PATENT SPECIFICATION

NO DRAWINGS

836,150

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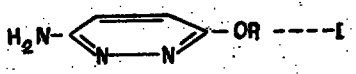
COMPLETE SPECIFICATION

New 3-Amino-6-Substituted Pyridazines and preparation of Sulfanilamidopyridazines therefrom

We, AMERICAN CYANAMID COMPANY, a corporation organized 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:—

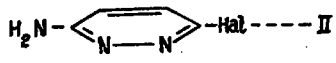
This invention relates to the preparation of new 3-amino-6-substituted pyridazines, which are useful as intermediates for the preparation of known sulfanilamidopyridazines.

These new 3-amino-6-substituted pyridazines of the present invention have the following formula:



wherein R is an alkyl, aryl or aralkyl radical. The alkyl radical may be methyl, ethyl, *n*-propyl, isopropyl, butyl, amyl, hexyl, or the like. The aryl radical may be phenyl, naphthyl, or the like, and the aralkyl radical may be benzyl, phenethyl, phenpropyl, phenbutyl, or the like.

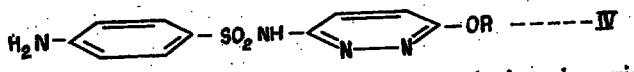
In accordance with the invention, the 3-amino-6-substituted pyridazines having the formula I are prepared by heating a 3-amino-6-halopyridazine having the formula:



with the reaction product of an alkali metal with the corresponding alcohols having the formula:

ROH III

Patent application No. 776,730 discloses sulfanilamido-pyridazines showing improved therapeutic effects as compared with sulfadiazine and sulfapyridazine, and having the formula:



wherein R is an alkyl, aryl or aralkyl radical. In accordance with the method of said patent application, these sulfanilamido-pyridazines are prepared by fusing 3,6-dichloropyridazine with sulfanilamide followed by displacement of the remaining chlorine atom by an alkoxy, aryloxy or aralkoxy group through the use of sodium methoxide or its appropriate homolog or analog.

According to the invention, these sulfanilamido pyridazines having the formula IV can be prepared more simply by reacting a *p*-acetylsulfanilyl halide with a 3-amino-6-substituted pyridazine having the formula I in an inert organic solvent, and deacetylating the resulting product.

In carrying out the invention to produce the 3-amino-6-substituted pyridazine having the formula I, 3-amino-6-chloropyridazine is reacted in solution with a soluble alkali metal alkoxide, aryloxide or aralkoxide, preferably at temperatures ranging from 50° to 200° C. for 2 to 100 hours, to form the new compounds of this invention. The solvent utilized in this method should preferably be the same as it is desired to substitute at the 6 position. Thus, in preparing 3-amino-6-methoxy pyridazine one should use methanol; in preparing 3-amino-6-*n*-hexoxy pyridazine one should use *n*-hexanol. This is so, since if one were, for example to react 3-amino-6-chloropyridazine with sodium methoxide in *n*-hexanol, one would produce a mixture of 3-amino-6-methoxy pyridazine and 3-amino-6-*n*-hexoxy

pyridazine requiring the separation of the mixture. Alternately, in place of the alcohols, one may utilize organic solvents, such as, for example, toluene xylene, and homologous aromatic hydrocarbons. The acyclic hydrocarbons may be used also, for example, hexane, heptane, and homologous acyclic hydrocarbons. In the purification procedure that follows the reaction, the resulting colored crystalline solid may be dissolved in an organic solvent and treated with an absorbent material such as activated charcoal and filtered. Suitable solvents for this procedure are a mixture of petroleum ether and chloroform wherein the petroleum ether content may vary from 10% to 90% of the mixture, and the chloroform, likewise, may be 90% to 10%. Alternately, diethyl ether may be used as the organic solvent in this step of this process. Following the clarification step, the crystalline solid may be recrystallized and again treated with an absorbent.

