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TETRASUBSTITUTED POLYMETHYLENEDIAMINE SALTS

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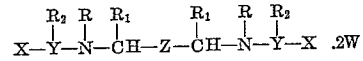
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4 Claims. (Cl. 260—583)

This invention relates to novel N,N,N',N'-tetrasubstituted polymethylenediamine salts which have valuable pharmacodynamic activity. Further, the novel N,N,N',N'-tetrasubstituted polymethylenediamine salts of this invention are highly effective hypotensive, ganglionic blocking and curariform agents which possess the property of being readily absorbed orally.

The novel N,N,N',N'-tetrasubstituted polymethylenediamine salts of this invention are represented by the following structural formula:

FORMULA 1



when:

R represents lower alkyl having 1 to 4 carbon atoms, benzyl or 2-thenyl;

R_1 represents hydrogen, methyl or ethyl;

R_2 represents hydrogen, methyl or ethyl;

X represents a reactive ester moiety such as a halogen having a molecular weight greater than 19, a lower alkyl sulfonate, benzene sulfonate, or p-toluene sulfonate.

Y represents a divalent, straight, alkylene chain having 4 to 5 carbon atoms;

Z represents a divalent, straight, alkylene chain having 1 to 10 carbon atoms;

W represents a nontoxic, pharmaceutically acceptable acid having a maximum pKa value of about 4.5, for example, sulfamic, phosphoric, nitric, maleic, fumaric, succinic, methanesulfonic, ethanedisulfonic, tartaric, citric, gluconic, itaconic, benzenesulfonic or p-toluenesulfonic acids.

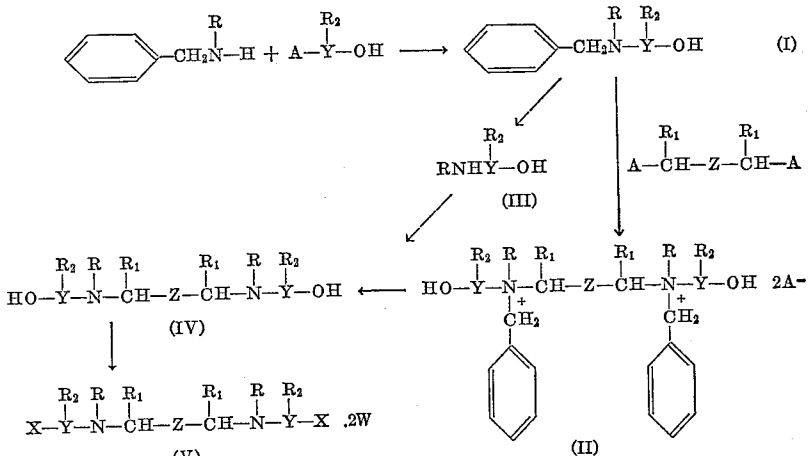
Where used herein the term "polymethylene" represents a straight or branched alkylene chain having from 3 to 16 carbon atoms, and "lower alkyl," when not otherwise limited, indicates an alkyl group having 1 to 2 carbon atoms.

Preferred compounds of this invention possessing ganglionic blocking activity are those according to Formula 1 in which R represents lower alkyl having 1 to 4 carbon atoms, R_1 and R_2 represent hydrogen, X represents chloro, Z represents a divalent, straight, alkylene chain having 2 to 4 carbon atoms, and Y and W are as previously defined.

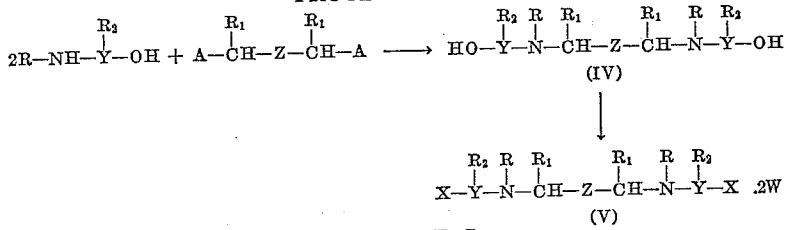
Particularly advantageous compound of this invention possessing curariform activity are those according to Formula 1 in which R represents lower alkyl having 1 to 4 carbon atoms, R_1 and R_2 represent hydrogen, X represents chloro, Z represents a divalent, straight, alkylene chain having 8 to 10 carbon atoms and Y and W are as previously defined.

