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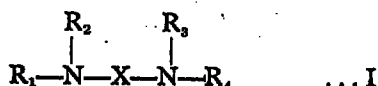
International Classification:—C 07 c, d (A 61 k)

COMPLETE SPECIFICATION

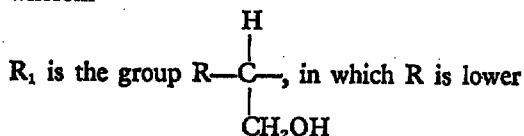
Amine Derivatives and process for their preparation

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 20, State of New York, United States of America, do hereby declare the invention for which we pray 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 novel hydroxy diamines. More particularly, this invention relates to hydroxy diamines of the formula



wherein



R_2 and R_3 are the same or different and are hydrogen atoms, lower alkyl (of 1 to 6 carbon atoms) or lower hydroxyalkyl groups (of 1 to 6 carbon atoms),

R_4 is a lower alkyl (of 1 to 6 carbon atoms) or lower hydroxyalkyl (of 1 to 6 carbon atoms) group,

X is a lower alkyl-substituted or unsubstituted alkylene group having 2 or 3 carbon atoms separating the two nitrogen atoms and at least one of these carbon atoms forms a methylene group in the chain and the non-toxic acid addition salts thereof.

Suitable lower alkyl groups may be, for example, methyl, ethyl, *n*-propyl, isopropyl and *n*-butyl. Suitable lower hydroxyalkyl groups may be, for example β -hydroxyethyl,

[Price 4s. 6d.]

α -methyl- β -hydroxyethyl, α -ethyl- β -hydroxyethyl, α -*n*-propyl- β -hydroxyethyl and α -iso-propyl- β -hydroxyethyl. The non-toxic acid-addition salts of the novel hydroxy diamines of the present invention with both organic and inorganic acids are also included within the scope of the invention. This invention also relates to pharmaceutical compositions useful in the treatment of tuberculosis wherein the active ingredients are the novel hydroxy diamines of formula I or their non-toxic acid-addition salts.

It is known that tuberculosis is a contagious disease which usually runs a protracted course, often lasting for years before death or recovery. Relapses are common. It is one of the most important causes of prolonged disability and chronic ill health. It is caused by the tubercle bacillus *Mycobacterium tuberculosis*. Human tuberculosis is usually caused either by the human strain or the bovine (cattle) strain of the bacillus. The bacillus is comparatively resistant. Tuberculosis is usually acquired either by the inhalation of droplets of infected sputum, either fresh or dried, or by the consumption of milk from tuberculous cows.

Until the discovery of streptomycin, it was impossible to attack the tubercle bacillus directly. Treatment was based on rest, nutrition, fresh air, good meals and collapse therapy; in other words on the recuperative powers of the body. The discovery of streptomycin ushered in a new era in the treatment of tuberculosis. Streptomycin, however, has a number of significant shortcomings, such as the fact that it is not always well tolerated and must be given by injection. Furthermore, the bacillus may become resistant to streptomycin so that it loses its therapeutic value. Paraaminosalicylic acid has also been found to be a weak antitubercular agent.

However, when used with streptomycin, it reinforces the action of streptomycin and delays the appearance of resistant strains of the bacillus. Nicotinamide and pyrazinamide have also been tried but both of these compounds also have significant shortcomings.

The novel substituted hydroxy diamines of formula I and their non-toxic acid-addition salts of the present invention have been found to be highly useful in the treatment of tubercle bacilli infections when administered in amounts ranging from about 10 mg. to about 500 mg. per kilogram of body weight per day. Surprisingly, the known 2,2'-(ethylenediimino)-di-1-ethanol and 2,2',2'-(ethylenediimino)-tetra-1-ethanol are utterly devoid of such therapeutic activity.

The novel compounds of the present invention are, in general, white crystalline solids, soluble in water and lower alkanols, less soluble in acetone, chloroform, and the like, and but sparingly soluble in ether, benzene, petroleum ether, and the like. The dihydrochloride 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 novel hydroxy diamines of the present invention may be administered either in the form of the free base or in the form of their non-toxic acid-addition salts. The inorganic acids which may be employed to prepare these acid-addition salts may be, for example, hydrochloric, hydrobromic, sulfuric, or nitric. The organic acids which may be employed to prepare these acid-addition salts may be, for example, benzoic, acetic, tartaric, citric, lactic, or para-aminosalicylic.

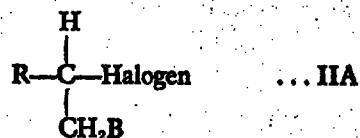
A dosage unit of the novel hydroxy diamines of formula I or their non-toxic acid-addition salts of the present invention comprises from about 10 mg. to about 500 mg. per kilogram of body weight per day. In the treatment of tuberculosis, such dosage units are employed that a total of from 0.6 to 30 g. of the hydroxy diamine of formula I or its acid-addition salt, for an adult patient, is administered orally in a 24-hour period. The preferred range for human adult patients is 1.25 to 10 grams of the novel hydroxy diamine of formula I or its acid-addition salt in a 24-hour period given in dosage units of 0.5 to 2 grams. For instance, 5 tablets containing 0.25 gram each of 5 tablets containing 2 grams each may be employed in each 24-hour period with beneficial results.

A preferred dosage unit form is a tablet containing the novel hydroxy diamine of formula I or its non-toxic acid-addition salt as the therapeutically active ingredient. For adults, such tablets should contain from 0.5 to 2 grams of the hydroxy diamine of formula I or its acid-addition salt. Of course, a tablet scored to be broken into dosage units such

as previously described or a number of tablets to be taken at one time to constitute a dosage unit may also be employed. A second preferred dosage unit form is a capsule containing as the therapeutically active ingredient from 0.5 to 2 grams of the novel hydroxy diamine of formula I or its acid-addition salt. The capsule may be of either the hard or soft variety and may be made of any suitable capsule material which will disintegrate in the digestive tract in from about 1 to 4 hours. Examples of such encapsulating materials are gelatin and methyl cellulose.

Of course, the dosage unit forms of the novel hydroxy diamines of formula I or their non-toxic acid-addition salts of the present invention may also contain either inert or medically active materials. For instance, when the dosage unit form is a tablet or granules there may also be present various binders, fillers, or solid diluents. There may also be present various medically active materials such as, for instance, para-aminosalicylic acid or isonicotinic acid hydrazide. 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. And regardless of the dosage unit form, there may be present various flavours and excipients. Of course, any materials used in preparing the dosage unit form must be pharmaceutically pure and substantially non-toxic in the amount employed.

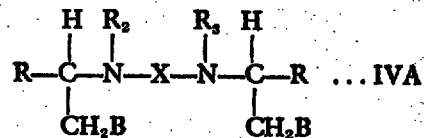
In accordance with this invention, there is provided a process for preparing the novel hydroxy diamines of formula I in which two moles of



are condensed with one mole of

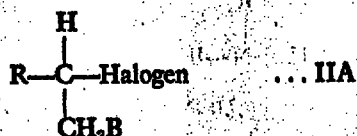


to form the following amine



wherein R, R₂, R₃, and X are as defined above and B is a hydroxy group or a substituted hydroxy group. As used herein the term "substituted hydroxy group" means a group, such as alkoxy or acyloxy, which is convertible into a hydroxy group by hydrolysis.

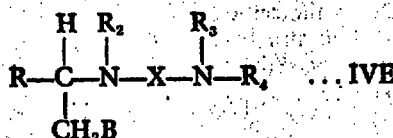
The reaction may also be one in which one mole of



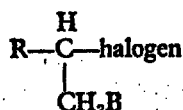
is condensed with one mole of



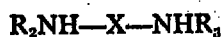
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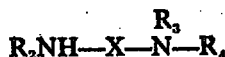
One can carry out these processes by reacting the secondary-alkyl halide



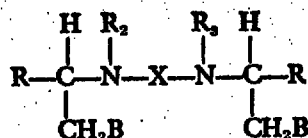
with the alkylenediamine



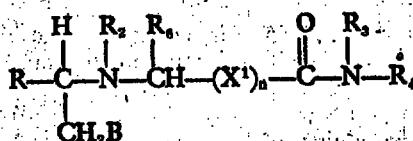
or



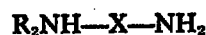
- 15 at a suitable temperature for an appropriate time in the presence or absence of an inert solvent such as *n*-propanol. When B is a hydroxyl group, the product



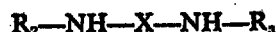
- 20 is preferably isolated as the dihydrochloride after passing in two moles or more of HCl gas. When B is a substituted hydroxy, such as alkoxy or acyloxy, the isolation is preferably preceded by hydrolysis at an elevated temperature to hydroxy, preferably by means



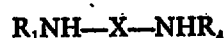
of acid which in the case of alkoxy may also be used in such a way as to mediate the transfer of the alkyl group from the oxygen to a secondary amino group. Tertiary nitrogens may also be formed by heating R_2 (or R_3)-halogen either with ethylenediamine to give the reagents



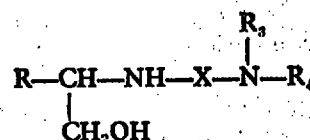
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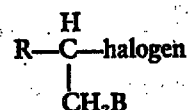
to which R_1 and R_4 may be introduced by the methods described herein or alternatively; the intermediate



may be reacted with R_2 -Halogen or R_3 -Halogen or similar alkylating agent to arrive at the product, or alternatively, the intermediate

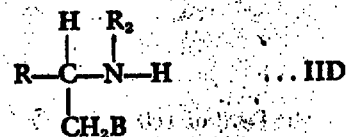


may be alkylated. As in other instances to be discussed, the reagent

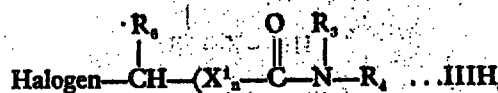


may conveniently utilize other displaceable groups besides halogen.

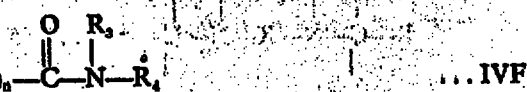
Or, the reaction is one in which one mole of



is condensed with one mole of



to form



tablets dosage d pre-taining t from iamine 70 The or soft e cap-in the hours. ils are 75

of the their 80 resent rt or when anules nders, 85 so be such id or losage addi-liquid ss of esent any unit sub-ved. re is novel two 100

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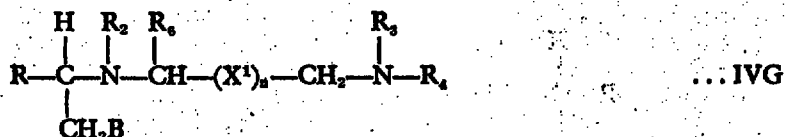
IIA

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VA

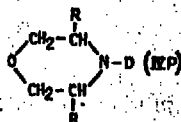
ned sti-rm up, 110 on-s.

and then the compound of formula IVF is reduced to form

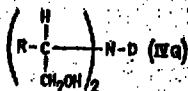


wherein X^1 is a lower alkyl substituted or unsubstituted methylene group, and n is zero or one and R_4 is a hydrogen atom or a lower alkyl group.

The condensation reaction includes one in which a compound of the formula



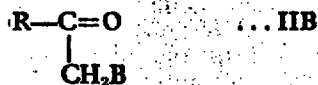
is treated with acid to form



wherein D is



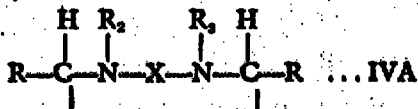
The process of this invention includes one in which two moles of



or the ketal of IIB are condensed under reducing conditions with one mole of



to form the following amine



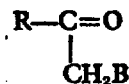
In carrying out this reaction the amine of formula IIIA may be produced *in situ* from

the corresponding difunctional alkylene derivative

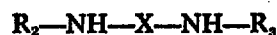


wherein Y is a nitrile, and X^1 is a lower alkyl substituted or unsubstituted methylene radical and n is zero or one, or Y is a nitro group, an oximino group or a hydroxylamino group and X^1 is the same as X.

