# PATENT SPECIFICATION (11) 1345478

1345478

(21) Application No. 3319/72 (22) Filed 24 Jan. 1972

(31) Convention Application No. 114725 (32) Filed 11 Feb. 1971 in

(33) United States of America (US)

(44) Complete Specification published 30 Jan. 1974

(51) International Classification C07C 91/12

(52) Index at acceptance

C2C 20Y 29X 29Y 30Y 322 32Y 360 361 36Y 456 45Y 630 633 790 LJ



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(19)

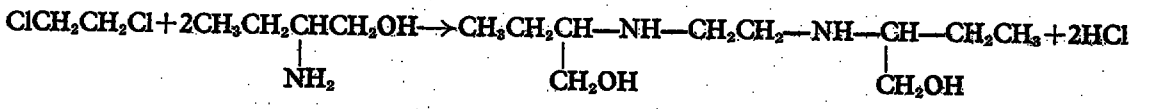
## (54) PREPARATION OF *d,d'*-2,2'-(ETHYLENEDIIMINO)-DI-1-BUTANOL HYDROCHLORIDE

(71) We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the laws of the State of Main, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, 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 improvements in preparing *d,d'* - 2,2' - (ethylenediimino)di - 1 - butanol dihydrochloride (ethambutol hydrochloride).

Ethambutol is a therapeutic agent for the treatment of turbercle bacilli infections, particularly human tuberculosis caused by *Mycobacterium tuberculosis*. The therapeutic activity of the *d* - isomer is discussed in J. Am. Chem. Soc. *83*, 2212 (1961).

The *d,d* - form of ethambutol may be made by reacting ethylene dichloride with *d* - 2 - amino - 1 - butanol. The overall reaction is illustrated by the followinig equation:



During the reaction, hydrogen chloride is produced which reacts with *d* - 2 - amino - 1 - butanol to form a hydrochloride salt. Therefore, at least 4 moles of the amine are used per mole of ethylene dichloride. The ethambutol can be separated as the base, and converted to the dihydrochloride salt.

By increasing the proportion of *d* - 2 - amino - 1 - butanol, the formation of by-products is depressed, but separation of ethambutol from *d* - 2 - amino - 1 - butanol is a problem.

To produce ethambutol, at a minimum cost to the using public, and with pharmaceutically acceptable purity, including a proper melting point, freedom from ash, proper optical rotation characteristics, and a satisfactory yield, is a problem.

Of the reacting materials, the ethylene dichloride is less expensive than the *d* - 2 - amino - 1 - butanol by more than an order of magnitude. Whereas in most chemical reactions, the least expensive component is added in excess, here for preferred purity, it is necessary that the *d* - 2 - amino - 1 - butanol be added in excess. Because *d* - 2 - amino - 1 - butanol reacts with hydrogen chloride formed, at least 4 moles of *d* - 2 - amino - 1 - butanol is required per mole of ethylene chloride. For better operating efficiency and purity, more than this, up to 16 or more moles, is added.

Because of the cost of the *d* - 2 - amino - 1 - butanol, it is necessary that it be recovered, to have a reasonably priced product.

We have now found an improved process for preparing ethambutol by reacting ethylene dichloride with a substantial excess of *d* - 2 - amino - 1 - butanol.

The process of the present invention is characterized by the steps of:

(1) adding to the mixture of *d,d'* - 2,2' - (ethylene - diimino)di - 1 - butanol, *d* - 2 - amino - 1 - butanol and the hydrochloride salts thereof formed by the reaction of the ethylene dichloride with the *d* - 2 - amino - 1 - butanol, sufficient finely divided sodium hydroxide to react with the hydrogen chloride present to form sodium chloride;

(2) distilling and thereby separating the unreacted *d* - 2 - amino - 1 - butanol from the mixture;

(3) adding a 2 to 4 carbon alkanol so as to form a solution of *d,d'* - 2,2' - (ethylenediimino)di - 1 - butanol in the alkanol;

(4) separating the undissolved sodium chloride from the solution;

(5) adding hydrogen chloride gas to the

solution to form *d,d'* - 2,2' - (ethylenediimino)di - 1 - butanol dihydrochloride, and precipitate the same; and

(6) separating the precipitate of *d,d'* - 2,2' - (ethylenediimino)di - 1 - butanol dihydrochloride from the alkanol.

In the process of this invention it is preferred to use an excess of *d* - 2 - amino - 1 - butanol of the order of 1:6 to 1:32 moles. More of the *d* - 2 - amino - 1 - butanol may be used but the recovery becomes disproportionately more costly without compensating advantages.

