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2,2'-(ETHYLENEDIIMINO)-DI-1-BUTANOLS

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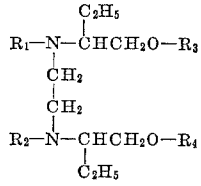
No Drawing. Original application Jan. 23, 1962, Ser. No. 168,241, now Patent No. 3,176,040, dated Mar. 30, 1965. Divided and this application Feb. 12, 1965, Ser. No. 432,419

Claims priority, application Great Britain, Feb. 7, 1961, 4,517/61, Patent 961,317

10 Claims. (Cl. 260—570.5)

This application is a division of our copending application Serial No. 168,241, filed January 23, 1962, and now U.S. Patent No. 3,176,040, which is a continuation-in-part of our application Serial No. 77,034, filed December 20, 1960, now abandoned, which is a continuation-in-part of our application Serial No. 33,399, filed June 2, 1960, now abandoned. Applicants claim priority under their British application Serial No. 4,517, filed February 7, 1961, now British Patent No. 961,317, for all that is disclosed therein which is not disclosed in their applications Serial No. 33,399 and Serial No. 77,034.

This invention relates to novel symmetrical ethylenediamines and, more particularly, is concerned with derivatives of N-[N'-(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol which may be represented by the following general formula:



wherein R_1 and R_2 are the same and are hydrogen, methyl or ethyl; and R_3 and R_4 are the same and are methyl, ethyl or benzyl.

The novel compounds of the present invention are, in general, white crystalline solids or colorless oils, soluble in lower alkanols and variably soluble in water, acetone, chloroform, ether, benzene, petroleum ether and the like. The acid-addition salts of the novel compounds of the present invention are, in general, soluble in water and hot alkanols, but relatively insoluble in non-polar organic solvents such as benzene, ether and the like. The non-toxic acid-addition salts of the novel symmetrical ethylenediamines of the present invention with a variety of organic and inorganic acids are also included within the scope of the invention. Thus, acid-addition salts formed by admixture of the organic free base with an acid, suitably in a neutral solvent, are formed with such acids as sulfuric, phosphoric, hydrochloric, hydrobromic, citric, lactic, tartaric, acetic, benzoic, ascorbic and the like. For purposes of this invention, the organic free bases are equivalent to their non-toxic acid-addition salts.

The novel compounds of the present invention are active against experimental human strain tuberculosis in mice. Furthermore, the chemical structures of these compounds are distinct from the drugs heretofore found effective against tuberculosis and should be particularly useful in treating resistant tuberculosis and also in combination therapy which is widely used in this field.

In testing the compounds of the present invention for anti-tuberculous activity the organism used in the test is *Mycobacterium tuberculosis* (H37Rv). The test animals are white female mice. The test animals are infected with the organisms by administration intravenously of 0.2 ml. of a buffered saline suspension containing approximately

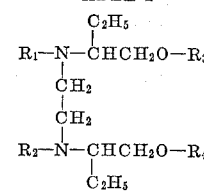
1.5 mg./ml., wet weight, of a 12 or 13 day culture of the test organism grown on solid Sauton's medium composed of: 0.05 gm. iron ammonium citrate; 0.5 gm. dipotassium phosphate; 0.5 gm. magnesium sulfate; 2.0 gm. citric acid; 4.0 gm. asparagine; 35.0 ml. glycerine; dist. water q.s. 1000 ml.

During a one year experience with this test, the standard infection defined above caused a 99.5% mortality, in that 756 of the 760 infected untreated control mice died within 30 days, the normal period of the test. Routinely, each week 200–300 mice are given the standard infection and then segregated in a random manner into cages each of which holds five or ten mice. Four groups of five mice each are retained as untreated controls, and the remaining mice are used to ascertain drug activity.

Drug treatment is administered orally as follows: A measured amount of the compound to be tested is mixed with a weighed amount of feed, and the test animals are allowed to feed at will for 14 days from the time of infection—the controls, of course, on untreated feed. All surviving animals are then allowed to feed at will on untreated feed for the remainder of the 30 day test period. A compound is judged active if it either saves 2 or more of the 5 mice in the test group, or prolongs average survival time by 4 or more days, compared to untreated controls.

The following table summarizes the relative activity of typical compounds compared to p-aminosalicyclic acid (as 100%) based on the minimum quantities of compounds required to give the same response shown by p-aminosalicyclic acid.