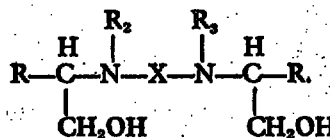
This process may preferably be carried out also by reductively reacting two moles of a ketone



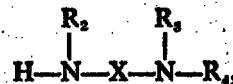
or its ketal with one mole of



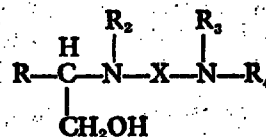
using hydrogen under pressure and metal catalysts without a solvent or using chemical reducing agents such as metal hydrides or formic acid in aqueous or organic solvent media. When B is alkoxy or acyloxy, the requisite hydroxy group is formed by acid or alkaline hydrolysis before purification of the final product



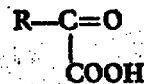
By employing the diamine reagent



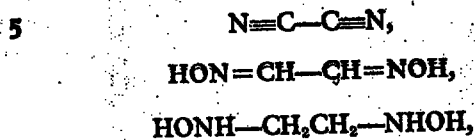
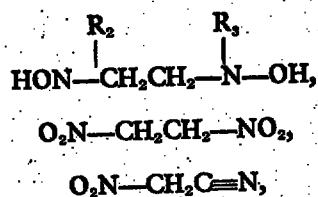
the unsymmetrical product



is obtained. The desired CH_2OH group is formed in the course of the reaction when the keto acid



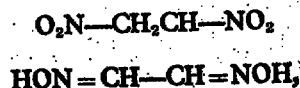
or its ester is used as a reagent. One or both of the amine groups may be formed in the reagent during the reaction by using compounds such as



10 and

as reagent precursors. In the case of

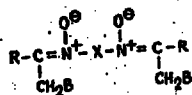
15 and



the intermediate



may condense first to give

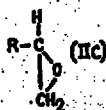


20

which is a suitable intermediate for reduction to the final product. R_2 , R_3 and R_4 may be introduced by reductive alkylation using the appropriate aldehyde or ketone.

25

The process includes the case in which two moles of an ethylene compound of the formula:

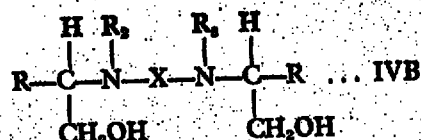


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are condensed with one mole of the following amine in the presence of a suitable acid catalyst.



to form the following amine



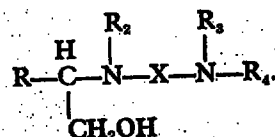
A suitable catalyst for condensation of the alkylene oxide is a Lewis acid, preferably in a polar solvent medium.

Under the same conditions, one mole of the alkylene oxide reacts with

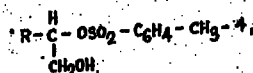
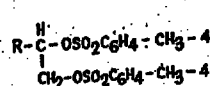
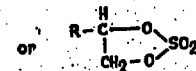


to give an unsymmetrical product

40



With some Lewis acid catalysts the reaction may proceed through discrete intermediates such as

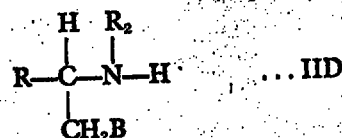


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formed from the alkylene oxide during the reaction, and indeed these and analogous substances may be used as the reagents when desired.

The process of this invention includes the case in which two moles of

50

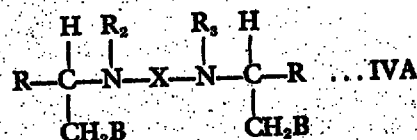


are condensed with one mole of



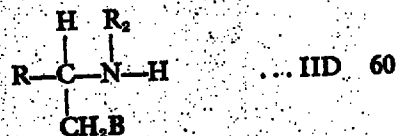
to form the following amine

55



wherein R_2 and R_3 are identical.

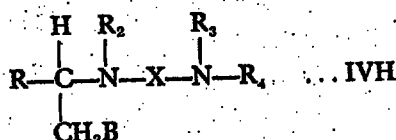
Also this invention includes the process in which one mole of



is condensed with one mole of



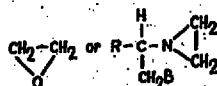
to form



- 5 The condensation of the halide and the amine can be carried out preferably in an inert solvent and preferably in the presence of an inorganic or organic base to serve as an acid acceptor. Instead of halogen, one can conveniently employ other displaceable groups
- 10 such as $-\text{OSO}_2\text{OH}$, $-\text{OSO}_2\text{OAlkyl}$, $-\text{OSO}_2\text{Alkyl}$, $-\text{OSO}_2\text{C}_6\text{H}_4-\text{CH}_3-4$, quaternary ammonium and $-\text{OH}$. In the latter case, one uses suitable Lewis acid catalysts which in some instances act by conversion
- 15 of the hydroxy to a displaceable group or one uses a metal hydrogenation-dehydrogenation catalyst such as copper chromite at elevated temperature and moderate pressure. In this
- 20 form of the process, the two displaceable groups need not be the same and good reaction occurs with an unsymmetrical reagent such as



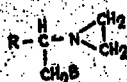
- 25 Also, the two displaceable groups may be united in a reactive ring in a reagent such as



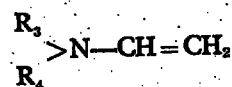
which react with two and one mole, respectively, of



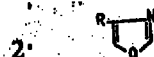
- in the presence of acid or base. Other ethylene imines and alkyl-substituted ethylene oxides may be used in the same way. The two displaceable groups may be united also in a multiple bond such as in acetylene $\text{HC}\equiv\text{CH}$
- 35 which with a primary amine forms



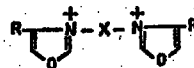
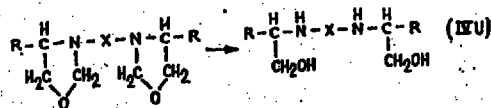
and the like and with a secondary amine forms



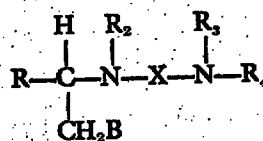
both of which compounds react further to give the desired final product. The two displaceable groups may be employed to unite one or two nitrogenous rings capable of conversion to hydroxy alkylamino group. For example, the uniting of two nitrogenous rings may be exemplified as follows:—



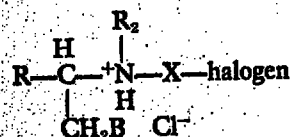
+ halogen—X—halogen—>



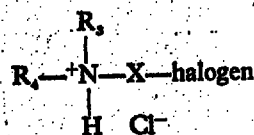
The intermediate bis quaternary is reduced and the reduction product is acid hydrolyzed before purification and crystallization as the acid salt, which is preferably the dihydrochloride salt. When an unsymmetrical product such as



is desired, the two displaceable groups may be reacted in stepwise fashion with one mole each two different amines. The two intermediates in the form of their hydrochloride salts



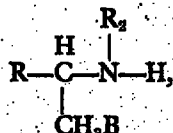
and



formed in this way are typical and are then reacted with



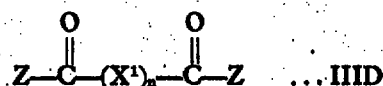
and



5

are condensed with one mole of

10

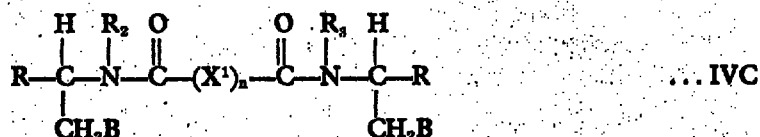


respectively, to give the desired product.

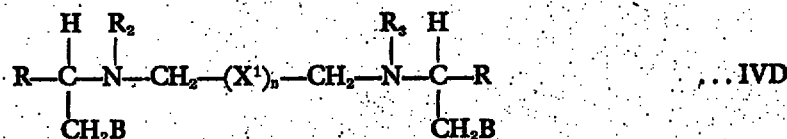
A reaction according to the process of this invention includes that in which two moles of

wherein Z is —OH or halogen or quaternary ammonium groups or —OR₅ where R₅ is an organic radical, to form

15



and the resulting compound IVC reduced to form



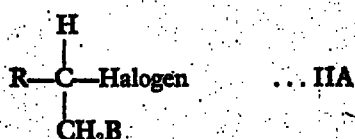
20

in which R₂ and R₃ are identical, X¹ is an unsubstituted or a lower alkyl substituted methylene group and n is zero or 1.

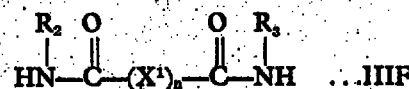
Alternatively, the process is one in which two moles of

are condensed with one mole of a suitable salt of

25

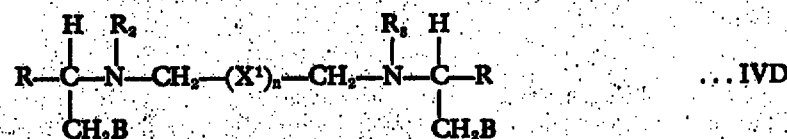


to form



and the resulting compound IVC reduced to form

30



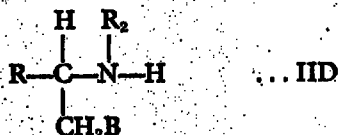
in which X^1 is an unsubstituted or lower alkyl-substituted methylene group and n is zero or 1.

Where part of the reactant is preformed, the reaction is one in which one mole of

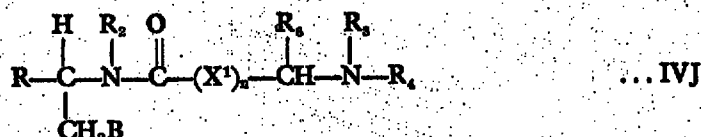
is condensed with one mole of



5



wherein Z is $-OH$, halogen, quaternary ammonium or $-OR_5$ where R_5 is an organic radical and R_6 is a hydrogen atom or a lower alkyl group to form 10



and the resulting compound IVJ reduced to form



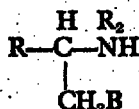
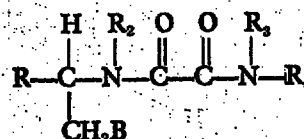
15 wherein R_5 and R_6 are as previously defined and X^1 is an unsubstituted or a lower alkyl substituted methylene group and n is zero or 1.

20 An alternative situation in which part of the reactant is preformed has been illustrated above in the preparation of compound IVG.