The compounds of this invention are prepared according to the following synthetic procedures:

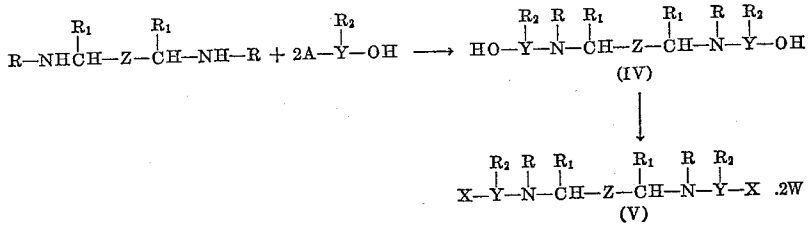
PROCEDURE A



PROCEDURE B



PROCEDURE C



In the procedure outlined above A is chlorine, bromide or iodine and R, R_1 R_2, X, Y, Z and W are as previously defined.

According to the preferred procedure A outlined above, an excess of an alkyl benzylamine of the formula benzyl-NH—R, where R represents lower alkyl having from 1 to 4 carbon atoms and "benzyl" alternatively is benzhydryl, triphenylmethyl or substituted benzyl having on the nucleus a substituent such as chloro, hydroxy or methoxy, is heated with a halohydrin of the structure indicated above at elevated temperatures such as from 100° to 150° C. for about 5 to 30 hours. The initial reaction is carried out either in an organic solvent not reactive under the conditions employed in which the reactants are at least partially soluble and which has a boiling point above the temperature given or preferably the reaction is carried out in an excess of the amine reactant. An aqueous miscible solvent such as a lower alkyl alcohol, for example, ethanol or methanol is added, followed by an excess of an aqueous solution of an alkali metal hydroxide, such as potassium or sodium hydroxide. The resulting mixture is refluxed for about 30 to 60 minutes, cooled and filtered. The filtrate is stripped of solvent and distilled to give benzylamino alcohol (I).

At least two molar equivalents of the benzylamino alcohol (I) are heated at reflux with about one molar equivalent of a polymethylene dihalide in a lower alkyl alcohol solvent, such as ethanol, methanol or isopropanol, for 3 to 4 days. The solvent is removed by evaporation and the residue taken up in water. The aqueous solution is extracted with ether, made acid with hydrohalic acid and filtered. In order to remove the protective benzyl moiety the filtrate is hydrogenated, for instance, under about 50–60 pounds of hydrogen pressure in the presence of an active metal catalyst such as a palladium, platinum or Raney nickel catalyst, preferably palladium on charcoal. The catalyst is removed by filtration and the toluene by distillation in vacuo. The aqueous residue is made strongly basic with an alkali metal hydroxide, for example, sodium or potassium hydroxide, and extracted with a water immiscible solvent, such as, preferably, ether. The solvent is evaporated leaving the dihydroxy compound, IV, as the residue which may be purified by distillation.

Alternatively, the benzylamino alcohol (I) is hydrogenated to remove the protective benzyl moiety in a lower alcohol such as methanol or ethanol, using an active metal catalyst such as palladium, platinum or Raney nickel catalyst, preferably palladium on charcoal. The catalyst is removed by filtration and the solvent by distillation. The amino alcohol residue (III) which may be purified by distillation is treated with about ¼ to ½ of a molar equivalent of a polymethylene dihalide. The mixture is heated at about 90–120° C. for approximately 20–24 hours. An excess of a sodium alkoxide, for example, sodium methoxide or ethoxide, and an absolute lower alkyl alcohol, for example, ethanol, are added and the mixture is refluxed for 30–60 minutes. Filtration and removal of solvent and excess starting materials by distillation leaves a residue (IV) which may be purified by distillation.