These new compounds are then dissolved in a solvent which is unreactive with the starting materials under the conditions of the reaction and *p*-acetylsulfanilyl chloride is reacted therewith for 10 minutes to 24 hours at temperatures of from 20° to 100° C. to form the 3-(N^4-acetylsulfanilamido) derivative of the compounds of this invention. In the procedure tertiary amines are recommended as the solvent of choice, for example, the heterocyclic tertiary amines, pyridine, picoline and analogs and homologs thereof. Acyclic tertiary amines may be used also, for example, triethyl amine and tripropyl amine. Moreover, aromatic tertiary amines such as N,N-dimethyl aniline and its analogs and homologs may be used. The product of this step of the reaction may also be recrystallized utilizing various alkanols or mixtures of alkanols with water. For example, 100% methanol, ethanol, propanol and other homologs may be used. Alternately, one may use any of the alkanols in combination with water wherein the alkanol varies from 75% to 90% and the water from 25% to 10%. This recrystallization then may be followed by a clarification step utilizing known absorbent such as activated charcoal. Alternately, any of the above recrystallizing steps can be replaced by vacuum sublimation or by precipitation by adding excess water to the organic solvent solution. These 3-(N^4-acetylsulfanilamido) derivatives can then be deacylated by hydrolysis, or some equivalent procedure, to produce the 3-sulfanilamido-6-substituted pyridazines. The hydrolysis takes place in any soluble strong base, for example, sodium hydroxide, potassium hydroxide and barium hydroxide, for a period of from 10 minutes to 4 hours. The concentration of the strong base may vary from 2% to 40%. After this period of time the solution is buffered with a soluble buffer, such as a mixture of acetic acid and ammonium acetate, to a pH of from about 4 to 6 to precipitate the product. The acetic acid content of this solution may vary from 1 to 2 parts by weight and the ammonium acetate from about 1 to 6 parts by weight in 2 to 30 parts by weight of water.

The preparation of the new compounds of this invention and their conversion to the therapeutically active compounds referred to above is described in greater detail in the following examples. These examples are presented by way of illustration only, the scope of the invention being limited by the scope of the appended claims.

EXAMPLE 1.

A total of 3.40 g. (0.026 mol) of 3-amino-6-chloropyridazine was placed in a Carius tube with a solution of sodium methoxide in methanol [prepared from 0.61 g. (0.027 mol) of clean sodium metal and 50 ml. of methanol] and the Carius tube was sealed. The tube was placed in a Carius furnace and maintained at 120° C. for 20 hours. After the tube was cooled and opened, the contents were removed and the light brown solid was filtered off. The filtrate was evaporated to dryness at room temperature under an air jet. The resulting orange-brown crystalline solid was dissolved in a 60:40 petroleum ether-chloroform solution, treated with activated charcoal and filtered. There was obtained, upon cooling, 1.1 g. (34%) of a pale yellow crystalline solid melting at 100°—104° C. Recrystallization of this crystalline solid from *n*-amyl chloride accompanied by treatment with activated charcoal yielded 0.51 g. of a white, crystalline solid melting at 103—105° C.

Calc'd. for $C_5H_7N_3O$: %C, 47.99; %H, 5.64, %N, 33.58. Found: %C, 47.72, %H, 5.73; %N, 33.73.

An infrared spectrum of the compound namely 3-amino-6-methoxypyridazine, indicated characteristic absorption bands of the primary aromatic amino group and of the methyl group.

A total of 0.29 g. (0.0023 mol) of 3-amino-6-methoxy-pyridazine was dissolved in 2 ml. of dry pyridine in a small test tube surrounded by an oil bath at 50° C. To this solution was added, in small amounts with stirring during 10 minutes, a solution of 0.57 g. (0.0024 mol) of *p*-acetylsulfanilyl chloride in 1.5 ml. of dry pyridine. The resulting light brown solution was maintained at 60° C. with intermittent stirring for 30 minutes; it was then cooled and poured into sufficient 0.1 N sodium hydroxide to give a pH of 7. The volatiles were removed at room temperature under vacuum, and the residue was triturated with water and filtered off. After recrystallization from 3:1 methanol-water accompanied by treatment with activated charcoal, there was obtained a slightly off-white crystalline product melting at 215—218° C. The melting point remained undepressed on admixture with a known sample of 3-(N^4-acetylsulfanilamido)-6-methoxy pyridazine.

The infrared absorption curves of these two samples were identical.