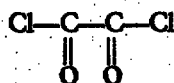
In the above reactions the amide may be formed usually without external heating. For example, the reaction may involve two moles of

40 $HOOC-CO-Cl$. In the case of carboxylic acid groups, a dehydrating agent is employed or one may use only heating to an elevated temperature. The reagent diacid chloride can be reacted stepwise with one mole each of two different amines added carefully to the acid chloride under the same conditions to give an 45 unsymmetrical diamide intermediate

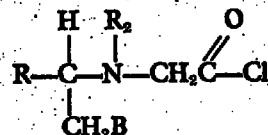
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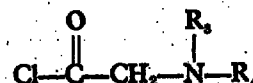
with one mole of



Under the same reaction conditions, one can condense

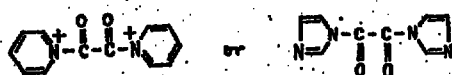


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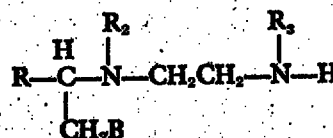
in the presence or absence of an inert solvent using an inorganic or organic base as acid acceptor. In the case of some organic bases, a discrete reactive intermediate is formed during the reaction or may be preformed, for example,



and similar acyl derivatives with amines to give monoamide intermediates. A diamine such as

35

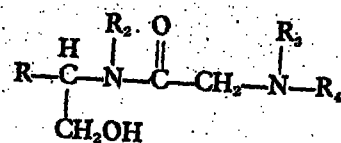
Instead of halogen, anhydrides with other inorganic acids or their partial esters and with organic acids may be employed as well as reagents with two different groups such as



55

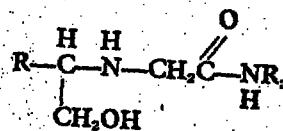
may be reacted with an acyl chloride to give a monoamide intermediate whose acyl group is suitable for conversion by reduction to R_4 . The reduction stage of the amide linkage or linkages of this form of the process is accomplished by hydrogen under pressure at an elevated temperature in the presence of a metal catalyst such as copper chromite or by chemical reducing agents such as lithium aluminium hydride. The reduction is applied to any of the amide intermediates just discussed. In the case particularly of the catalytic hydrogenation, the amine groups can be formed from nitro, oximino or nitrile groups at low temperature and pressure in the presence of an ester reagent such as

The amine substituents may be reversed to give



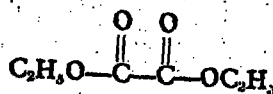
35

by using the amines in the reverse order; in either sequence of using the amines the two reactions may be carried out successively in the same solution without isolation. When one uses this reaction to prepare an amide intermediate such as

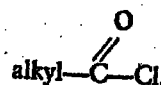


40

which will react with the amine to form the amide in the course of reaching the elevated temperature and pressure suited for reduction of the amide. In addition to the method described above for preparing the monoamide intermediate

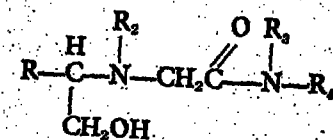


or its isomer, one can very conveniently introduce specifically a third substituent onto the basic nitrogen by an alkylating agent such as



45

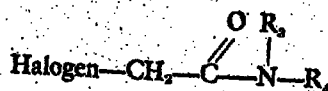
and the like, one can use



In the latter instance, both amide groups are subsequently reduced together. Suitable amide intermediates may be prepared by reaction of an alkyl halide with a metal salt of a diamide. The process of this invention includes the sequence in which two moles of

50

(prepared from



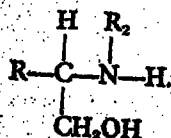
by careful addition thereto of one mole of



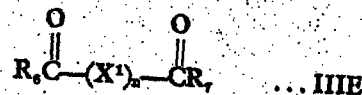
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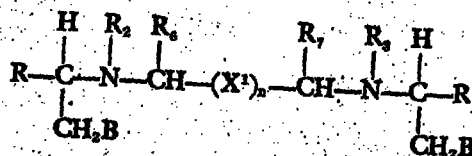
plus an acid acceptor) which is heated with



are condensed under reducing conditions with

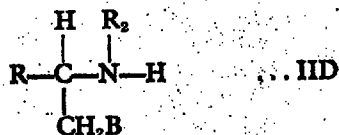


or the acetal of IIIE to form



... IVD

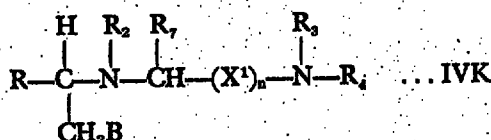
wherein R_2 and R_3 are identical. In this sequence, n is zero or one. The process also includes the sequence in which one mole of



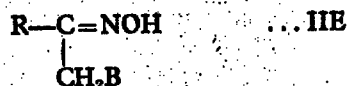
- 5 is condensed under reducing conditions with one mole of



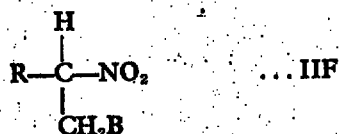
to form



- 10 In this sequence, n is one or two. In both the above sequences, R_6 and R_7 when present are the same or different and are hydrogen atoms or lower alkyl groups and X^1 is an unsubstituted or a lower alkyl substituted methylene group. In the process, the compound of formula IID may be prepared *in situ* by the reduction of the corresponding oximino compound



- 20 or by the reduction of the corresponding nitro compound



or by the reduction of the corresponding hydroxylamino compound

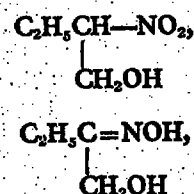
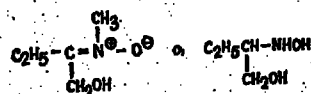


Example of the above is the reductive condensation of an amine such as 2-aminobutanol with a dicarbonyl compound or its acetal or ketal such as glyoxal, acetoacetaldehyde dimethylacetal. The reductive condensation can be carried out using hydrogen under moderate pressure with a metal catalyst such as palladium on charcoal using a slightly

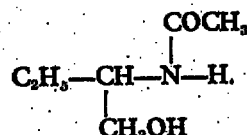
elevated temperature if necessary to get adequate uptake of hydrogen. Chemical reduction is also conveniently accomplished with reagents such as lithium aluminium hydride in tetrahydrofuran or sodium borohydride in aqueous medium. If desired, a mono- or dialdehyde reagent can be generated in the reaction by reduction of an acid chloride. The same conditions can be employed to introduce nitrogen substituents into diamines such as



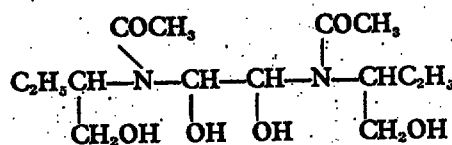
The amine reagent may be reductively generated in the reaction solution by using, for example



instead of the amine reagent. The amine reagent may also be an amide such as



If the reagent is a dialdehyde such as glyoxal, the reaction presumably proceeds through



as intermediate. This embodiment of the process can also conveniently be carried out by using aminoaldehydes and aminoketones such as

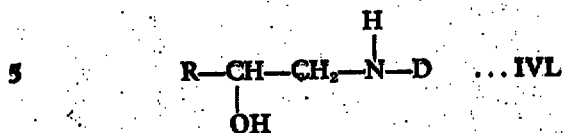


and

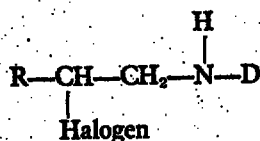
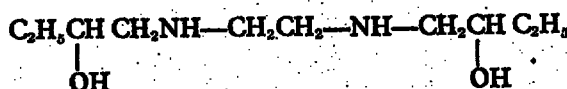


with an appropriate amine. Acetals and ketals of such substances may also be employed.

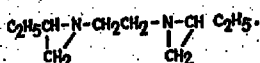
The process of this invention includes the case in which a compound of the formula:



is treated with a suitable reagent to form



20 is converted to the chloro compound with thionyl chloride or similar reagents, and treated with base to form



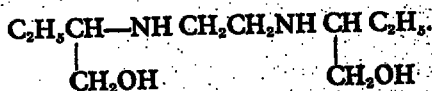
The latter may also be formed from



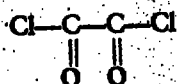
and



Treatment with acid or base of the bis ethyleneimine then forms



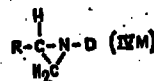
30 An alternative is to react an acid chloride such as oxalyl chloride



with

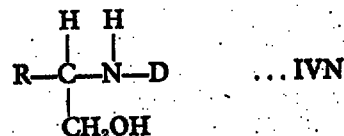


and the halo-derivative is then treated with base to form

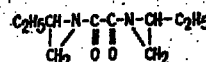


10

and the product of formula IVM treated with acid or base to form

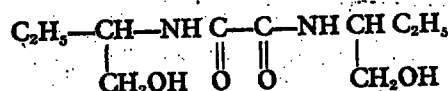


The process of this invention may be carried out through various ethyleneimine 15 intermediates. For example,

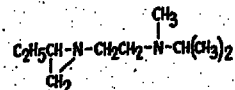


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which is then converted to

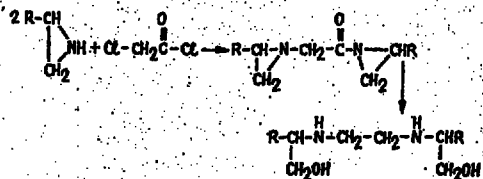


40 followed by chemical or catalytic reduction (as discussed more fully above) to the alkylene-diamine. It is clear, of course, that other groups can be used in place of chlorine in the reactions just cited. Also, it is obvious that one can carry out this process with an unsymmetrical intermediate such as

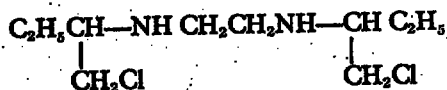


45

Another possibility is illustrated by the following sequence:



- 5 In order to form the desired hydroxymethylene group in the hydroxy diamines of this invention, one can use the corresponding compounds in which the CH_2OH is formed by catalytic or chemical reduction of the corresponding COOH or COOR_s compounds, wherein R_s is an alkyl, aryl or aralkyl group. Where it is desired to employ

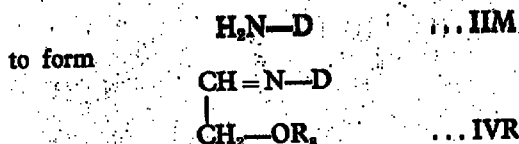


- 10 as the intermediate to the desired final product, one can convert the chlorine or other such group to hydroxy by heating in a polar solvent with a base such as hydroxide ion, acetate ion or methoxide ion. The latter two would require a hydrolysis which could be carried out on the reaction mixture. In other instances the alkoxy- or acyloxy-substituted alkylendiamines may be formed in various condensation reactions and then subjected to acid and alkaline hydrolysis, respectively, usually without need for isolation of the intermediate.

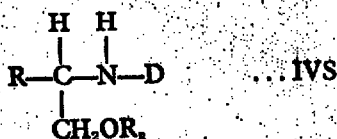
- 20 Also, the process of this invention includes the reaction in which the following compound



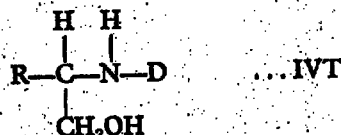
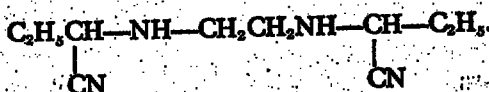
- 25 or the acetal thereof is condensed with



- 30 and the product reacted with an organo metallic reagent to form



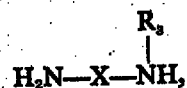
which is then hydrolyzed to form



wherein R_s is an alkyl, aryl or aralkyl group. The reaction can be achieved by condensing a compound such as

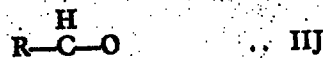


or its acetal with a diamine such as



the water formed being removed, and under anhydrous conditions in an inert atmosphere (e.g. under nitrogen), subsequent addition of an organometallic reagent such as butyl lithium, or ethyl magnesium chloride, using at least one mole of organometallic reagent for each primary or secondary group in the diamine reagent.

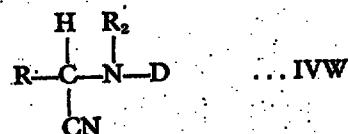
The process of this invention includes the sequence in which one mole of



is condensed with



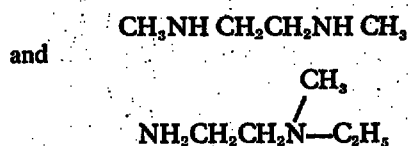
in the presence of hydrocyanic acid to form



and the nitrile group of the resulting compound then converted to a hydroxymethylene group.