In the process according to the present invention, the hydrogen chloride formed during the reaction is converted to sodium chloride by the addition of finely-divided sodium hydroxide which converts the amine hydrochloride salts to the corresponding free bases. From the resulting mixture, the unreacted, and hence excess, *d* - 2 - amino - 1 - butanol is distilled, preferably under reduced pressure, and thereby separated. Typical conditions are starting at about 80°C. at below 20 millimeters mercury pressure absolute and continuing distillation to about 130°C. with no additional overhead coming over. A 2 to 4 carbon alkanol is now added to the distillation residue. Isopropanol is particularly satisfactory because it presents no tax problems such as are often connected with the use of ethanol, and no odor problems such as may occur with butanols. Isopropanol is more economical than n-propanol. Normally sufficient of the alkanol is added so that on heating, the organic materials are dissolved and sodium chloride remains undissolved and is readily separated, as by filtration.

The solution is then treated with hydrogen chloride gas to convert the *d,d'* - 2,2' - (ethylene diimino) - di - 1 - butanol to the dihydrochloride salt and to precipitate this crystalline material (i.e. ethambutol hydrochloride) which then may be readily separated, as by filtration. Thereafter, if desired, it can be washed with an alkanol, preferably isopropanol, and dried.

It is found that the addition to the ($C_2$—$C_4$)alkanol of up to about 1/3 of a part of methanol per part of ($C_2$—$C_4$) alkanol and up to about 1/10 this amount of water may aid the recovery of ethambutol hydrochloride of good purity. Usually a product is desired having a melting point of at least 190°C. and assay of not less than 99%, an ash content of not more than 0.1% and a specific rotation (10.0% in water) of not less than 6.0°.

The use of sodium hydroxide gives uniquely useful results. Other bases are either not strong enough as a base or less advantageous in solubility or filtration.

The sodium hydroxide added is finely divided and hence has a high surface area. Preferably, it should be free flowing and be less than 5 mm, in particle size. Powder and prills of less than 5 mesh per lineal inch, equivalent to a maximum particle size of about 4.0 mm., are particularly satisfactory. A particle size of 3.0 mm. or less is preferred for low ash content in the final product.

Prills are particularly desirable as the particle size is uniform, and rapid dispersion is obtained.

A preferred procedure for carrying out the process of the invention will now be described.

The amount of sodium hydroxide used should be sufficient to react with all of the hydrogen chloride present. The sodium hydroxide is added over about 15—20 minutes at a temperature of from 80° to 110°C., preferably from 85° to 100°C. The temperature is then maintained at from 100° to 125°C., preferably at from 110°C. to 115°C., for about 1 hour, to permit complete reaction of the hydrogen chloride and the sodium hydroxide.

The reaction mixture is then cooled, and vacuum distilled at a pressure less than 20 mm. and a temperature below about 130°C., starting at a temperature which gives an acceptable distillation rate, until the unreacted *d* - 2 - amino - 1 - butanol has been distilled off, and recovered for subsequent usage.

At the completion of the distillation, the residue is cooled below about 90°C. to prevent flashing, and isopropanol is added. A reflux condenser can control escaping vapors, and return to the reactor. The amount of isopropanol used is between about 3.0 and about 4.0, preferably between 3.3 and 3.6, parts to 1 part of the ethambutol base in the distillation residue. The mixture is then maintained at a temperature above 50°C., preferably a temperature of about 70—75°C., but not above reflux, until solution is complete, about 30 minutes. The solution is filtered, advantageously, at a temperature between about 50° and 65°C., to remove sodium chloride and any other insoluble materials which may be present. An additional amount of isopropanol, about 1/5 part per part of isopropanol in the distillation residue, is used to wash the filter cake.

For best results, the combined filtrate and washings are treated with diatomaceous earth and refiltered at 40—45°C. through a fine filter.

To the clear solution is added sufficient hydrogen chloride gas to convert all of the *d,d'* - 2,2' - (ethylenediimino)di - 1 - butanol to the dihydrochloride salt, plus a small excess. Conveniently, the hydrogen chloride is introduced over the surface of the solution in a closed vessel while maintaining a pressure of about 5—7 psig in the vessel. During the addition of hydrogen chloride, the temperature is maintained below about 55°C.

The solution is slowly cooled over about 2 hours to about 30°C. It should test acid to

Congo Red indicator paper. The crystalline precipitate of ethambutol hydrochloride is separated by filtration, conveniently, but not necessarily, at a temperature of 27—30°C. The crystals are washed with isopropanol, and are dried at a temperature below about 80°C.

Obviously centrifugation or other solid liquid separation procedure may be used instead of filtration, if plant equipment therefor is more conveniently available, at any step where solid liquid separation is desired.

The invention is illustrated by the following example in which parts are by weight unless otherwise clearly indicated.

Example

A mixture of 4620 g. of *d* - 2 - amino - 1 - butanol and 320 g. of ethylene dichloride is heated to 80°C. and the temperature is allowed to rise exothermally to about 130°C. After 1 hour, the mixture is cooled to about 95°C., 253 g. of sodium hydroxide is slowly added, and a temperature of about 112°C. is maintained for 1 hour. The sodium hydroxide is in the form of prills of about 4 mm. diameter. The mixture is cooled to 70°C. and unreacted *d* - 2 - amino - 1 - butanol is recovered by vacuum distillation. The distillation is at a pressure below 20 mm. mercury, and below 130°C., heat being applied at a rate within the capacity of the condenser.