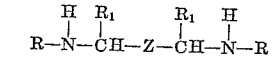
The dihydroxy compound (IV) is converted to an acid addition salt by treating with an excess of a hydrohalic acid, then with an esterifying agent capable of replacing the hydroxyl group by the desired reactive ester group X. Typical esterifying agents are, for example, thionyl chloride, hydrobromic acid, hydroiodic acid, lower alkyl sulfonic chloride, benzene sulfonic chloride and p-toluene sulfonic chloride. For example, when X is the preferred chloro group, the dihydroxy compound (IV) in an inert, organic solvent preferably a halogenated alkane such as chloroform or carbon tetrachloride, is saturated with a hydrohalic acid and then treated with an excess of thionyl chloride, advantageously in the presence of a few drops of pyridine. The solution is heated to complete the reaction usually at reflux for 5 to 25 hours, then concentrated by evaporation of lower-boiling material. The residue, which is a compound of this invention (V), may be purified by recrystallization from a suitable solvent, such as, for example, ethanol-ether, acetone-isopropanol-ether or ethanol-diisopropyl ether.

Alternatively, when X is to be bromo, the intermediate dihydroxy compound (IV) is refluxed with 48% hydrobromic acid for approximately 4–8 hours. The reaction mixture is concentrated in vacuo. The residue is washed with ether and may be purified by recrystallization from a suitable solvent such as ethanol-ether to give the dihydrobromide of V. Alternatively, when X is to be lower alkyl or benzene sulfonate, the dihydroxy compound (IV) is dissolved in an inert, organic solvent, such as chloroform. This solution is reacted with 2 equivalents of a hydrohalic acids, such as, hydrochloric acid. Approximately two equivalents of an organic base such as pyridine or dimethylaniline are added and the mixture cooled to about 0° C. The appropriate lower alkyl or benzene sulfonylchloride is added and the resulting mixture is allowed to stand overnight, then chilled to about 0° C., poured into ice water, made basic with ammonia and extracted rapidly with an inert organic solvent such as chloroform. The chloroform solution is made acidic with a mineral acid such as hydrochloric acid, dried and stripped of solvent in vacuo. The residue, which is a compound of this invention (V), may be purified by recrystallization from ethanol-ether.

According to procedure B outlined above, a polymethylene dihalide is refluxed with at least two molar equivalents of

for 20–24 hours in a lower alcohol solvent such as ethanol or methanol. The solution is made basic by the addition of an alkali metal hydroxide, such as for example, sodium or potassium hydroxide. The resulting mixture is refluxed for about 30 to 60 minutes. Filtration, drying and evaporating the solvent leaves the dihydroxy compound (IV) as the residue which may be purified by distillation. The dihydroxy compound (IV) is then treated as described under procedure A to replace the hydroxyl group by the desired group X to obtain the compound of this invention (V).

According to procedure C, one molar equivalent of



is refluxed with at least two molar equivalents of a methylene halohydrin in a non-aqueous solvent, such as, for example, absolute ethanol for 24–60 hours. The solution is made basic by the addition of an alkali metal hydroxide, for example, sodium or potassium hydroxide, then refluxed for 30 to 60 minutes. Filtration and evaporation of the solvent leaves the dihydroxy compound (IV), which may be purified by distillation. The dihydroxy compound (IV) is converted to the compound of this invention (V) by the methods described under procedure A.

Conveniently, acid addition salts other than the hydrohalic salts, are pepared by dissolving the hydrohalide salt of (V) in a lower alkyl alcohol, such as methanol or ethanol, adding two molar equivalents of a nontoxic, pharmaceutically acceptable acid having a maximum pKa value of about 4.5, such as maleic, fumaric, succinic, methanesulfonic, ethanedisulfonic, tartaric, citric, gluconic, itaconic, benzenesulfonic, p-toluenesulfonic, sulfamic, sulfuric, nitric or phosphoric, and evaporating the resulting solution to obtain the new acid addition salt.

Alternatively, these salts may also be prepared by the classical method of double decomposition of appropriate salts. For example, a hydrohalide salt of (V) may be reacted in a lower alkyl alcohol solution, such as meth-

anol or ethanol solution, with two equivalents of silver nitrate. Filtration and evaporation yields the nitrate salt of (V).

The following examples are not limiting but are illustrative of compounds of this invention and will serve to make fully apparent all of the compounds embraced by the general formula given above.