TABLE I



Compound (Example No.)	R_1	R_2	R_3	R_4	Relative Activity, percent
6, 7	H	H	CH_3	CH_3	12,800
9	H	H	C_2H_5	C_2H_5	5,600
10	H	H	$CH_2C_6H_5$	$CH_2C_6H_5$	400
11	CH_3	CH_3	CH_3	CH_3	6,400

The intermediate N-[N'-(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol may be readily prepared by the interaction of an ethylene dihalide with two equivalents of 2-amino-1-butanol. In like manner, the intermediate N,N'-dimethyl and N,N'-diethyl derivatives of N-[N'-(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol may also be readily prepared by the interaction of an ethylene dihalide with two equivalents of 2-methylamino-1-butanol or 2-ethylamino-1-butanol, respectively. This preparative method is illustrated by Examples 1 and 3 hereinafter. The N-[N'-(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-amino ethanol and its N,N'-dimethyl and N,N'-diethyl derivatives may also be conveniently prepared by the interaction of glyoxal with 2-amino-1-butanol, 2-methylamino-1-butanol or 2-ethylamino-1-butanol, respectively, followed by reduction of the Schiff base intermediates with lithium aluminum hydride. This method is illustrated by Example 5 hereinafter. The N,N'-dimethyl derivative of N-[N'-(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol may also be readily prepared by treatment of N-[N'-(α-ethyl-

β - hydroxyethyl) - β-aminoethyl]-β-ethyl-β-aminoethanol with formaldehyde in concentrated formic acid. This method is illustrated by Example 2 hereinafter. The N,N' - diethyl derivative of N-[N'-(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol may also be readily prepared by treating the N-[N'(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol with excess acetic anhydride and reducing the intermediate N,N',O,O'-tetra-acetyl derivative with lithium aluminum hydride, the O-acetyl functions being removed during the reduction. This method is illustrated by Example 4 hereinafter.

The O,O'-dimethyl, O,O'-diethyl and O,O'-dibenzyl derivatives of N-[N'-(α - ethyl - β-hydroxyethyl)-β-aminoethyl]-β - ethyl-β-aminoethanol, N-methyl-N-[N'-methyl-N'-(α - ethyl - β - hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol and N-ethyl-N-[N'-ethyl-N'-(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol may be readily prepared by treating the sodium salt of the appropriate ethylenediamine base with methyl iodide, ethyl iodide or benzyl chloride. This method is illustrated by Examples 6, 7, 8, 9 and 10 hereinafter. They are also prepared from N,O-disubstituted 2-aminobutanol using glyoxal or ethylene dichloride.

The dosage units of the drug may contain other inert or medically active materials, for instance, when the dosage unit form is a tablet, pill or granules, there may also be present various binders, fillers or solid diluents. Suitable materials for this purpose may be, for example, starch such as corn starch or sugar such as lactose or sucrose. There may also be present various medically active materials such as, for example, p-amino salicyclic acid. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. The dosage unit form may also have present various flavors, oil of wintergreen, and excipients such as dicalcium phosphate. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit, for instance, pills or capsules may be coated with shellac, sugar or both. Of course, any material used in preparing the dosage unit form must be pharmaceutically pure and substantially nontoxic in the amounts employed.

The following examples illustrate the preparation of typical symmetrical ethylenediamines of the present invention.

Example 1.—N-[N'-(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol

To 227 g. (2.55 moles) of 2-amino-1-butanol was added 100 g. (1.0 mole) of ethylene dichloride. The mixture was heated at reflux and in a few minutes the exothermic reaction required the removal of exterior heating. After 10 minutes, exterior heating was recommenced for an additional 20 minutes. The hot mixture was then treated with 300 ml. of methanol and then cautiously with 84 g. (2.1 moles) of sodium hydroxide in 80 ml. of water. The precipitated sodium chloride was removed by filtration. The excess 2-amino-1-butanol distilled as a light yellow oil at 83–87° C./13 mm. The viscous residue distilled at 165–170° C./0.6 mm. as a light yellow oil which tended to solidify in the air condenser; yield, 108 g. Recrystallization by dissolving in 80 ml. of hot ethanol, adding about 150 ml. of petroleum ether (B.P. 90–100° C.), and cooling at 5° C. overnight, gave 64 g. of white crystals melting at 128–132.5° C. This, on recrystallization from 100 ml. of 95% ethanol, gave 35 g. of white crystals melting at 135.5–136° C. and a second crop of 10 g. melting at 132.5–134° C. which is the meso base. Its dihydrochloride melts at 202–203° C.