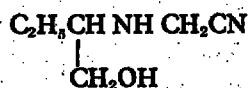
The above reaction can, of course, be carried out to form the diamine. Thus, an aldehyde, such as propionaldehyde, can be reacted with an alkylendiamine such as ethylene diamine in the presence of hydrocyanic acid to form

Diamines such as

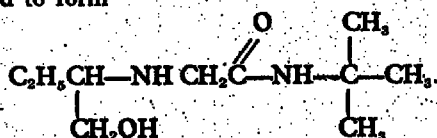


5 can be used to give analogous products. The cyano group may be converted to the CH_2OH group desired through the aldehyde or ester analogs, which are readily formed therefrom by conventional processes.

10 The formation of the alkyl-amine linkage can be effected by reaction of a nitrile with an alcohol. For example, a substituted amino alkanoylnitrile such as

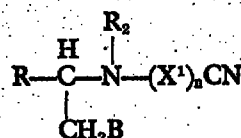


15 can be reacted with *t*-butanol in conc. sulfuric acid to form



The latter amide is then reduced as described previously.

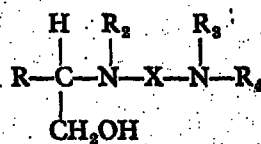
Also this invention provides a process for 20 preparing a compound of formula I, in which R_3 and/or R_4 are inserted by treating a compound of the formula:



with a tertiary alcohol or an olefin containing 25 a tertiary carbon atom using an acid catalyst and then reducing the amide so formed, wherein R_3 is hydrogen, R_4 is a tertiary alkyl group X^1 is unsubstituted or a lower alkyl-substituted methylene group and n is 0, 1 30 or 2.

The following examples illustrate the pre- 35 paration and formulation of the novel therapeutic compounds of the present invention, and the compounds so prepared are summarized in Table I below.

TABLE I



Example No.	X	R	R ₂	R ₃	R ₄
1	-CH ₂ CH ₂ -	-CH ₃	H	H	$ \begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}-\text{CH}_2-\text{OH} \end{array} $
2,12	-CH ₂ CH ₂ -	-C ₂ H ₅	H	H	$ \begin{array}{c} \text{C}_2\text{H}_5 \\ \\ -\text{CH}-\text{CH}_2-\text{OH} \end{array} $
3	-CH ₂ CH ₂ -	$ \begin{array}{c} \text{CH}_3 \\ \\ -\text{CH} \\ \\ \text{CH}_3 \end{array} $	H	H	$ \begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \diagdown \quad \diagup \\ \text{CH} \\ \\ -\text{CH}-\text{CH}_2-\text{OH} \end{array} $
4	-CH ₂ CH ₂ -	-C ₂ H ₅	H	H	$ \begin{array}{c} \text{CH}_3 \\ \\ -\text{CH} \\ \\ \text{CH}_3 \end{array} $
5	-CH ₂ CH ₂ -	-C ₂ H ₅	-CH ₃	-CH ₃	$ \begin{array}{c} \text{C}_2\text{H}_5 \\ \\ -\text{CH}-\text{CH}_2-\text{OH} \end{array} $
6	-CH ₂ CH ₂ -	-C ₂ H ₅	-C ₂ H ₅	H	$ \begin{array}{c} \text{CH}_3 \\ \\ -\text{CH} \\ \\ \text{CH}_3 \end{array} $
7	$ \begin{array}{c} \text{CH}_3 \\ \\ -\text{CHCH}_3- \end{array} $	-C ₂ H ₅	H	H	$ \begin{array}{c} \text{C}_2\text{H}_5 \\ \\ -\text{CH}-\text{CH}_2-\text{OH} \end{array} $
8	-CH ₂ CH ₂ CH ₂ -	-C ₂ H ₅	H	H	$ \begin{array}{c} \text{C}_2\text{H}_5 \\ \\ -\text{CH}-\text{CH}_2-\text{OH} \end{array} $
9	-CH ₂ CH ₂ -	-C ₂ H ₅	-CH ₂ CH ₂ OH	-CH ₂ CH ₂ OH	$ \begin{array}{c} \text{C}_2\text{H}_5 \\ \\ -\text{CH}-\text{CH}_2-\text{OH} \end{array} $
10,11	-CH ₂ CH ₂ -	-C ₂ H ₅	-C ₂ H ₅	-C ₂ H ₅	$ \begin{array}{c} \text{C}_2\text{H}_5 \\ \\ -\text{CH}-\text{CH}_2-\text{OH} \end{array} $

EXAMPLE 1.

N - [N¹ - (α - methyl - β - hydroxyethyl) - β - aminoethyl] - β - methyl - β - aminoethanol.

- 5 A mixture of 37.7 g. (0.50 mole) of 2-amino-1-propanol and 12.4 g. (0.125 mole) of ethylene dichloride was refluxed for one hour. To the cooled mixture was added a solution of 30 g. (0.55 mole) of sodium methoxide in 75 ml. of methanol and the precipitated sodium chloride was removed by filtration. 10 Distillation gave 11 g. (49% of theory) of a yellow viscous oil, b.p. 150—170° C./0.2 mm. This product crystallized in the receiver and was recrystallized from ethanol 6.8 ml./g.) to yield 2.6 g. of *meso* base as white crystals, m.p. 137—145° C.

- 15 Fractional crystallization from the filtrate gave some additional product predominantly *meso* base, but the *dl* base did not readily crystallize. Addition of ethanolic HCl to the 20 filtrate followed by fractional crystallization from methanol gave 2.0 g. of the *dl* dihydrochloride as white crystals, m.p. 184—186.5° C.

- 25 The *meso* base was converted to its dihydrochloride which on recrystallization from methanol weighed 3.5 g., m.p. 201.5—204.5° C.

EXAMPLE 2.

- 30 N - [N¹ - (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 to 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 poured 40 into a flask, washing with and adding 300 ml. of methanol. To this was added cautiously 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 45 distilled at 165—170° C./0.6 mm. as a light yellow oil which tended to solidify in the air condenser; yield, 108 g. (58% of theory).

- 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, 50 gave 35 g. of white crystals melting at 134.5—136° C. and a second crop of 10 g. melting at 132.5—134° C. (total yield 45 g., 22% of theory) which is the *meso* base. The dihydrochloride of this melts at 202—203° C.

- 60 From the ethanolic filtrates on addition of 130 ml. of about 4N 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. 65

EXAMPLE 3.

N - [N¹ - (α - isopropyl - β - hydroxyethyl) - β - aminoethyl] - β - isopropyl - β - aminoethanol. 70

A solution of 40 g. (0.22 mole) of ethyl *dl*-valinate hydrochloride in 100 ml. of pyridine was treated dropwise with stirring and cooling with a solution of 13.97 g. (0.11 mole) of oxalyl chloride in 100 ml. of anhydrous ether over a period of 45 minutes. Sufficient 1N hydrochloric acid was added to bring the pH to 5 and this solution was extracted several times with ether. The ethereal extract on concentration gave a gum which crystallized from 50 ml. of ethanol on adding 100 ml. of water and cooling to 0° C. The product, 29 g., was a white crystalline solid, m.p. 44°—48° C. 75

The above oxamide (17.2 g., 0.05 mole), dissolved in 250 ml. of ether, was added dropwise to a solution of 10.0 g. (0.26 mole) of lithium aluminium hydride in 500 ml. of ether followed by a 2 hour refluxing period. Addition of ethyl acetate followed by 200 ml. of 10 N sodium hydroxide gave a clear solution. The ether layer was separated and combined with two additional ether extracts. On concentration of the ethereal extracts, adding ethanolic hydrogen chloride and acetone, 7.2 g. of the dihydrochloride salt as white crystals (47% yield) were obtained, m.p. 216—224° C. Recrystallization from ethanol and water gave 6.6 g. of white needles, m.p. 231.5—233.5° C. 80

EXAMPLE 4.

(a) Preparation of β -Isopropylaminoethyl-chloride hydrochloride. 100

A solution of 48.5 g. (0.470 mole) of β -isopropylaminoethanol in 100 ml. of chloroform was cooled, and a solution of 59 ml. (0.82 mole) of thionyl chloride in 600 ml. of chloroform was added dropwise over 40 minutes with vigorous stirring, keeping the reaction temperature below 10° C. After standing at 5° C. for 1 hour the mixture was allowed to come to room temperature over 3 hours. Most of the chloroform was distilled, 50 ml. of ethanol was added and distilled leaving a black viscous residue which solidified on standing overnight. The residue was dissolved in 200 ml. of boiling ethanol treated with about 5 g. of "Norite". The red filtrate was concentrated to 80 ml. and 180 ml. of acetone was added. After cooling to 0° C. the resulting crystals were filtered and dried in a vacuum oven to give a white product weighing 59 g. (80% yield) and melting at 179.5—188° C. (corr.). The word "Norite" is a registered Trade Mark. 105 110 115 120

(b) N - [N¹ - (isopropyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

A mixture of 15.8 g. (0.1 mole) of β -isopropylaminoethylchloride hydrochloride and 35.6 g. (0.4 mole) of 2-aminobutanol was heated at reflux for 4 hours. The cooled viscous oil was treated with 100 ml. of 10N NaOH and the organic layer extracted into benzene. Several additional benzene extractions followed and the combined extracts dried over anhydrous Na₂CO₃, concentrated, and the residue distilled. The first fraction collected consisted of 2-amino-butanol, b.p. 80—85° C./15 mm. Further distillation yielded the product as a light yellow oil, 11 g. (63% yield), b.p. 85—86° C./0.005 mm.

In a similar manner N - [N¹ - (*sec*-butyl - β - aminoethyl) - β - ethyl - β - aminoethanol was prepared using β -*sec*-butylaminoethanol in place of β -isopropyl aminoethanol.

Also in a similar manner N - [N¹ - (*tert*-butyl) - β - aminoethyl] - β - ethyl - β - aminoethanol and N - [N¹ - (*tert*-amyl) - β - aminoethyl] - β - ethyl - β - aminoethanol were prepared using β - *tert* - butylaminoethanol and β - *tert* - amylaminoethanol, respectively.

EXAMPLE 5.

N - methyl - N - [N¹ - methyl - N¹ - (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 - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol in portions, with cooling. 9.0 g. (0.105 mole) of 35—37% formaldehyde was added and the mixture was heated on the steam bath with considerable effervescence, due to evolution of carbon dioxide during the first hour. Refluxing was continued for an additional seven hours. The solution was cooled and treated with 15 ml. of conc. HCl, and the excess formaldehyde and formic acid was removed by evaporation on the steam bath. The resulting gum was treated with 25% NaOH and the organic layer extracted into benzene. The combined extracts were dried over anhydrous Na₂CO₃ and concentrated leaving an oily residue which on distillation under high vacuum yielded the product as a colorless oil, 7.4 g. (67%), b.p. 132—134° C./0.01 mm.

EXAMPLE 6.

N - ethyl - N - [N¹ - (isopropyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

A mixture of 25 g. (0.21 mole) of 2-ethylamino-1-butanol and 11.1 g. (0.07 mole) of β -isopropylaminoethyl chloride hydrochloride was heated to 180° C. After 20 minutes of heating a vigorous reaction ensued and the solution turned a deep red. The mixture was refluxed for an additional 18 hours after which the cooled viscous liquid was treated with ca.