Example 1

Pentamethylene chlorohydrin (174 g.) is added with stirring to 342 g. of N-methyl benzylamine. After heating the mixture for 24 hours at 100° C., the mixture is cooled and 300 ml. of absolute ethanol is added followed by 60 g. of sodium hydroxide in a solution of 75 ml. of water. The resulting mixture is refluxed for one hour, cooled and filtered. The solid material which is filtered off is washed with ether. The filtrate and the washings are combined, dried and solvents removed under reduced pressure. Distillation of the residue gives a colorless liquid, N-(5-hydroxypentyl)-N-methyl benzylamine, B.P. 175°–177° C. at 7.5 mm.

A mixture of 182.2 g. of N-(5-hydroxypentyl)-N-methyl benzylamine, 99.6 g. of pentamethylene bromide and 180 ml. of ethanol is refluxed for 90 hours. The ethanol is evaporated and the viscous residue is dissolved in 350 ml. of water. After seven hours of continuous ether extraction, the aqueous solution is acidified with 40% hydrobromic acid solution and filtered. The filtrate is divided into three portions. To each portion is added 2.2 g. of activated charcoal and 1.95 ml. of 10% palladium chloride solution. Fifty pounds of H_2 pressure is applied in a Parr apparatus; each portion absorbs 0.23 mole of H_2. The catalyst is removed by filtration and the toluene is removed by distillation in vacuo. The aqueous solution is made strongly basic with sodium hydroxide solution and continuously extracted with ether for seven hours. The ether extract is washed, dried and distilled to give a yellow liquid, N,N'-bis-(5-hydroxypentyl) - N,N' - dimethyl - 1,5-diaminopentane, B.P. 130–220° at 0.6 mm.

Anhydrous hydrogen chloride is bubbled into a solution of 9.3 g. of N,N'-bis(5-hydroxypentyl)-N,N'-dimethyl-1,5-diaminopentane in 150 ml. of absolute ethanol until a slight excess is present. The solvent is removed in vacuo. The white solid residue is stirred briefly with 240 ml. of dry chloroform heated at reflux. With cooling, a solution of 15 g. of thionyl chloride in 120 ml. of dried chloroform is added over a 50 minute period. The mixture is warmed on a steam bath and 18 drops of pyridine is added. After refluxing for 24 hours, the solvent is removed by distillation under reduced pressure. The residue is recrystallized from a mixture of absolute ethanol and ether after treatment with activated charcoal. Subsequent recrystallizations from acetone-isopropanol-ether and absolute ethanol-diisopropyl ether gives white crystals of the product, N,N'-bis-(5-chloropentyl)-N,N'-dimethyl-1,5-diaminopentane dihydrochloride, M.P. 190–193° C.

Example 2

Tetramethylene chlorohydrin (176 g.) is dropped into 384 g. of N-methyl benzylamine at 100–105° C. over a two hour period. The mixture is heated at 120–130° C. for five hours. Working up the mixture as described in Example 1 yields a colorless oil, N-(4-hydroxybutyl)-N-methyl benzylamine.

A mixture of 61.0 g. of N-(4-hydroxybutyl)-N-methyl benzylamine, 0.5 g. of palladium black and 300 ml. of methanol are put in a rocking autoclave at 70° C. and 75–90 lbs. of hydrogen pressure for 10 hours. The palladium black is filtered off and washed with methanol. The solvent is removed by distillation and the residue is distilled to yield a colorless oil, N - (4-hydroxybutyl)-N-methylamine.

Hexamethylene dibromide (35.0 g.) is dropped into 57.2 g. of N-hydroxybutyl-N-methylamine at 80° C. over a two hour period. The mixture is stirred and heated at 100° C. for 20 hours. Sodium methylate (15.0 g.) and 150 ml. of absolute ethanol were added at 60° C. The mixture was refluxed for 30 minutes, then cooled in a water and ice bath. Precipitated sodium bromide is filtered off and washed with absolute ethanol. The solvent and excess N-hydroxybutyl-N-methylamine are removed from the filtrate by distillation in vacuo. Chloroform (200 ml.) is added to the residue, the mixture filtered and the solvent removed in vacuo to yield the crude residue, N,N'-bis-(4-hydroxybutyl)-N,N'-dimethyl-1,6-diaminohexane.

