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N-SUBSTITUTED AMINO-ETHANOLS

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6 Claims. (Cl. 260—570.8)

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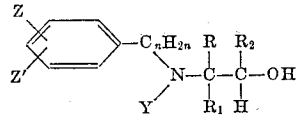
This invention relates to certain new chemical compounds, more particularly certain new amino alcohols. The new chemical compounds according to this invention have utility as intermediates for the preparation of certain new halogen-containing amines which have utility as physiologically active agents and, more particularly, have adrenolytic or sympathicolytic activity.

From the broad standpoint the new compounds according to this invention have the structure shown by the following formula:



in which:

n=3–9 incl. (is greater than 2 and less than 10) and chain may be straight or branched.

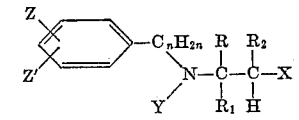
Z and Z′ are chosen from the group consisting of hydrogen, alkyl, hydroxy, alkoxy, halogen, amino, acylamino and alkylamino.

Y is a member of the group consisting of alkyl of less than 10 carbon atoms, alkenyl of less than 10 carbon atoms, cyclohexylalkyl in which the alkyl portion is less than 6 carbon atoms.

R, R_1 and R_2 are members of the group consisting of hydrogen and alkyl groups, the sum of the carbon atoms of which does not exceed six.

And organic and inorganic salts of said compounds.

The compounds in accordance with this invention will, for example, have utility as intermediates in the preparation of, for example, halogen amines having the structure exemplified by the following formula:



in which:

n=3–9 incl. (is greater than 2 and less than 10) and chain may be straight or branched.

Z and Z′ are chosen from the group consisting of hydrogen, alkyl, hydroxy, alkoxy, halogen, amino, acylamino and alkylamino.

Y is a member of the group consisting of alkyl of less than 10 carbon atoms, alkenyl of less than 10 carbon atoms, cyclohexylalkyl in which the alkyl portion is less than 6.

R, R_1 and R_2 are members of the group consisting of hydrogen and alkyl groups, the sum of the carbon atoms of which does not exceed six.

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X is a member of the group consisting of chlorine, bromine and fluorine.

And organic and inorganic salts of said compounds.

The above compounds form the subject-matter of a separate application for United States patent filed by us.

When in the several formulae given hereinafter in connection with description of procedure for the preparation of compounds according to this invention and as illustrative of specific compounds according to this invention the radicals are indicated by the symbols Z′, Z, Y, R, R_1, R_2 and X, they will be as given above.

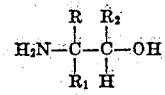
The compounds in accordance with this invention and as identified by the above structural formula may be prepared variously by one of three general methods, from the following general description of which procedure for the preparation of the several compounds will be apparent to those skilled in the art.

The compounds used as starting materials for the synthesis of compounds of this invention are either known substances or being made obvious can be prepared by well known methods.

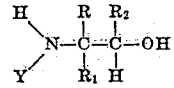
The organic and inorganic salts contemplated by this invention include by way of example salts of the bases formed with organic acids such, for example, as tartaric, succinic, glycolic, camphorsulfonic, etc. and inorganic acids such as, for example, sulfamic, hydrochloric, hydrobromic, sulfuric, phosphoric, etc.

METHOD A

Step 1.—A mixture or solution, in methyl alcohol, ethyl alcohol, acetic acid, or the like, of an amino alcohol of the type



and an aldehyde or ketone selected so that on reaction with the amino alcohol and hydrogenation will introduce the group Y, as, for example, benzylmethyl ketone, methyl isopropyl ketone, isovaleraldehyde, cyclohexyl acetone, is reduced with hydrogen in the presence of a hydrogenation catalyst as, for example, platinum, palladium, Raney nickel, or the like, to form a compound having the structure:



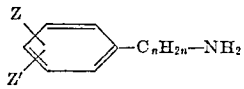
Step 2.—The product of step 1 above is then subjected to alkylation by means of a phenalkyl

halide, as, for example, phenylbutyl bromide, phenylpropyl bromide, or the like.