A total of 0.32 g. (1.0 mol) of 3-(N^4-acetylsulfanilamido)-6-methoxypyridazine was dissolved in 8 g. of a 10% solution of sodium hydroxide. The solution was refluxed 45 minutes then cooled and buffered to pH 5.5 by addition to a solution of acetic acid and ammonium acetate in water. The resulting white, crystalline precipitate was filtered off, washed and dried; its weight was 0.22 g. Its melting point, 182.5° to 183.5° C., remained undepressed on admixture with a known sample of 3-sulfanilamido-6-methoxypyridazine. A comparison of an infrared absorption curve of this product with that of a known sample of 3-sulfanilamido-6-methoxypyridazine indicated the product to consist essentially of the same compound.

EXAMPLE 2.

A total of 3.95 g. (0.0305 mol) of 3-amino-6-chloropyridazine was added to a solution of 1.22 g. (0.0305 mol) of clean sodium metal in 50 ml. of freshly distilled *n*-hexanol, and the mixture was refluxed for 24 hours. The sodium chloride was filtered off, and the excess hexanol was stripped from the filtrate under vacuum. The dark residue was subjected to a vacuum sublimation (100°—125° C. at about 0.3 mm. of Hg.) which yielded 3.1 g. of a light orange-brown waxy solid melting at 25—30° C. Analysis and infrared spectrum indicated it to be 3-amino-6-*n*-hexoxypyridazine.

A total of 0.90 g. (0.0046 mol) of 3-amino-6-*n*-hexoxypyridazine was dissolved in 4 ml. of pyridine in a tube surrounded by a bath at 50° C. To this solution was added during 10 minutes with stirring a solution of 1.23 g. (0.0052 mol) of *p*-acetylsulfanilyl chloride, the temperature being maintained at 50° to 55° C. On completion of the addition, the reddish-brown solution was maintained at 60°—65° C. with intermittent stirring for 4 hours. The solution was cooled and neutralized with 0.2 N sodium hydroxide solution. The volatiles were removed under vacuum to leave an amorphous, brown, somewhat gummy residue; this residue was partially dissolved with 20 ml. of 0.5 N sodium hydroxide. The aqueous fraction was separated from a lower, dark brown oily layer by centrifuging. The aqueous layer was buffered to pH 5 by addition to an acetic acid-ammonium acetate solution. After the resulting light brown, gummy precipitate was separated, it was dissolved in methanol, treated with activated charcoal and clarified. The methanol solution was diluted by the dropwise addition of water with stirring. The resulting pale yellow precipitate was filtered, washed and dried; it had a melting point of 152°—159.5° C. The product was redissolved in sodium hydroxide, filtered and reprecipitated at pH 5. The precipitate was dissolved in methanol, treated with activated charcoal and clarified. Dropwise addition of water to the methanol solution with stirring yielded a white, flocculent, precipitate which was filtered off, washed, and dried in an oven at 85° C. yielding a product having a melting point of 164.5°—165.5° C. The infrared absorption curve was consistent with the structure 3-(N^4 - acetylsulfanilamido - 6 - *n* - hexoxypyridazine).

Analysis: Calc'd. for $C_{16}H_{24}N_4O_4S$: %N, 14.28, Found: %N, 14.53.

The hydrolysis of this product to 3-sulfanilamido-6-*n*-hexoxypyridazine proceeds in a manner similar to the hydrolysis of the methoxy derivative.

EXAMPLE 3.

A solution of 3.9 g. (0.03 mol) of 3-amino-6-chloropyridazine in 50 g. of phenol was treated with 3.5 g. (0.03 mol) of sodium phenolate and heated in an oil bath with stirring at 150° C. for 24 hours. The cooled reaction mixture was poured into dilute sodium hydroxide to dissolve the excess phenol. The insoluble residue thereby produced was recrystallized from ether to obtain 3-amino-6-phenoxypyridazine. This new compound is then converted to the corresponding 3-sulfanilamido-6-phenoxypyridazine in substantially the same manner as in the foregoing examples.

EXAMPLE 4.

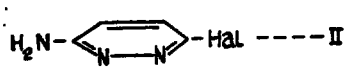
To a solution of 0.03 mol of sodium benzylate in benzyl alcohol (prepared by dissolving 0.7 g. of clean sodium metal in 50 cc. of benzyl alcohol) was added 3.9 g. (0.03 mol) of 3-amino-6-chloropyridazine. The mixture was heated with stirring at 150° C. for 24 hours. Most of the benzyl alcohol was then distilled off at reduced pressure. The residue was treated with an excess of dilute hydrochloric acid. The acid solution was extracted with ether and the extracts discarded. The aqueous solution was then made alkaline with sodium hydroxide and the precipitated 3-amino-6-benzyloxypyridazine was separated and purified by recrystallization from ether. This new compound was then converted to the corresponding 3-sulfanilamido-6-benzyloxypyridazine in substantially the same manner as in the foregoing examples.