30 ml. 10N NaOH. The insoluble oil was extracted into benzene followed by several successive extractions of the aqueous layer with benzene. The combined extracts were dried over anhydrous Na₂CO₃. The benzene solution was concentrated and the residue distilled under reduced pressure to remove excess 2-ethylamino-1-butanol; b.p. 75—85° C./15 mm. Further distillation at 0.03 mm. afforded 7 g. of the desired product, a pale yellow liquid b.p. 82—83° C.

EXAMPLE 7.

(a) Preparation of N - [1 - (hydroxymethyl)propyl] - α - [1 - (hydroxymethyl) - propylamino] - propionamide.

178.2 g. (2.0 moles) of 2-amino-1-butanol was dissolved in 100 ml. benzene and placed in a 3-necked flask equipped with a dropping funnel, a condenser, and a magnetic stirrer. A solution of 25.0 g. (0.2 mole) of α -chloropropionyl chloride in 50 ml. benzene was added dropwise with cooling and stirring whereupon white fumes were evolved. The solution was heated for one hour, allowing the benzene to escape through the air condenser. The resulting viscous yellow oil was treated with a methanolic solution of KOH (0.4 mole). The white product (KCl) which precipitated was removed by filtration. The filtrate was concentrated to remove the methanol and the residue distilled at reduced pressure to remove the excess 2-aminobutanol, b.p. 80—85° C./15 mm. The residue remaining in the distilling flask was used to prepare N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - methyl - β - aminoethyl] - β - ethyl - β - aminoethanol.

(b) N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - methyl - β - aminoethyl] - β - ethyl - β -aminoethanol.

15.2 g. (0.4 mole) of lithium aluminium hydride was added to 700 ml. of dry tetrahydrofuran in a 3-necked flask equipped with a condenser, a mechanical stirrer and a dropping funnel, and the suspension was refluxed with stirring for 1 hour. A solution of ca. 46 g. (0.2 mole) of N - [1 - (hydroxymethyl)propyl] - α - 1 - (hydroxymethyl)propylamino] - propionamide in 250 ml. of dry tetrahydrofuran was added slowly to the lithium aluminium hydride suspension. After addition was completed the mixture was refluxed for an additional 16 hours. The excess lithium aluminium hydride was decomposed by successive additions of 15 ml. of water, 11 ml. 20% NaOH, and 50 ml. of water. The white precipitate was removed by filtration and the filtrate concentrated by distillation at atmospheric pressure. The residue was distilled under reduced pressure giving 30 g. of product, b.p. 149° C./0.01—0.02 mm.

EXAMPLE 8.

N - [N¹ - (α - ethyl - β - hydroxyethyl) - γ - aminopropyl] - β - ethyl - β - aminoethanol.

- 20.2 g. (0.1 mole) of 1,3 - dibromopropane
 5 was mixed with 44.57 g. (0.5 mole) of 2-
 amino-1-butanol and on slight heating a
 vigorous reaction occurred. Dense white
 fumes were liberated and the colorless solu-
 10 tion turned deep red. The solution was heated
 for an additional 2 hours, then cooled to give
 a viscous liquid. The mixture was
 neutralized by treatment with excess 10N
 NaOH and the insoluble base extracted into
 15 ethyl acetate. The combined ethyl acetate
 extracts were dried over anhydrous Na₂CO₃.
 The extract was concentrated and the result-
 ing residue distilled at 15 mm. to remove
 the excess 2-amino-1-butanol, b.p. 80—85°
 20 C. By further distillation of the residue, yellow
 viscous oil boiling at 130—170° C./0.08 mm.
 was collected. The oil was dissolved in
 ethanol and ethanolic HCl added to pH 1.
 Addition of acetone to the acid solution caused
 25 precipitation of 9.4 g. of a dihydrochloride
 salt which on recrystallization from a 1:4
 ethanol-acetone mixture gave 8.8 g. of white
 crystals, m.p. 139—142° C. and tentatively
 30 assigned the *meso* configuration. Concentra-
 tion of the acidic mother liquor gave a gummy,
 low-melting dihydrochloride salt which could
 not be purified. The dihydrochloride salt was
 converted to the corresponding base by treat-
 ment with excess aqueous alkali. A yellow
 35 oil (1.7 g.) was isolated by distillation, b.p.
 150—170° C./0.3 mm. This product is
 probably the *dl* racemate.

EXAMPLE 9.

N - (β - hydroxyethyl) - N - [N¹ - (β - hydroxyethyl) - N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

- To 4.08 g. (0.02 mole) of *dl* N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol dissolved in 25
 45 ml. of dimethylformamide was added 2.95
 ml. (5.0 g., 0.04 mole) of ethylenebromo-
 hydrin. The mixture was refluxed for four
 hours at which time a quantitative test for
 ionic bromine indicated complete reaction.
 50 The mixture was concentrated under reduced
 pressure to a viscous oil.

EXAMPLE 10.

N - ethyl - N - [N¹ - ethyl - N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

- A mixture of 33 g. (0.28 mole) of 2-ethyl-
 55 amino-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 10N NaOH was
 added and the resulting oil layer was
 60 extracted with benzene. After drying over
 anhydrous Na₂CO₃ the benzene and excess

2 - ethylamino - 1 - butanol were distilled off
 and the residue, 12 g., distilled at 90—130°
 C./0.02 mm.

On redistillation, the product was obtained
 at 125—140° C./0.07 mm.

EXAMPLE 11

N - ethyl - N - [N¹ - ethyl - N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

An alternative method of preparing the pro-
 duct of Example 12 is to treat N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol with excess acetic
 75 anhydride to obtain the N,N¹, O,O¹-tetra-
 acetyl derivative. By reduction of this inter-
 mediate with lithium aluminium hydride as in
 Examples 3 and 7, the desired N,N¹-diethyl
 80 derivative is obtained, the O-acetyl functions
 being removed during the reaction.

EXAMPLE 12.

N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

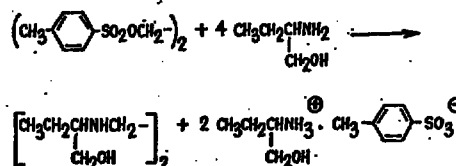
To 6.0 g. (0.03 mole) of 30% aqueous
 glyoxal was added 9.2 g. of 2-aminobutanol
 (with moderate heat evolution) and 30 ml. of
 absolute ethanol. A total of 3.7 g. (0.1 mole) of
 sodium borohydride was added in portions over
 10 minutes. The reaction mixture, after the
 vigorous reaction had subsided, was heated for
 30 minutes. On adding water and extracting
 with chloroform, the *meso* isomer, m.p.
 132—134° C., was isolated on cooling. The
 90 *dl* isomer was isolated as the dihydrochloride
 salt, m.p. 176—178° C. on acidifying the
 filtrate with ethanolic HCl.

EXAMPLE 13.

A mixture of 30 parts of *dl*-N-[N¹-(α-ethyl-
 β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol dihydrochloride, 15
 parts of starch, and 1 part of magnesium
 stearate was thoroughly blended and then
 screened through a 60 mesh screen. The
 105 resulting powder was tableted in an automatic
 tableting machine whereby suitable 500 mg.
 scored white tablets were obtained.

EXAMPLE 14.

N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.



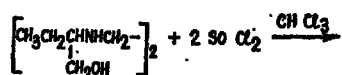
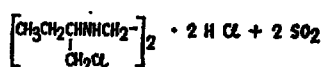
A mixture of 25.0 g. (0.068 mole) ditosyl-
 glycol and 24.24 g. (0.272 mole) 2-amino-
 butanol was refluxed for 18 hours giving a
 115 viscous red oil. Both the *dl* (dihydrochloride

m.p. 176.5—178°) and *meso* (base, m.p. 132.5—134° C.) isomers of 2,2'-(ethylenediimino)di-1-butanol were isolated from the cooled reaction mixture by a procedure similar to that previously described.

EXAMPLE 15.

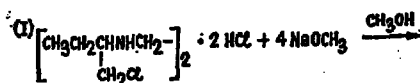
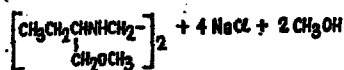
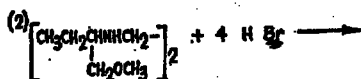
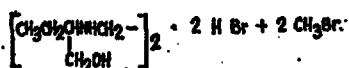
N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

A. 2,2'-(ethylenediimino)di-1-chlorobutane.



A solution of 100 g. (0.49 mole) 2,2'-(ethylenediimino)di-1-butanol *dl* dissolved in 250 cc. chloroform was added dropwise with cooling and stirring to 260 ml. (3.7 moles) thionyl chloride over a period of 20 minutes. The red-orange solution was refluxed for 3 hours on steam bath after which the solution was concentrated under aspirator pressure. The resultant gum was treated with benzene and on concentrating, yellow crystals precipitated. Water (39 ml.) was added to the filtrate to decompose the excess thionyl chloride whereupon additional product precipitated. The mesh was dissolved in *n*-propanol, the solution cooled giving 147.4 g. (96%) of crude product. Recrystallization from *n*-propyl alcohol afforded white crystals m.p. 235° C. (dec.).

B.

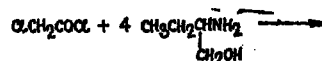
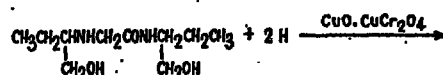
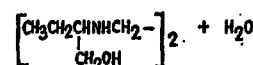


Sodium methylate, 1.59 g. (0.03 mole) was added to a solution of 2,2'-(ethylenediimino)di-1-chlorobutane 1.57 g. (0.005 moles) dissolved in 75 ml of absolute methanol, and the mixture refluxed for 15 minutes. The insoluble portion was removed by filtration and the filtrate diluted to 100 cc. and refluxed for an additional 20 hours to give the desired 2,2'-(ethylenediimino)di-1-methoxy butane *dl*.

Half of the reaction mixture obtained as described above was refluxed with 10 ml (0.19 mole) 48% hydrobromic acid for 20 hrs. to give *dl* 2,2'-(ethylenediimino)di-1-butanol (dihydrochloride, m.p. 176.5—178° C.).

EXAMPLE 16.

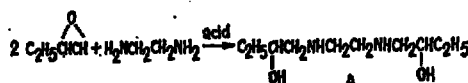
N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

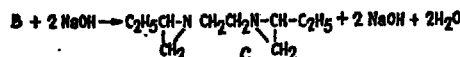
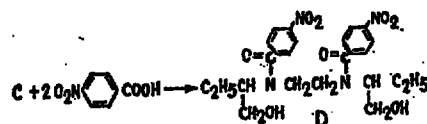


A solution of 11.3 g (0.1 mole) α-chloroacetylchloride in 50 ml benzene was added dropwise with cooling and stirring to a solution of 71.2 g (0.8 mole) 2-aminobutanol in 25 cc benzene. The pale yellow solution was refluxed for ½ hour and the resultant viscous oil neutralized by treatment with KOH. The precipitated KCl was removed by filtration, and the solvent and excess 2-amino butanol removed by distillation. The residue, the amino amide, was dissolved in 50 ml dioxane and reduced at 245° C., 3500 p.s.i. H₂, for 3½ hours using 3.3 g CuO·CuCr₂O₄ as catalyst to give the desired 2,2'-(ethylenediimino)di-1-butanol (*meso* base, m.p. 132.5—134° C.; *dl* dihydrochloride, m.p. 176.5—178° C.).

EXAMPLE 17.

N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.