Isopropanol (2900 g.) is added to the distillation residue at a temperature not above about 90°C., and followed by a refluxing period of 30 minutes. The mixture is cooled to and filtered at 60°C. to remove sodium chloride, and the filter cake is washed with 470 g. of isopropanol, at 60°C. The volume of the filtrate is diluted to 4300 ml. with isopropanol and the temperature is adjusted to 40—45°C., 15 g. of diatomaceous earth filter aid is added, and a second filtration is carried out.

To the clear filtrate there is added 1200 g. of methanol and 150 g. of water. The vessel is closed and hydrogen chloride (about 250 g.) is introduced over the surface of the charge at a gas pressure of 5—7 psig, while the temperature is allowed to rise to 55°C., to a pH of 2 to 2.5. The charge is cooled very slowly to 28°C. and is stirred for about 1 hour.

Conveniently, a small aliquot is titrated, and a calculated quantity of hydrogen chloride added. Proper final pH is confirmed by testing as acid to wet Congo Red test paper. Other methods of measuring the pH can be used. The white crystalline product, *d,d'* - 2,2' - (ethylenediimino)di - 1 - butanol dihydrochloride is separated by filtration, and washed with isopropanol. The product, carefully dried at a maximum temperature of 75°C., is about 700 g., has a decomposition range of 198.5—204°C. and an ash content of 0.1%.

This is a pharmaceutically acceptable, elegant grade of ethambutol hydrochloride without further treatment or refinement. The product may be tabletted or encapsulated by conventional procedures.

WHAT WE CLAIM IS:—

1. A process for preparing *d,d'* - 2,2' - (ethylenediimino)di - 1 - butanol dihydrochloride by reacting ethylene dichloride with a substantial excess of *d* - 2 - amino - 1 - butanol to form a mixture of *d,d'* - 2,2' - (ethylenediimino)di - 1 - butanol, *d* - 2 - amino - 1 - butanol and the hydrochloride salts thereof, characterized by:

(1) adding to the mixture of *d,d'* - 2,2' - (ethylenediimino)di - 1 - butanol, *d* - 2 - amino - 1 - butanol and the hydrochloride salts thereof, sufficient finely divided sodium hydroxide to react with the hydrogen chloride present to form sodium chloride;

(2) distilling and thereby separating the unreacted *d* - 2 - amino - 1 - butanol from the mixture;

(3) adding a 2 to 4 carbon alkanol so as to form a solution of *d,d'* - 2,2' - (ethylenediimino)di - 1 - butanol in said alkanol;

(4) separating the undissolved sodium chloride from the solution;

(5) adding hydrogen chloride gas to the solution to form *d,d'* - 2,2' - (ethylenediimino)di - 1 - butanol dihydrochloride, and precipitate the same; and

(6) separating said precipitate of *d,d'* - 2,2' - ,ethylenediimino)di - 1 - butanol dihydrochloride from said alkanol.

2. A process according to Claim 1, in which the sodium hydroxide used in step (1) is free-flowing and less than 5 mm. in particle size.

3. A process according to Claim 2, in which the sodium hydroxide used in step (1) has a particle size of 3.0 mm. or less.

4. A process according to any preceding claim, in which the distillation of step (2) is performed under reduced pressure.

5. A process according to Claim 4, in which the distillation of step (2) is performed under a pressure of less than 20 mm. and a temperature below 130°C.

6. A process according to any preceding claim, in which isopropanol is the alkanol added in step (3).

7. A process for preparing *d,d'* - 2,2' -

Congo Red indicator paper. The crystalline precipitate of ethambutol hydrochloride is separated by filtration, conveniently, but not necessarily, at a temperature of 27—30°C. The crystals are washed with isopropanol, and are dried at a temperature below about 80°C.

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(1) adding to the mixture of *d,d'* - 2,2' - (ethylenediimino)di - 1 - butanol, *d* - 2 - amino - 1 - butanol and the hydrochloride salts thereof, sufficient finely divided sodium hydroxide to react with the hydrogen chloride present to form sodium chloride;

(2) distilling and thereby separating the unreacted *d* - 2 - amino - 1 - butanol from the mixture;

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5. A process according to Claim 4, in which the distillation of step (2) is performed under a pressure of less than 20 mm. and a temperature below 130°C.

6. A process according to any preceding claim, in which isopropanol is the alkanol added in step (3).

7. A process for preparing *d,d'* - 2,2' -

* C L M S *

(ethylenediimino)di - 1 - butanol dihydrochloride, according to Claim 1 and substantially as hereinbefore described.

8. *d,d'* - 2,2' - (Ethylenediimino)di - 1 - butanol dihydrochloride whenever prepared by a process according to any preceding claim.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1974.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.