This crude residue is dissolved in acetone (100 ml.) filtered and the solvent removed. The residue is dissolved in chloroform and cooled to 0–10° C. Thionyl chloride (60 g.) in 100 ml. chloroform is added and the resulting mixture stirred one hour, then refluxed for four hours. After standing 15 hours, the solvent and excess thionyl chloride are distilled off in vacuo. The residue is refluxed with 40 ml. absolute ethanol for five minutes, then the solvent is removed. Additional absolute ethanol is added to the residue, followed by the addition of ether and cooling. Crystallization occurs at about —10° C. The solid is filtered off and washed with ethanol-ether. Another recrystallization from ethanol-ether yield white crystals of N,N'-bis-(4-chlorobutyl)-N,N'-dimethyl - 1,6 - diaminohexane dihydrochloride, M.P. 163–165° C.

Example 3

N-(4-hydroxybutyl)-N-methyl benzylamine (104.0 g.), prepared as in Example 2, pentamethylene dibromide (63.0 g.) and 100 ml. of absolute ethanol are refluxed for 24 hours. The warm solution (40° C.) is dropped slowly into 1300 ml. of stirred ethyl ether. A viscous resin separates. After standing for 15 hours, the ether is poured off the resin at the bottom. The resin is washed with ether and dried at 80° C. at 4 mm. It is dissolved in 250 ml. of water and hydrogenated in the presence of 4 g. of palladium charcoal in a rocking autoclave at 50–55° C. at 50 lbs. pressure for 12 hours.

The mixture is cooled and the catalyst removed by filtration. A few milliliters of 48% hydrobromic acid is added and the toluene layer which separates is removed. The aqueous layer is made strongly basic with sodium hydroxide solution. Continuous extraction with ether for 24 hours, subsequent drying and removal of the solvent yields the crude material, N,N'-bis-(4-hydroxy-butyl)-N,N'-dimethyl-1,5-diaminopentane.

Treatment of this product with anhydrous hydrogen chloride and then with excess thionyl chloride and working up the reaction mixture as described in Example 1 gives white crystals of N,N'-bis-(4-chloro-butyl)-N,N'-dimethyl-1,5-diaminopentane dihydrochloride, M.P. 170–171° C.

Example 4

A mixture of 29.0 g. of 1-ethylamino-4-pentanol, 23.0 g. of 2,4-dibromopentane and 300 ml. of absolute ethanol is refluxed for 24 hours. Ten grams of sodium hydroxide in a concentrated aqueous solution are added and the resulting mixture refluxed for 30 minutes, cooled and filtered. The filtrate is dried, the solvent removed and the residue distilled under reduced pressure (180–220° C. at 0.5 mm.) to yield the colorless oil, N,N'-bis-(4-hydroxypentyl)-N,N'-diethyl-2,4-diaminopentane.

A mixture of 10.0 g. of N,N'-bis-(4-hydroxypentyl)-N,N'-diethyl-2,4-diaminopentane and 22.0 g. of a 48% aqueous solution of hydrobromic acid is refluxed for six hours. The water is removed in vacuo and the residue is washed with ether. Recrystallization from absolute ethanol-ether yields the dihydrobromide of N,N'-bis-(4-bromopentyl)-N,N'-diethyl-2,4-diaminopentane.

Example 5

A mixture of 15.0 g. of 7-chloro-3-heptanol (prepared

by mixing 7-chloro-3-heptanone (74 g.) with 80 ml. of 3 M aluminum isopropoxide in isopropyl alcohol and distilling as rapidly as possible, adding fresh alcohol to keep the volume constant. The reaction is continued 40–45 minutes. The solution is concentrated, and the residue poured into a mixture of 150 ml. of hydrochloric acid and 100 g. of cracked ice, keeping the temperature below 50° C. The solution is filtered and extracted with ether. The ether extracts are washed with saturated magnesium sulfate solution and dried over anhydrous magnesium sulfate. The ether is removed, keeping the temperature below 60° C. The residue is again taken up in ether, dried, solvent removed and the residue distilled in vacuo to yield 7-chloro-3-heptanol) and 21.0 g. of benzylamine is heated at 100° C. for 24 hours. The mixture is cooled, treated with 150 ml. absolute ethanol followed by 5.0 g. of sodium hydroxide in 20 ml. of water. The resulting mixture is refluxed for one hour, cooled and filtered. The solid material which is obtained is washed with ether. The filtrate and washings are combined, dried and solvents removed by distillation. Distillation of the residue yields N-(5-hydroxyheptyl)benzylamine.

