3-sulfanilamido-6-benzyloxypyridazine

0.6 Parts of clean sodium metal is dissolved in 150 parts of benzyl alcohol. 2.9 Parts of 3-sulfanilamido-6-chloropyridazine is added and the mixture heated 13 hours at 145°—147° C. The excess alcohol is then vacuum distilled. The residue is suspended in ether, filtered, washed two times with ether, then dissolved in 20 parts of water and acidified with dilute acetic acid. The crude product is filtered, then recrystallized from ethyl alcohol to give 3 - sulfanilamido - 6 - benzyloxypyridazine, melting point 200°—201° C.

Example 8.
3-sulfanilamido-6-phenethoxypyridazine

0.6 Parts of clean sodium metal is dissolved in 150 parts beta-phenethyl alcohol. 2.9 Parts of 3-sulfanilamido-6-chloropyridazine is added and the mixture refluxed two and one-half hours at 220° C. The excess alcohol is then vacuum distilled. The residue is suspended in ether, washed two times with ether, dissolved in 20 parts of water and acidified with dilute acetic acid. The crude product is filtered, then recrystallized from absolute alcohol to give 3-sulfanilamido-6-phenethoxypyridazine of melting point 173°—174° C.

The compounds of the present invention, when given orally, show greater survival in mice against pneumococcus Strain SVI than related compounds. The following Table I shows the detailed results obtained when using sulfadiazine, sulfapyridazine and 3-sulfanilamido-6-methoxypyridazine.

TABLE I

Pneumococcus Strain SVI

% Drug in Diet	Drug Intake * Mg./Kg./Day	Blood Level Mg. %	Mice Alive/Total	% Effect
		Sulfadiazine		
0.4	850	14.5	40/40	100.0
0.2	390	8.6	20/40	50.0
0.1	160	4.8	10/40	25.0
0.05	49	2.2	2/39	5.0
0.025	18	1.1	0/40	0.0
	Median Effective Dose = 290 (220—380) mg./kg./day			
		Sulfapyridazine		
0.8	1800	6.6	39/39	100.0
0.4	660	2.8	10/40	25.0
0.2	270	1.3	8/40	20.0
0.1	76	—	1/40	2.5
0.05	43	—	0/40	0.0
	Median Effective Dose = 880 (310—2500) mg./kg./day			
		3-Sulfanilamido-6-methoxypyridazine		
0.4	940	19.0	40/40	100.0
0.2	450	11.0	36/40	90.0
0.1	180	6.0	10/39	25.6
0.05	65	3.0	8/40	20.0
0.025	19	1.3	1/40	2.5
	Median Effective Dose = 180 (140—220) mg/kg./day			

* Drug intake values are averages based on four tests of each drug diet.

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

When the present compounds are fed to mice infected with several different bacteria along with related compounds they show a greater activity. This is illustrated in Table II below.

TABLE II

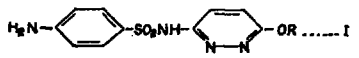
Relative Antibacterial Activities

Drug	Pneumococcus Strain SVI	Streptococcus Strain C—203	Klebsiella Strain AD	Pasteurella Strain 310
	Relative Activity Based on Oral Dosage *			
Sulfadiazine (Standard)	1.0	1.0	1.0	1.0
Sulfapyridazine	0.3	0.5	0.1	0.3
Sulfamethoxypyridazine	1.6	0.9	0.5	0.9
Gantrisin (Registered Trade Mark)	0.3	0.2	0.1	0.1

* Relative activity based on dosage = ED_{50} of Sulfadiazine/ED_{50} of other drug.

What we claim is:—

1. New compounds comprising 3-sulfanilamido-6-substituted pyridazines having the general formula:



in which R is an alkyl, aralkyl or aryl radical.

2. 3-Sulfanilamido-6-methoxypyridazine.

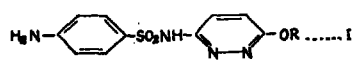
3. 3-Sulfanilamido-6-ethoxypyridazine.

4. 3 - Sulfanilamido - 6- iso - propyloxypyridazine.

5. 3-Sulfanilamido-6-phenoxypyridazine.

6. 3-Sulfanilamido-6-benzyloxypyridazine.

7. A method of preparing 3-sulfanilamido-6 - substituted pyridazines having the general formula:



in which R is an alkyl, aralkyl or aryl radical, which comprises reacting 3-sulfanilamido-6-chloropyridazine with an alkali metal alcoholate or phenolate resulting from the reaction of an alcohol or phenol having the formula ROH and an alkali metal.

8. A method according to claim 7, in which the reaction mixture is heated to a temperature of 50° C. to 250° C.

9. A method according to claim 7 or 8, in which said chloropyridazine is prepared by reacting 3,6-dichloropyridazine with sulfanilamide.

10. A method according to claim 9, in which the reaction is carried out at a temperature of at least 130° C. in the presence of an acid acceptor.

11. A method of preparing 3-sulfanilamido-6-substituted pyridazines having the general formula I substantially as hereinbefore described.

12. 3-Sulfanilamido- 6 -substituted pyridazines having the general formula I whenever prepared by the method according to any of the preceding claims.

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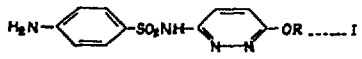
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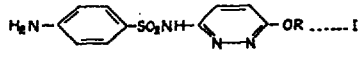
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5. 3-Sulfanilamido-6-phenoxypyridazine.

6. 3-Sulfanilamido-6-benzyloxypyridazine.

7. A method of preparing 3-sulfanilamido-6 - substituted pyridazines having the general formula:



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