From the ethanolic filtrates upon addition of 130 ml. of about 4 N ethanolic hydrochloric acid and cooling, there was obtained 55 g. of white crystals melting at 176.5–178° C. and a second crop of 10 g. melting at 171.5–174.5° C. This is the *dl* racemate dihydrochloride.

Example 2.—N-methyl-N-[N'-methyl-N'-(α-ethyl-β- hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol

To 16.5 g. (0.36 mole) of 98% formic acid was added 10.0 g. (0.048 mole) of N-[N'-(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol in portions, with cooling. Then, 9.0 g. (0.105 mole) of 37% formaldehyde was added and the mixture was heated on the steam bath. After evolution of carbon dioxide ceased, refluxing was continued for an additional six hours. The solution was cooled, treated with 15 ml. of conc. HCl and filtered prior to refluxing for 1.5 hours. After vacuum evaporation, the resulting yellow viscous liquid was treated with 25% NaOH and the organic layer extracted into benzene. The combined extracts were dried over anhydrous Na_2CO_3 and concentrated leaving an oily residue which on distillation under high vacuum yielded the product as a colorless oil, 7.4 g., B.P. 132–134° C./0.01 mm.

Example 3.—N-ethyl-N-[N'-ethyl-N'-(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol

A mixture of 33 g. (0.28 mole) of 2-ethylamino-1-butanol and 13.2 g. (0.07 mole) of ethylene dibromide was heated to reflux for 2 hours with a vigorous initial reaction. To the cooled mixture 30 ml. of 10 N NaOH was added and the resulting oil layer was extracted with benzene. After drying over anhydrous Na_2CO_3 the benzene and excess 2-ethylamino-1-butanol were distilled and the residue, 12 g., distilled at 90–130° C./0.02 mm. On redistillation, the product boiled at 135.138° C./0.07 mm.

Example 4.—N-ethyl-N-[N'-ethyl-N'-(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol

An alternate method of preparing the product of Example 3 is to treat N-[N'-α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol with excess acetic anhydride to obtain the N,N',O,O'-tetra-acetyl derivative. By reduction of this intermediate with lithium aluminum hydride in diethyl ether at the reflux temperature for a period of several hours, the desired N,N'-diethyl derivative is obtained, the O-acetyl functions being removed during the reaction.

Example 5.—N-[N'(α-ethyl-β-hydroxyethyl)-β-aminoethyl]-β-ethyl-β-aminoethanol

To 6.0 g. (0.03 mole) of 30% aqueous glyoxal was added 9.2 g. of 2-aminobutanol (with moderate heat evolution) and 30 ml. of absolute ethanol. A total of 3.7 g. (0.1 mole) of sodium borohydride was added in portions over 10 minutes. The reaction mixture, after the vigorous reaction had subsided, was heated for 30 minutes. On adding water and extracting with chloroform, the meso isomer, M.P. 131–134° C., was isolated on cooling. The *dl* isomer was isolated as the dihydrochloride salt, M.P. 172–175° C. on acidifying the filtrate with ethanolic HCl.

Example 6.—N,N'-bis-(α-methoxymethylpropyl)ethylenediamine

To a solution of 21.0 g. of dextro 2,2'-(ethylenediimino)-di-1-butanol in 225 ml. of t-butanol was added a suspension of 9.50 g. of sodium hydride (51.5% NaH in oil) in 30 ml. of ether and the reaction mixture was heated to deflux for 1 hour whereby a clear solution was obtained. This was cooled to 35° C. with some solid forming. Dropwise addition of a solution of 28.0 g. of methyl iodide in 25 ml. of t-butanol caused some temperature rise and a clearing of the solution. The solution was refluxed for 18 hours and the solvent removed under vacuum. Addition of 80 ml. of 6 N hydrochloric acid gave a deep red solution which was extracted with benzene. The aqueous phase was made strongly alkaline with sodium hydroxide causing separation of a red oil. Extraction with benzene followed by drying with anhydrous sodium carbonate and distillation gave a fraction, B.P. 152–163° C./13 mm. Acidification of the distillate with ethanolic hy-

drochloric acid, followed by the addition of a large volume of acetone, gave white crystals of dextro N,N'-bis-(α-methoxymethylpropyl)ethylenediamine dihydrochloride, M.P. 181–183° C.