1,12-dibromododecane (16.0 g.) is added slowly with stirring to 25.0 g. of N-(5-hydroxyheptyl)benzylamine and 100 ml. of absolute ethanol. The resulting mixture is refluxed for 24 hours. A solution of 9.0 g. of sodium hydroxide in 20 ml. of water is added and the resulting mixture refluxed for 30 minutes, cooled and filtered. The filtrate is dried and the solvent evaporated in vacuo. The residue is distilled in vacuo to give N,N'-bis-(5-hydroxyheptyl)-N,N-dibenzyl-1,12-diaminododecane.

Anhydrous hydrogen chloride is bubbled into a solution of 10.0 g. of N,N'-bis-(5-hydroxyheptyl)-N,N'-dibenzyl-1,12-diaminododecane in 150 ml. of absolute ethanol and the mixture treated as described in Example 1. Reaction with thionyl chloride (15 g.) and 18 drops of pyridine yields, after working up as outlined in Example 1, the dihydrochloride of N,N'-bis-(5-chloroheptyl)-N,N'-dibenzyl-1,12-diaminododecane.

Example 6

Pentamethylene chlorohydrin (12.2 g.) is added with stirring to 33.0 g. of N-butyl benzylamine. The mixture is heated for 24 hours at 100° C., then cooled and treated with 150 ml. of absolute ethanol. Five grams of sodium hydroxide in a concentrated aqueous solution is added and the resulting mixture refluxed for one hour, cooled and filtered. The filtrate is dried and the solvent evaporated. Distillation of the residue yields N-(5-hydroxypentyl)-N-butyl benzylamine.

A mixture of 2.5 g. of N-(5-hydroxypentyl)-N-butyl benzylamine, 5.8 g. of 1,8-dibromooctane and 75 ml. of ethanol is refluxed for 24 hours. The solvent is evaporated and the residue taken up in 150 ml. of water. By hydrogenating the mixture as outlined in Example 1, N,N'-bis-(5-hydroxypentyl)-N,N'-dibutyl-1,8 - diaminooctane is obtained.

Concentrated hydrochloric acid (2.0 g.) is added to a solution of 4.0 g. of N,N'-bis-(5-hydroxypentyl)-N,N'-dibutyl-1,8-diaminooctane in 100 ml. of chloroform. Pyridine (1.6 g.) is added and the mixture cooled to 0° C. Methane sulfonic chloride (2.3 g.) is added and the resulting mixture is allowed to stand at 0° C. for 17 hours, then cooled to −10° C. The following workup is carried out rapidly. Excess ammonia is added and the solution is extracted with chloroform. The chloroform solution is acidified with hydrochloric acid, dried and the solvent removed in vacuo. The residue is crystallized from ethanol-ether solution to yield crystals of the di-(methylsulfonate) ester of N,N'-bis-(5-hydroxypentyl)-N,N'-dibutyl-1,8-diaminooctane dihydrochloride.

Example 7

A mixture of 22.8 g. of 2-thenylamine and 10.8 g. of tetramethylene chlorohydrin is heated at 100° C. for 24 hours. Upon cooling, 150 ml. of absolute ethanol is added, followed by 5.0 g. of sodium hydroxide in 20 ml. of water. The resulting mixture is refluxed for 40 minutes, cooled and filtered. The filtrate is dried, solvent is removed and the residue distilled to give N-(4-hydroxybutyl)-2-thenylamine.