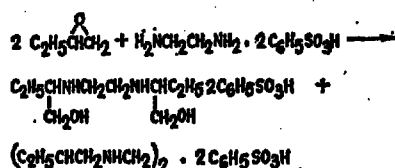
5 A mixture of 3.3 ml (3.0 g, 0.05 mole) of ethylene diamine and 7.2 g (0.10 mole) of 1,2-butylene oxide with a trace of an acidic ion exchange resin was refluxed for four hours with some white solid forming in the flask. On cooling, the mixture solidified and was dissolved in 40 ml. of boiling methanol.

10 The resin was removed by filtration and the methanol removed by distillation. To the solid residue was added 35 ml of chloroform and 15 ml (24 g, 0.2 mole) of thionyl chloride obtaining a vigorous reaction. The excess thionyl chloride and the chloroform were removed by distillation first at atmospheric pressure and then at 20 mm. The residue gave white solid from a methanol *n*-propanol, acetone mixture. To 3.3 g (0.01 mole) of this crude product was added 7.0 ml (0.07 mole) of 10N sodium hydroxide. The brown oil which separated was extracted with 10 ml of benzene. The benzene was removed and the residue dissolved in 30 ml of dioxane.

15 To this solution was added 4.0 g (0.024 mole) of *p*-nitrobenzoic acid and the solution was refluxed for 2 hours, allowing it to stand at room temperature overnight. The solution was then refluxed with 3.5 ml (0.035 mole) of 10N sodium hydroxide for 3 hours with solid depositing. From the dioxane solution after removing the sodium *p*-nitrobenzoate the desired *meso* (base, m.p. 132.5—134° C.) and *dl* (dihydrochloride, m.p. 176.5—178° C.) isomers of 2,2'-(ethylenediimino)-di-1-butanol could be isolated as previously described.

EXAMPLE 18.

40 N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

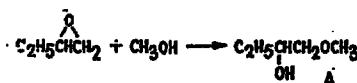
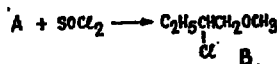
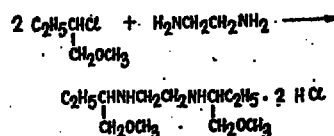
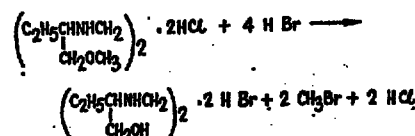


To 4.4 g (0.02 mole) of ethylenediamine dibenzenesulfonic acid salt dissolved in 15 ml of pyridine was added 2.9 g (0.04 mole) of 1,2-butylene oxide. The mixture was refluxed for about 4 hours. The pyridine was then removed under reduced pressure and from the solid residue by neutralization with alkali, extraction with butanol and chromatography the isomeric products [*dl* and *meso* 2,2'-(ethylenediimino) - di - 1 - butanol and *dl* and *meso* 1,1 - (ethylenediimino) - di - 2-butanol] could be separated.

Alternatively the mixture could be treated as in Example 18 converting it to a mixture of halides with thionyl chloride cyclizing to the bis butyleneimine derivative and opening to give the desired 2,2' - (ethylenediimino)-di-1-butanol isomers.

EXAMPLE 19.

60 N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.



To 72 g (1.0 mole) of 1,2-butylene oxide in 80 ml of absolute methanol was added 5.0 g (0.09 mole) of sodium methoxide. The

solution was refluxed for 20 hours during which time the vapor temperature rose from 57° to 67° C. On adding solid CO₂ a white precipitate formed and was removed by filtration. On distillation of the filtrate the 1-methoxy-2-butanol distilled at 135—139° C. as a colorless liquid.

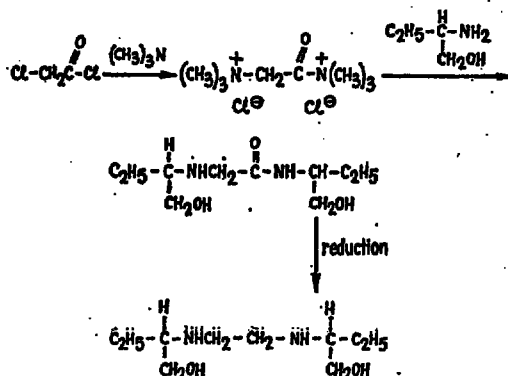
To 63 g (0.603 mole) of this methoxy alcohol in 25 ml of benzene was added 72 ml (1.0 mole) of thionyl chloride with stirring and cooling in an ice bath. The mixture was brought to room temperature over 40 min. and then refluxed for 1 hr. After distilling off the benzene and excess thionyl chloride, the residue was flash distilled at reduced pressure. On redistillation at 1 atm a center cut of 17.9 g of colorless oil was obtained at 115—128° C.

To 12.3 g (0.10 mole) of this chloromethoxybutane in 20 ml of ethanol was added 13.9 ml (0.10 mole) of triethylamine and 3.3 ml (0.05 mole) ethylene diamine. A reaction occurred on mixing these reagents with some solid depositing. The mixture was refluxed for 3 hours to complete the reaction.

A portion of this reaction mixture was heated for two hours with 70% aqueous sulfuric acid and from this mixture by the previously discussed isolation procedure both the *meso* (base, m.p. 132.5—134° C.) and *dl* (dihydrochloride m.p. 176.5—178° C) 2,2'-(ethylenediimino) - di - 1 - butanol isomer could be obtained.

EXAMPLE 20.

N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

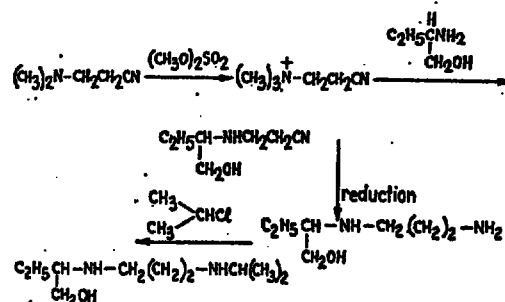


A. 113 g of chloroacetyl chloride in 50 ml. of 1,2-dimethoxyethane is reacted with 13.0 g (a 10% excess) of trimethylamine gas which is passed into the solution. After heat evolution subsides, the reaction mixture is heated at 50° C. and 17.8 g of 2-amino-1-butanol added. After the initial reaction, the mixture is refluxed for one hour and then the volatiles distilled off to give the amide as residue. This residue is used directly for reduction to the ethylenediamine, 2,2'-(ethylenediimino)di-1-butanol.

B. This reaction may be carried out using trimethylamine or triethylamine primarily as acid acceptor for the reaction of the halide groups but in any case the reaction probably goes partly through the quaternary intermediate.

EXAMPLE 21.

2 - [(3 - isopropylamino - n - propyl)amino] - 1-butanol.



To 9.8 g of β-dimethylaminopropionitrile in 50 ml. of 1,2-dimethoxyethane is added 6.3 g of dimethyl sulfate. After heating one-half hour at 80° C., 17.8 g of 2-amino-1-butanol is added and the temperature is raised to the boiling point. After refluxing for one hour, the reaction mixture is subjected to catalytic reduction and then reacted at the boiling point for one hour with 7.9 g 2-chloropropane. The product is isolated by the method described herein; b.p. 85—86° C./0.005 mm.

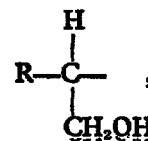
WHAT WE CLAIM IS:—

1. Hydroxy diamines of the formula



wherein

R₁ is the group



in which R is lower alkyl (of 1 to 6 carbons), R₂ and R₃ are the same or different and are hydrogen atoms, lower alkyl (of 1 to 6 carbons) or lower hydroxyalkyl groups (of 1 to 6 carbons),

R₄ is a lower alkyl (of 1 to 6 carbons) or lower hydroxyalkyl (of 1 to 6 carbons) group,

X is a lower alkyl-substituted or unsubstituted alkylene group having 2 or 3 carbon atoms separating the two nitrogen atoms and at least one of these carbon atoms forms a methylene group in the chain, and the non-toxic acid addition salts thereof.



5 solution was refluxed for 20 hours during which time the vapor temperature rose from 57° to 67° C. On adding solid CO₂ a white precipitate formed and was removed by filtration. On distillation of the filtrate the 1-methoxy-2-butanol distilled at 135—139° C. as a colorless liquid.

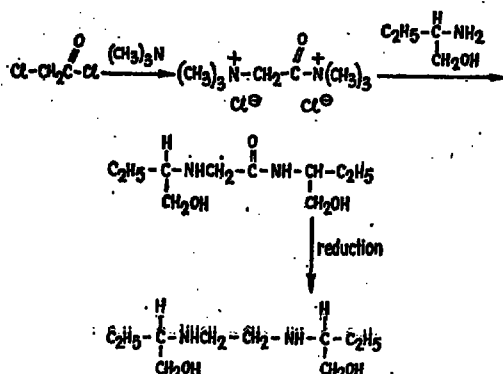
10 To 63 g (0.603 mole) of this methoxy alcohol in 25 ml of benzene was added 72 ml (1.0 mole) of thionyl chloride with stirring and cooling in an ice bath. The mixture was brought to room temperature over 40 min. and then refluxed for 1 hr. After distilling off the benzene and excess thionyl chloride, the residue was flash distilled at reduced pressure. On redistillation at 1 atm a center cut of 17.9 g of colorless oil was obtained at 115—128° C.

20 To 12.3 g (0.10 mole) of this chloromethoxybutane in 20 ml of ethanol was added 13.9 ml (1.0 mole) of triethylamine and 3.3 ml (0.05 mole) ethylene diamine. A reaction occurred on mixing these reagents with some solid depositing. The mixture was refluxed for 3 hours to complete the reaction.

25 A portion of this reaction mixture was heated for two hours with 70% aqueous sulfuric acid and from this mixture by the previously discussed isolation procedure both the *meso* (base, m.p. 132.5—134° C.) and *dl* (dihydrochloride m.p. 176.5—178° C) 2,2'-(ethylenediimino) - di - 1 - butanol isomer could be obtained.

EXAMPLE 20.

35 N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

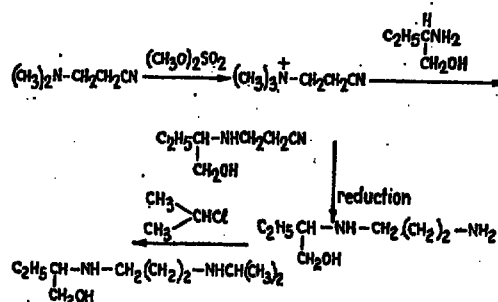


40 A. 113 g of chloroacetyl chloride in 50 ml. of 1,2-dimethoxyethane is reacted with 13.0 g (a 10% excess) of trimethylamine gas which is passed into the solution. After heat evolution subsides, the reaction mixture is heated at 50° C. and 17.8 g of 2-amino-45 butanol added. After the initial reaction, the mixture is refluxed for one hour and then the volatiles distilled off to give the amide as residue. This residue is used directly for reduction to the ethylenediamine, 2,2'-(ethylenediimino)di-1-butanol.

B. This reaction may be carried out using trimethylamine or triethylamine primarily as acid acceptor for the reaction of the halide groups but in any case the reaction probably goes partly through the quaternary intermediate.

EXAMPLE 21.

2 - [(3 - isopropylamino - n - propyl)amino]-1-butanol.



To 9.8 g of β-dimethylaminopropionitrile in 50 ml. of 1,2-dimethoxyethane is added 6.3 g of dimethyl sulfate. After heating one-half hour at 80° C., 17.8 g of 2-aminobutanol is added and the temperature is raised to the boiling point. After refluxing for one hour, the reaction mixture is subjected to catalytic reduction and then reacted at the boiling point for one hour with 7.9 g 2-chloropropane. The product is isolated by the method described herein; b.p. 85—86° C./0.005 mm.