WHAT WE CLAIM IS:—

1. A method of preparing 3-amino-6-substituted pyridazines having the formula:



wherein R is an alkyl, aryl or aralkyl radical, which comprises heating a 3-amino-6-halopyridazine having the formula:



with the reaction product of an alkali metal with the corresponding alcohol having the formula:

The infrared absorption curves of these two samples were identical.

A total of 0.32 g. (1.0 mol) of 3-(N^4-acetylsulfanilamido)-6-methoxypyridazine was dissolved in 8 g. of a 10% solution of sodium hydroxide. The solution was refluxed 45 minutes then cooled and buffered to pH 5.5 by addition to a solution of acetic acid and ammonium acetate in water. The resulting white, crystalline precipitate was filtered off, washed and dried; its weight was 0.22 g. Its melting point, 182.5° to 183.5° C., remained undepressed on admixture with a known sample of 3-sulfanilamido-6-methoxypyridazine. A comparison of an infrared absorption curve of this product with that of a known sample of 3-sulfanilamido-6-methoxypyridazine indicated the product to consist essentially of the same compound.

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Analysis: Calc'd. for $C_{18}H_{24}N_4O_4S$: %N, 14.28, Found: %N, 14.53.

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EXAMPLE 4.

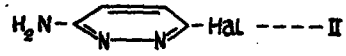
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WHAT WE CLAIM IS:—

1. A method of preparing 3-amino-6-substituted pyridazines having the formula:



wherein R is an alkyl, aryl or aralkyl radical, which comprises heating a 3-amino-6-halopyridazine having the formula:



with the reaction product of an alkali metal with the corresponding alcohol having the formula:

* C L M S *

ROH III

2. A method according to claim 1, in which the reaction is carried out at a temperature of 50° C. to 200° C.

3. A method according to claims 1 or 2, in which the reaction is carried out in an excess of one or more of said alcohols.

4. A method according to claims 1 or 2, in which the reaction is carried out in an inert organic solvent.

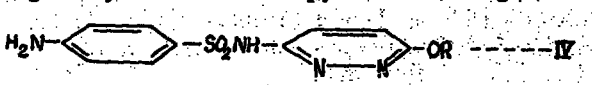
5. A method according to any of claims 1 to 4, in which said alcohol or phenol is methanol, *n*-hexanol, phenol or benzyl alcohol.

6. A method according to any of claims 1 to 5, in which said alkali metal is sodium.

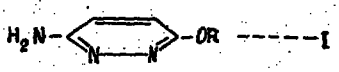
7. A method of preparing 3-amino-6-substituted pyridazines having the formula I substantially as hereinbefore described.

8. 3-Amino-6-substituted pyridazines whenever prepared by the method according to any of the preceding claims.

9. A method of preparing sulfanilamidopyridazines having the formula:



wherein R is an alkyl, aryl or aralkyl radical, which comprises reacting a *p*-acetylsulfanilyl halide with a 3-amino-6-substituted pyridazine having the formula:



in an organic solvent, which is unreactive with the starting materials under the conditions of the reaction and deacetylating the resulting product.

10. A method according to claim 9, in which said first step is carried out at temperatures of 20° C. to 100° C.

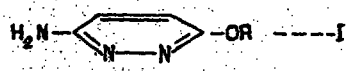
11. A method according to claims 9 and 10, in which the solvent is a tertiary amine.

12. A method according to any of claims 9 to 11, in which said second step is carried out by hydrolyzing said reaction product in a strong base.

13. A method of preparing sulfanilamidopyridazines having the formula IV substantially as hereinbefore described.

14. Sulfanilamidopyridazines having the formula IV whenever prepared by the method according to any of claims 9 to 13.

15. New compounds comprising 3-amino-6-substituted pyridazines having the formula:



wherein R is an alkyl, aryl or aralkyl radical.

16. 3-Amino-6-methoxypyridazine.

17. 3-Amino-6-*n*-hexoxypyridazine.

18. 3-Amino-6-phenoxypyridazine.

19. 3-Amino-6-benzyloxypyridazine.

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