1,10-dibromodecane (15.0 g.) is added slowly to 18.6 g. of N-(4-hydroxybutyl)-2-thenylamine and 100 ml. of absolute ethanol. The mixture is refluxed for 24 hours. Concentrated sodium hydroxide solution (5 g. in 15 ml. of water) is added and the mixture refluxed for 30 minutes, then cooled and filtered. The filtrate is dried and the solvent evaporated in vacuo. The residue is distilled in vacuo to yield N,N'-bis-(hydroxybutyl)-N,N'-di-(2-thenyl)-1,10-diaminodecane.

Concentrated hydrochloric acid (4.0 g.) is added to a chloroform solution of the above described diaminodecane (5.1 g.). Pyridine (1.6 g.) is added and the mixture cooled to 0° C. Benzene sulfonic chloride (3.5 g.) is added. The resulting mixture is allowed to stand overnight at 0° C. After cooling to −10° C., excess ammonia is added and the solution is extracted with chloroform. The chloroform extraction is acidified with hydrochloric acid, dried and the solvent removed in vacuo. The residue is crystallized from ethanol-ether to give crystals of the di-(benzenesulfonate)ester of N,N'-bis(4-hydroxybutyl) - N,N'-di-(2-thenyl)-1,10-diaminodecane dihydrochloride.

Example 8

A mixture of 15.0 g. of 7-chloro-3-heptanol and 29.8 g. of N-propyl benzylamine is heated at 100° C. for 24 hours. The mixture is worked up as outlined in Example 1 to yield N-(5-hydroxyheptyl)-N-propyl benzylamine.

This amine (5.5 g.), 3.3 g. of 1,12-dibromododecane and 7.5 ml. of ethanol are refluxed for 48 hours. Hydrogenating the reaction mixture as described in Example 1 yields N,N'-bis-(5-hydroxyheptyl)-N,N'-dipropyl-1,12-diaminododecane.

A chloroform solution of N,N'-bis-(5-hydroxyheptyl)-N,N'-dipropyl-1,12-diaminododecane (4.8 g. in 100 ml. of chloroform) is treated with 2.0 g. of concentrated hydrochloric acid. Pyridine (1.6 g.) is added, the mixture cooled to 0° C., and p-toluene sulfonic chloride (3.8 g.) is added. After standing overnight at 0° C., the mixture is cooled to −10° C. and treated with excess ammonia. The solution is extrated rapidly with chloroform, acidified with hydrochloric acid, dried and the solvent removed in vacuo. The residue is recrystallized from ethanol-ether to give crystals of the di-(p-toluene sulfonate) ester of N,N' - bis-(5-hydroxyheptyl)-N,N'-dipropyl-1,2-diaminododecane dihydrochloride.

Example 9

A mixture 11.6 g. of 1,4-di-(methylamino)-butane and 27.2 g. of 5-chloro-1-hexanol in 100 ml. of absolute ethanol is refluxed for 48 hours. A concentrated aqueous solution containing 11.2 g. of potassium hydroxide is added and the mixture refluxed for 30 minutes, cooled and filtered. The solvent is evaporated and the residue distilled in vacuo to give N,N'-bis-[5-(1-hydroxyhexyl)]-N,N'-dimethyl-1,4-diaminobutane.

This diamine (3.2 g.) is dissolved in 100 ml. chloroform and treated with 2.0 g. of concentrated hydrochloric acid and 1.6 g. of pyridine. After cooling the mixture to 0° C., ethane sulfonic chloride (2.6 g.) is added and the mixture is allowed to stand for 17 hours at 0° C. The mixture is cooled to −10° C., treated with excess ammonia and extracted rapidly with chloroform. The chloroform extracts are made acidic with hydrochloric acid, dried and the solvent evaporated in vacuo. Recrystallization of the residue from ethanol-ether gives crystals of the di-(ethane sulfonate) ester of N,N'-bis-[5-(1-hydroxyhexyl)]N,N'-dimethyl-1,4-diaminobutane dihydrochloride.

Example 10

A mixture of 14.4 g. of 1,4-di-(ethylamino)-butane and 24.4 g. of pentamethylene chlorohydrin in 150 ml. of ethanol is refluxed for 30 hours. Nine grams of sodium hydroxide in a concentrated aqueous solution are added and the mixture refluxed for one hour. After cooling and filtering, the solvent is evaporated and the residue distilled in vacuo to give N,N'-bis-(5-hydroxypentyl)-N,N'-diethyl-1,4-diamino-butane.