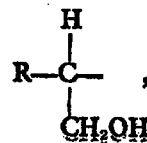
WHAT WE CLAIM IS:—

1. Hydroxy diamines of the formula



wherein

R₁ is the group



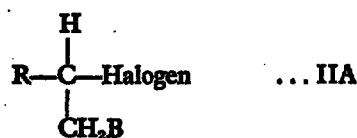
in which R is lower alkyl (of 1 to 6 carbons), R₂ and R₃ are the same or different and are hydrogen atoms, lower alkyl (of 1 to 6 carbons) or lower hydroxyalkyl groups (of 1 to 6 carbons),

R₄ is a lower alkyl (of 1 to 6 carbons) or lower hydroxyalkyl (of 1 to 6 carbons) group,

X is a lower alkyl-substituted or unsubstituted alkylene group having 2 or 3 carbon atoms separating the two nitrogen atoms and at least one of these carbon atoms forms a methylene group in the chain, and the non-toxic acid addition salts thereof.



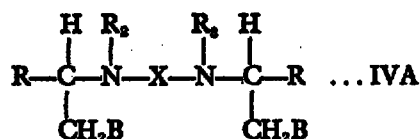
2. N - [N¹ - (α - methyl - β - hydroxyethyl) - β - aminoethyl] - β - methyl - β - aminoethanol.
- 5 3. N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.
4. N - [N¹ - (α - isopropyl - β - hydroxyethyl) - β - aminoethyl] - β - isopropyl - β - aminoethanol.
- 10 5. N - [N¹ - (isopropyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.
6. N - methyl - N - [N¹ - methyl - N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.
- 15 7. N - ethyl - N - [N¹ - (isopropyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.
8. N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - methyl - β - aminoethyl] - β - ethyl - β - aminoethanol.
- 20 9. N - [N¹ - (α - ethyl - β - hydroxyethyl) - γ - aminopropyl] - β - ethyl - β - aminoethanol.
10. N - (β - hydroxyethyl) - N - [N¹ - (β - hydroxyethyl) - N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.
- 25 11. N - ethyl - N - [N¹ - ethyl - N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.
- 30 12. N - [N¹ - (sec. - butyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.
13. N - [N¹ - (tert. - butyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.
- 35 14. N - [N¹ - (tert. - amyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.
15. A process for preparing the compounds of general formula I herein, in which two moles of



- 40 are condensed with one mole of



to form the following amine



- 45 wherein R, R₂, R₃ and X are as defined in claim 1 and B is a hydroxy group or a substituted hydroxy group (as hereinbefore defined).

16. A process for preparing the compounds of general formula I herein, in which two moles of



or the ketal of IIB are condensed under reducing conditions with one mole of



to form the following amine



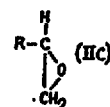
wherein R, R₂, R₃ and X are as defined in claim 1, and B is a hydroxy group or a substituted hydroxy group.

17. A process according to claim 16, wherein the amine of formula IIIA is produced *in situ* from the corresponding difunctional alkylene derivative



wherein Y is a nitrile, and X¹ is a lower alkyl-substituted or unsubstituted methylene radical and n is zero or one, or Y is a nitro group or an oximino or a hydroxylamino group and X¹ is the same as X in claim 1.

18. A process for preparing the compounds of general formula I herein, in which two moles of an ethylene compound of the formula:



are condensed with one mole of the following amine in the presence of a suitable acid catalyst

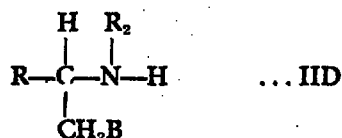


to form the following amine



wherein R, R₂, R₃ and X are as previously defined in claim 1.

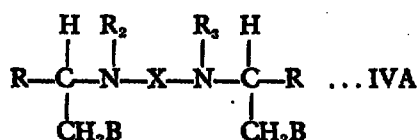
19. A process for preparing the compounds of general formula I herein, in which two moles of



5 are condensed with one mole of

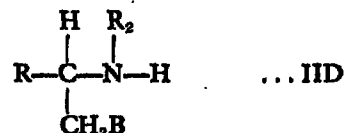


to form the following amine

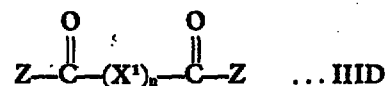


wherein R, R₂, R₃ and X are as defined in claim 1, and R₂ and R₃ are identical; and B is a hydroxy group or a substituted hydroxy group.

20. A process for preparing the compounds of general formula I herein, in which two moles of



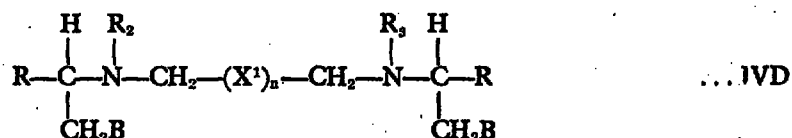
are condensed with one mole of



wherein Z is -OH or halogen or quaternary ammonium or -OR_s where R_s is an organic radical, to form

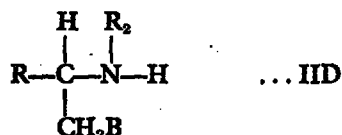


and the resulting compound IVC reduced to form

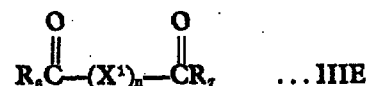


25 wherein R, R₂ and R₃ are as defined in claim 1, R₂ and R₃ being identical and X¹ is an unsubstituted or a lower alkyl-substituted methylene group and n is zero or 1, and B is a hydroxy group or a substituted hydroxy group.

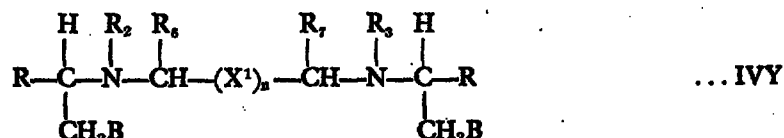
30 21. A process for preparing the compounds of general formula I herein, in which two moles of



are condensed under reducing conditions with

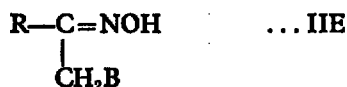


or the acetal of IIIE to form



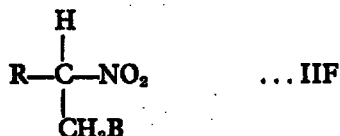
wherein R , R_2 and R_3 are as defined in claim 1, R_2 and R_3 being identical, R_4 and R_5 are the same or different and are hydrogen atoms or lower alkyl groups, X^1 is an unsubstituted or a lower alkyl-substituted methylene group, and n is zero or one, and B is a hydroxy group or a substituted hydroxy group.

22. A process according to claim 21, in which the compound of formula IID in which R_2 is hydrogen is prepared *in situ* by the reduction of the corresponding oximino compound of the formula:

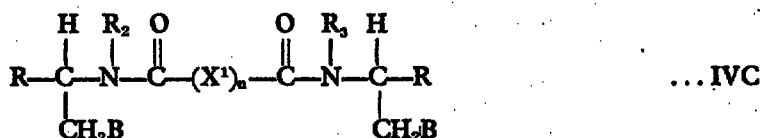


wherein R is as defined in claim 1, and B is a hydroxy group or a substituted hydroxy group.

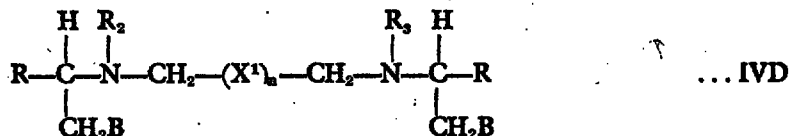
23. A process according to claim 21, in which the compound of formula IID in which R_2 is hydrogen is prepared *in situ* by the reduction of the corresponding nitro compound of the formula:



wherein R is as defined in claim 1, and B to form



and the resulting compound IVC reduced to form



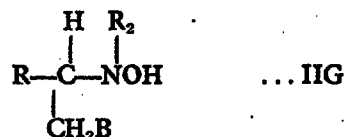
wherein R , R_2 and R_3 are as defined in claim 1, and X^1 is an unsubstituted or lower alkyl-substituted methylene group and n is zero or 1, and B is a hydroxy group or a substituted hydroxy group.

26. A process for preparing the compounds of general formula I herein, in which one mole of



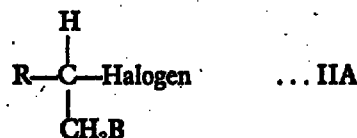
is a hydroxy group or a substituted hydroxy group.

24. A process according to claim 21, in which the compound of formula IID is prepared *in situ* by the reduction of the corresponding hydroxylamino compound of the formula:

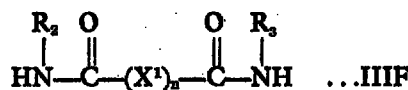


wherein R and R_2 are as defined in claim 1, and B is a hydroxy group or a substituted hydroxy group.

25. A process for preparing the compounds of general formula I herein, in which two moles of

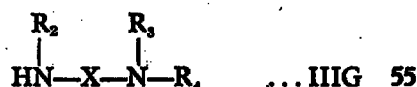


are condensed with one mole of a salt of

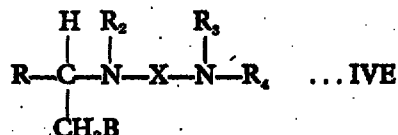


to form

is condensed with one mole of

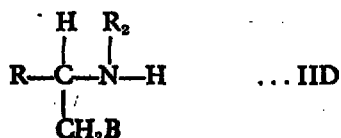


to form

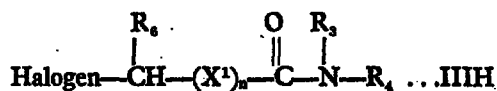


wherein R_1 , R_2 , R_3 , R_4 and X are as defined in claim 1, and B is a hydroxy group or a substituted hydroxy group.

- 5 27. A process for preparing the compounds of general formula I herein, in which one mole of

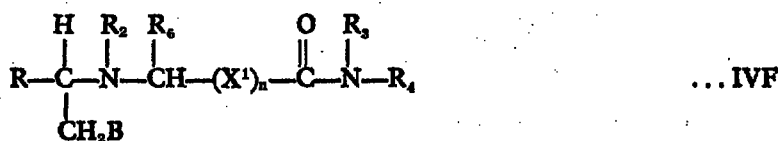


is condensed with one mole of

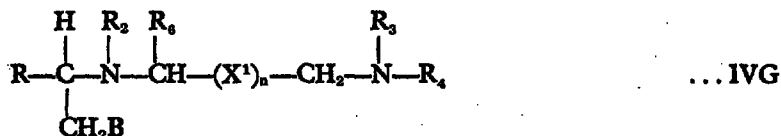


to form

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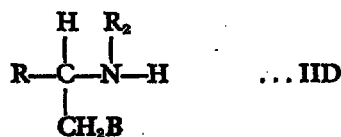


and the compound of formula IVF then reduced to form



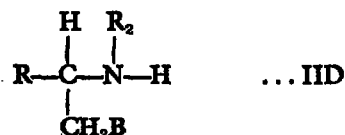
- 15 wherein R_1 , R_2 , R_3 and R_4 are as defined in claim 1, X^1 is a lower alkyl-substituted or unsubstituted methylene group, and n is zero or one and R_6 is a hydrogen atom or a lower alkyl group, and B is a hydroxy group or a substituted hydroxy group.

- 20 28. A process for preparing the compounds of general formula I herein, in which one mole of



wherein R_1 , R_2 , R_3 , R_4 and X are as defined in claim 1, and B is a hydroxy group or a substituted hydroxy group.