Example 7.—N,N'-bis-(α-methoxymethylpropyl) ethylenediamine

Example 6 was repeated but an equimolar amount of the racemic form was employed in place of the dextro starting material of that example. There was obtained the racemic N,N'-bis-(α - methoxymethylpropyl)ethylenediamine dihydrochloride as white crystals, M.P. 148–150° C.

Example 8.—N,N'-bis-(α-methoxymethylpropyl) ethylenediamine

By replacing the dextro starting material employed in Example 6 by an equimolar quantity of the meso isomer and following substantially the same procedure described in Example 6, there was obtained the meso N,N'-bis-(α-methoxymethylpropyl)ethylenediamine as a colorless oil, B.P. 144–146° C./13 mm.

Example 9.—N,N'-bis-(α-ethoxymethylpropyl) ethylenediamine

The procedure of Example 6 was repeated substituting an equimolar amount of ethyl iodide for the methyl iodide employed in that example. There was thus obtained on distillation dextro N,N'-bis-(α-ethoxymethylpropyl) ethylenediamine, B. P. 157–160° C./8 mm.

Example 10.—N,N'-bis-(α-benzyloxymethylpropyl) ethylenediamine

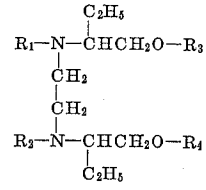
By replacing the methyl iodide employed in Example 6 by an equimolar quantity of benzyl chloride and following substantially the same procedure described in Example 6, there was obtained the dextro N,N'-bis-(α-benzyloxymethylpropyl)ethylenediamine, B.P. 215–225° C./0.12 mm.

Example 11.—N,N'-bis-(α-methoxymethylpropyl)-N,N'-dimethylethylenediamine

A solution of 4.1 g. of *dl*-2,2'-(ethylenediimino)-di-1-butanol in 20 ml. of hot toluene was added dropwise to a suspension of 0.96 g. of sodium hydride in 5 ml. of toluene, the temperature being kept at 100° C. After stirring this mixture for several hours at room temperature, a solution of 6.3 g. of dimethyl sulfate in 5 ml. of toluene was added slowly, keeping the temperature below 50° C. The resulting mixture was treated with water and the toluene layer separated. The water layer was extracted several times with methylene chloride and the combined extracts (toluene and CH_2Cl_2) were dried over anhydrous sodium carbonate, and concentrated to 50 ml. The concentrate was extracted with dilute hydrochloric acid. The extract was basified, and the insoluble organic layer extracted into CH_2Cl_2. The extract was dried over anhydrous sodium carbonate, concentrated, and the residue distilled under reduced pressure to give the tetramethyl derivative as a liquid fraction, B.P. 90–95° C./0.01 mm.

What is claimed is:

1. A member of the class consisting of symmetrical ethylenediamines of the formula:



wherein R_1 and R_2 are the same and are selected from the group consisting of hydrogen, methyl and ethyl, and R_3 and R_4 are the same and are selected from the group consisting of methyl, ethyl and benzyl; and the non-toxic acid-addition salts thereof.

2. The compound N,N'-bis-(α-methoxymethylpropyl) ethylenediamine.

3. The compound N,N'-bis-(α-ethoxymethylpropyl) ethylenediamine.

4. The compound N,N'-bis-(α-benzyloxymethylpropyl) ethylenediamine.

5. The compound N,N'-bis-(α-methoxymethylpropyl)-N,N'-dimethylethylenediamine.

6. The compound N,N'-bis-(α-ethoxymethylpropyl)-N,N'-dimethylethylenediamine.

7. The compound N,N'-bis-(α-benzyloxymethylpropyl)-N,N'-dimethylethylenediamine.

8. The compound N,N'-bis-(α-methoxymethylpropyl)-N,N'-diethylethylenediamine.

9. The compound N,N'-bis-(α-ethoxymethylpropyl)-N,N'-diethylethylenediamine.

10. The compound N,N'-bis-(α-benzyloxymethylpropyl)-N,N'-diethylethylenediamine.

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