Six grams of this diamine are refluxed with 18.0 g. of 57% hydroiodic acid for six hours. The solvent is removed in vacuo and the residue is washed with ether. Recrystallization of the residue from ethanol-ether gives the dihydroiodide salt of N,N'-bis-(5-iodopentyl)-N,N'-diethyl-1,4-diaminobutane.

Example 11

A mixture of 27.2 g. of 3,6-dibromooctane, 42.0 g. of N-(5-hydroxypentyl)-N-methyl benzylamine (made as in Example 1) and 150 ml. of ethanol is refluxed for 50 hours. The ethanol is exaporated and the residue dissolved in 150 ml. of water. After eight hours of continuous ether extraction, the aqueous solution is acidified with hydrobromic acid and filtered. The filtrate is hydrogenated in the presence of 2.0 g. of palladium charcoal in an autoclave at 50–60° C. at 50 lbs. of hydrogen pressure. The catalyst is removed by filtration and the toluene is distilled off. The aqueous solution is made strongly basic with sodium hydroxide solution. The product is extracted into ether, washed, dried and distilled to yield N,N'-bis-(5-hydroxypentyl)-N,N'-dimethyl-3,6-diaminooctane.

This diamine (3.4 g.) is dissolved in 75 ml. of chloroform, cooled to 0° C. and treated with an excess of hydrochloric acid. A solution of 10.0 g. of thionyl chloride in 50 ml. of chloroform is added and the resulting mixture is allowed to stand overnight. After refluxing for two hours, the solvent and excess thionyl chloride are removed in vacuo. The residue is washed with ether and recrystallized from ethanol-ether to give white crystals of N,N'-bis-(5-chloropentyl)-N,N'-dimethyl-3,6-diaminooctane dihydrochloride.

Example 12

A solution of 2.0 g. of N,N'-bis-(5-chloropentyl)-N,N'-dimethyl-1,5-diaminopentane dihydrochloride, made as in Example 1, in 100 ml. of ethanol is treated with 1.2 g. of maleic acid. Evaporation in vacuo leaves as the residue, the dimaleate salt of N,N'-bis-(5-chloropentyl)-N,N'-dimethyl-1,5-diaminopentane.

Example 13

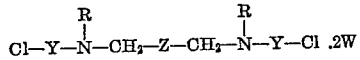
A solution of 2.0 g. of N,N'-bis-(4-chlorobutyl)-N,N'-dimethyl-1,6-diaminohexane dihydrochloride, made as in Example 2, in 100 ml. of ethanol is treated with 1.7 g. of silver nitrate. The resulting mixture is filtered and evaporated to give as the residue the dinitrate salt of N,N'-bis-(4-chlorobutyl)-N,N'-dimethyl-1,6-diaminohexane.

Example 14

A solution of 1.3 g. of the dihydrochloride salt of the di-(methylsulfonate)-ester of N,N'-bis-(5-hydroxypentyl) N,N'-dibutyl-1,8-diaminooctane, made as in Example 6 in 75 ml. of ethanol is treated with 0.4 g. of methane sulfonic acid. Evaporation of the solution in vacuo leaves the di-(methylsulfonate) ester of N,N'-bis-(5-hydroxypentyl)-N,N'-dibutyl-1,8-diaminooctane dimethane sulfonate.

What is claimed is:

1. A chemical compound having the following formula:



R is lower alkyl having 1 to 4 carbon atoms; Y is a divalent alkylene chain having 4 to 5 carbon atoms; Z is a divalent alkylene chain having 2 to 4 carbon atoms and W is a nontoxic, pharmaceutically acceptable acid having a maximum pKa value of about 4.5.

2. N,N'-bis-(5-chloropentyl)-N,N'-dimethyl-1,5-diaminopentane dihydrochloride.

3. N,N' - bis-(4-chlorobutyl)-N,N'-dimethyl-1,6-diaminohexane dihydrochloride.

4. N,N' - bis-(4-chlorobutyl)-N,N'-dimethyl-1,5-diaminopentane dihydrochloride.

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