29. A process for preparing the compounds of general formula I herein, in which one mole of



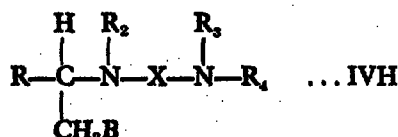
is condensed with one mole of

35

- 25 Halogen-X-N(R)₂ ... IIJJ

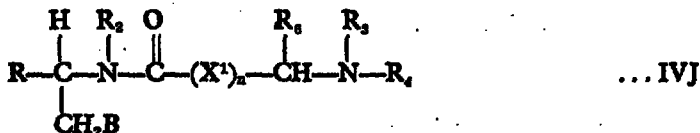


to form

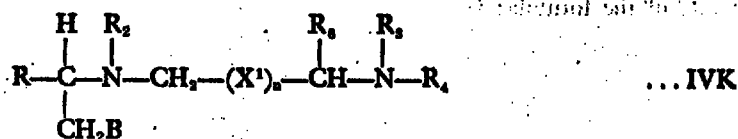


wherein Z is $-\text{OH}$, halogen or a quaternary ammonium group or $-\text{OR}_5$ where R_5 is an organic radical, and R_6 is a hydrogen atom or a lower alkyl group to form

40

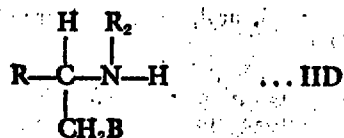


and the resulting compound IVJ reduced to form



wherein R , R_2 , R_3 and R_4 are as defined in claim 1, R_5 and R_6 are as defined above and X^1 is an unsubstituted or a lower alkyl-substituted methylene group and n is zero or 1, and B is a hydroxy group or a substituted hydroxy group.

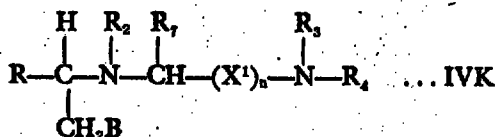
30. A process for preparing the compounds of general formula I herein, in which one mole of



is condensed under reducing conditions with one mole of

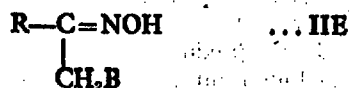


to form



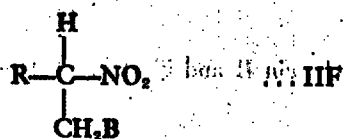
wherein R , R_2 , R_3 and R_4 are as defined in claim 1, R_7 is a hydrogen atom or a lower alkyl group, X^1 is a lower alkyl substituted or unsubstituted methylene group and n is one or two, and B is a hydroxy group or a substituted hydroxy group.

31. A process according to claim 30, in which the compound of formula IID in which R_2 is hydrogen is prepared *in situ* by the reduction of the corresponding oximino compound of the formula



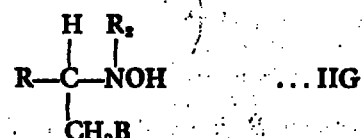
wherein R and B are as defined in claim 30.

32. A process according to claim 30, in which the compound of formula IID in which R_2 is hydrogen is prepared *in situ* by the reduction of the corresponding nitro compound of the formula:



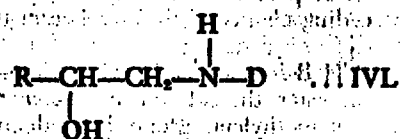
wherein R and B are as defined in claim 30.

33. A process according to claim 30, in which the compound of formula IID is prepared *in situ* by the reduction of the corresponding hydroxylamino compound of the formula:

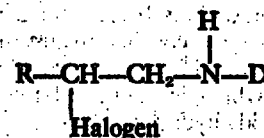


wherein R and R_2 and B are as defined in claim 30.

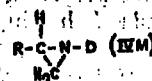
34. A process for preparing the compounds of general formula I herein, in which a compound of the formula:



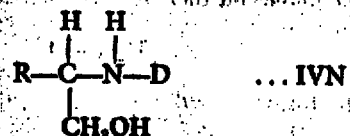
is treated with a halogenating agent to form



and the halo-derivative is then treated with base to form



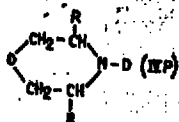
and the product of formula IVM treated with acid or base to form



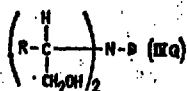
wherein R is as defined in claim 1, and wherein D is



35. A process for preparing the compounds of general formula I herein, in which a compound of the formula:



5 is treated with acid to form



wherein R is as defined in claim 1, and wherein D is



10 36. A process according to any one of the preceding claims 15 to 35, wherein the group-

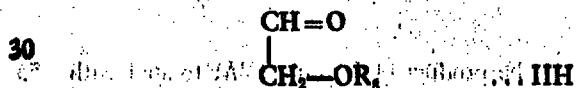
ing CH_2B forms a carboxylic acid ($-\text{COOH}$) or an ester thereof which is converted to a hydroxymethylene group by reduction.

15 37. A process according to any one of the preceding claims 15 to 36, wherein B is a halogen and is converted to a hydroxy group by hydrolysis with a base.

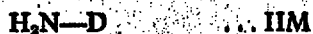
20 38. A process according to any one of the preceding claims 15 to 37, wherein B is an ether group which is converted to a hydroxy group by acid hydrolysis.

25 39. A process according to any one of the preceding claims 15 to 38, wherein B is an esterified hydroxy group which is converted to a hydroxy group by hydrolysis.

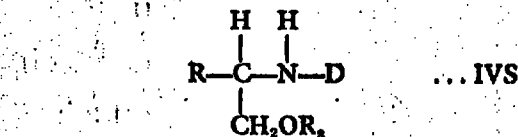
40. A process for preparing the compounds of general formula I herein, in which the following compound



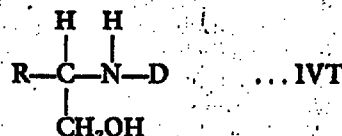
or the acetal thereof is condensed with



to form



which is then hydrolyzed to form



wherein R is as defined in claim 1 and R_s is an alkyl, aryl, or aralkyl group, and wherein D is



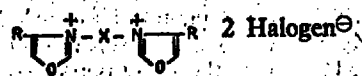
41. A process for preparing the compounds of general formula I herein, in which two moles of the following compound



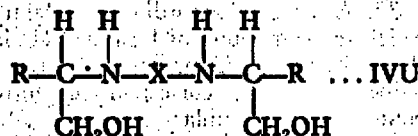
are condensed with one mole of



to form



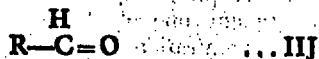
and the product then reduced and hydrolyzed to form



wherein R and X are as defined in claim 1.



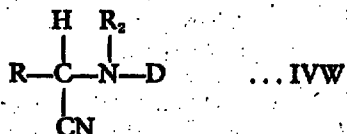
42. A process for preparing the compounds of general formula I herein, wherein one mole of



5 is condensed with



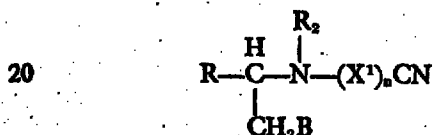
in the presence of hydrocyanic acid to form



10 and the nitrile group of the resulting compound then converted to a hydroxymethylene group by hydrolysis of the nitrile to an aldehyde, ester or acid followed by reduction wherein R and R₂ are as defined in claim 1, and wherein D is



43. A process according to any one of the preceding claims, in which R₂ and/or R₁ are inserted by treating a compound of the formula:



with a tertiary alcohol or an olefin containing a tertiary carbon atom using an acid catalyst and then reducing the amide so formed, wherein R₂ is hydrogen, R₁ is a tertiary alkyl group, X¹ is an unsubstituted or a lower alkyl-substituted methylene group and n is 0, 1 or 2.

44. The preparation of hydroxy diamines of formula I substantially as described.

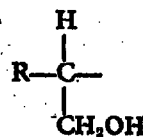
30 45. Hydroxy diamines of formula I whenever prepared substantially as described.

46. A pharmaceutical composition containing as an active ingredient at least one hydroxy diamine of the formula:



wherein

R₁ is the group



in which R is lower alkyl (of 1 to 6 carbons), R₂ and R₃ are the same or different and are hydrogen atoms, lower alkyl (of 1 to 6 carbons) or lower hydroxyalkyl groups (of 1 to 6 carbons),

R₄ is a lower alkyl (of 1 to 6 carbons) or lower hydroxyalkyl (of 1 to 6 carbons) group

X is a lower alkyl-substituted or unsubstituted alkylene group having 2 or 3 carbon atoms separating the two nitrogen atoms and at least one of these carbon atoms forms a methylene group in the chain, and the non-toxic acid addition salts thereof, and a pharmaceutically acceptable carrier.

47. A pharmaceutical composition according to claim 46, wherein the hydroxy diamine is N - [N¹ - (α - methyl - β - hydroxyethyl) - β - aminoethyl] - β - methyl - β - aminoethanol.

48. A pharmaceutical composition according to claim 46, wherein the hydroxy diamine is N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

49. A pharmaceutical composition according to claim 46, wherein the hydroxy diamine is N - [N¹ - (α - isopropyl - β - hydroxyethyl) - β - aminoethyl] - β - isopropyl - β - aminoethanol.

50. A pharmaceutical composition according to claim 46, wherein the hydroxy diamine is N - [N¹ - (isopropyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

51. A pharmaceutical composition according to claim 46, wherein the hydroxy diamine is N - methyl - N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

52. A pharmaceutical composition according to claim 46, wherein the hydroxy diamine is N - ethyl - N - [N¹ - (isopropyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

53. A pharmaceutical composition according to claim 46, wherein the hydroxy diamine is N - [N¹ - (α - ethyl - β - hydroxyethyl) - β - methyl - β - aminoethyl] - β - ethyl - β - aminoethanol.

54. A pharmaceutical composition according to claim 46, wherein the hydroxy diamine is N - [N¹ - (α - ethyl - β - hydroxyethyl) - γ - aminopropyl] - β - ethyl - β - aminoethanol.

55. A pharmaceutical composition according to claim 46, wherein the hydroxy diamine is N - (β - hydroxyethyl) - N - [N¹ - (β -



hydroxyethyl) - N^1 - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

- 5 56. A pharmaceutical composition according to claim 46, wherein the hydroxy diamine is N - ethyl - N - [N^1 - ethyl - N^1 - (α - ethyl - β - hydroxyethyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

- 10 57. A pharmaceutical composition according to claim 46, wherein the hydroxy diamine is N - [N^1 - (*sec.* - butyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

- 15 58. A pharmaceutical composition according to claim 46, wherein the hydroxy diamine is N - [N^1 - (*tert.* - butyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

59. A pharmaceutical composition accord-

ing to claim 46, wherein the hydroxy diamine is N - [N^1 - (*tert.* - amyl) - β - aminoethyl] - β - ethyl - β - aminoethanol.

- 20 60. A pharmaceutical composition according to any one of claims 46 to 59, wherein the concentration of the active ingredient of formula I is in the range of 10 mg. to 500

- 25 61. A pharmaceutical composition according to any one of claims 46 to 59, wherein the concentration of the active ingredient of formula I is from 0.6 g. to 30 g.

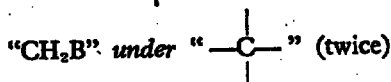
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ERRATA

SPECIFICATION No. 961,317

Page 4, line 22, Formula IV A, insert



Page 6, line 58, insert "of" after "each"

Pages 12 and 26, lines 26 and 32, for "IIM" read "IIIM"

Page 12, line 52, for " —C—O— " read " —C=O— "

Page 13, line 29, insert "an" after "x"

THE PATENT OFFICE
28th July 1964



* C L M S *