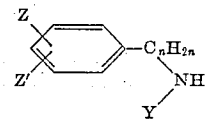
When the compounds are used as intermediates for the production of the halogen-containing amines described above, the hydroxy group is replaced by a halogen by treatment of the compounds produced, for example, by step 2 above, with a halogenating agent, as, for example, thionyl chloride, thionyl bromide, concentrated hydrobromic acid, or the like.

METHOD B

Step 1.—A mixture or solution, in methyl alcohol, ethyl alcohol, acetic acid, or the like, of a primary amine of the structure:

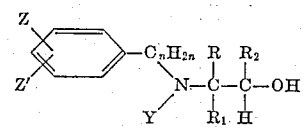


and an aldehyde or ketone selected so that on reaction with the primary amine and hydrogenation will introduce the group Y as, for example, benzyl methyl ketone, methyl isopropyl ketone, isovaleraldehyde, cyclohexyl acetone, is reduced with hydrogen in the presence of a hydrogenation catalyst as, for example, platinum, palladium, Raney nickel, or the like, to form a secondary amine having the structure:



The secondary amine may also be formed from an aralkyl aldehyde or ketone, such as benzyl methyl ketone, phenylbutyraldehyde, or the like, and a primary amine of the structure Y—NH_2.

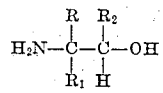
Step 2.—The secondary amine formed as above is reacted with an alkylene oxide, as, for example, ethylene oxide, propylene oxide, butylene oxide, or with an alkylene halohydrin to form an amino alcohol having the following structure:



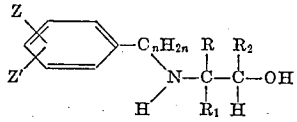
Procedure for producing halogen-containing amines using the product of Method B above will be the same as described with reference to use of the product of Method A above, i, e, replacement of the hydroxy group in the product of step 2 by a halogen by treatment with a halogenating agent.

METHOD C

Step 1.—A solution of an aralkyl aldehyde or ketone, such as phenylpropionaldehyde or benzylmethyl ketone and an amino alcohol of the type



is reduced with hydrogen in the presence of a hydrogenation catalyst in the manner described in Method A to form a compound having the structure



Step 2.—The product of step 1 above is then

subjected to alkylation with an alkyl halide alkenyl halide or cyclohexylalkyl halide such as isobutyl bromide, propyl bromide, allyl bromide, or the like.

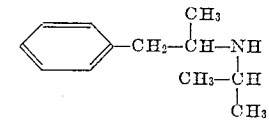
Procedure for use of the product of Method C above for the preparation of halide-containing amines will be as described above in Method A.

The following examples will be illustrative of the various types of compounds and of specific compounds in accordance with this invention and procedure for their preparation and will, it is believed, serve to make fully apparent all of the compounds embraced by the general formula given above and the preparation thereof, respectively, it being noted that the utility indicated for the several compounds flows from the existence of the OH group in the general structure common to all of them.

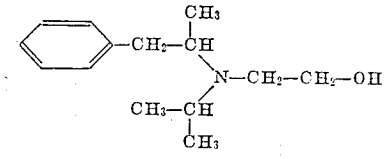
Example 1

N-(β - phenylisopropyl) - N - isopropylaminoethanol will be prepared by general Method B above as follows:

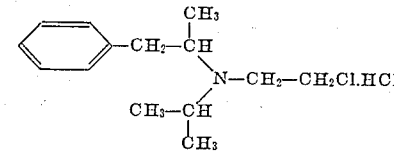
Step 1.—A solution of 201 grams of benzylmethyl ketone and 103.5 grams of isoproylamine in 150 ml. of alcohol are subjected to catalytic hydrogenation in the presence of platinum catalyst at 500 lbs. pressure. On distillation of the reaction mixture, there is obtained N-isopropyl-β-phenylisopropylamine, B. P. 60–65° C. at 3 mm. and having the formula:



Step 2.—A mixture of 126 grams of N-isopropyl-β-phenylisopropylamine and 28.8 grams of ethylene chlorohydrin is heated at 150–160° C. for five hours. The reaction mixture is shaken with sodium hydroxide solution and distilled to yield an oil boiling at 142–145° C. at 5 mm. having the formula:

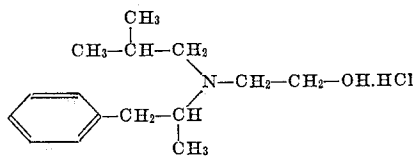


As illustrative of the production of a salt of halide-containing amine with the product of step 2 above, a solution of 35 g. of N-(β-phenylisopropyl) -N-isopropylaminoethanol in 50 ml. of chloroform is acidified with dry hydrogen chloride and then 23.8 grams of thionyl chloride are added and the solution heated at 50–55° for an hour. Evaporation of the solvent and recrystallization of the residue gives the end product, a solid melting at 128–129.5° C. and having the formula:



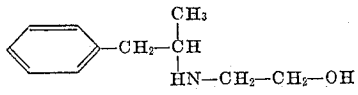
Example 2

N - (β - phenylisopropyl) - N - isobutylaminoethanol hydrochloride having the formula:

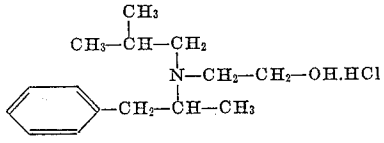


will be prepared by general Method C above as follows:

Step 1.—A solution of 122 g. of ethanolamine, 268 g. of benzyl methyl ketone and 300 cc. of alcohol is shaken in an atmosphere of hydrogen in the presence of platinum catalyst. After removal of the catalyst and solvent, the remainder is distilled in vacuo and the fraction boiling at 118–122°/3 mm. has the formula:



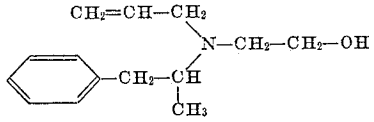
Step 2.—A mixture of 85 g. of N-(β-phenylisopropyl)-aminoethanol, 84.5 g. of isobutyl bromide and 40 g. of anhydrous potassium carbonate is stirred and refluxed for twelve hours. The liquid is then decanted from the solid and distilled to give 50 g. of oil boiling at 133–145°/3 mm. The distillate, comprising N-(β-phenylisopropyl)-N-isobutylaminoethanol, may be converted to the hydrochloride salt in ether solution and the salt is recrystallized several times from alcohol-ether mixtures to give N-(β-phenylisopropyl)-N-isobutylaminoethanol hydrochloride which melts at 118.5–119.5° C. and has the structure:



As illustrative of use of the product of Example 2, twenty grams of the hydrochloride prepared as described in step 2, 11 g. of thionyl chloride and 100 ml. of chloroform are heated at 50–60° C. for one and one-half hours. After the solvent is distilled in vacuo, the residue is recrystallized from alcohol and ether to yield the end product, N - (β-phenylisopropyl)-N-isobutyl-β-chlorethylamine hydrochloride which melts at 137–138° C.

Example 3

N - (β - phenylisopropyl)-N-allylaminoethanol having the following formula:

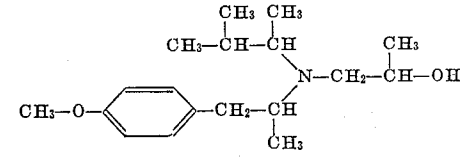


will be prepared by general Method C above, reducing benzylmethyl ketone and ethanolamine in step 1 and alkylating with allyl bromide in step 2. The hydrochloride salt, prepared from the free base, melts at 89–91° C.

A halide-containing amine salt will be prepared with this compound by reacting it with thionyl chloride, thus effecting substitution of a halogen radical for the OH group.

Example 4

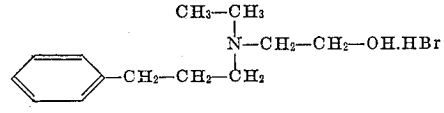
N - (2-methyl-3-butyl)-N-(p-methoxyphenylisopropyl)-aminoethanol having the following formula:



will be prepared by general Method B above, reducing a mixture of methyl isopropyl ketone and p-methoxyphenylisopropylamine in step 1 and reacting with 1-bromo-2-propanol in step 2, which will give N-(2-methyl-3-butyl)-N-(p-methoxyphenylisopropyl) - aminoethanol. Reacting with thionyl chloride will produce a halogen-containing amine salt.

Example 5

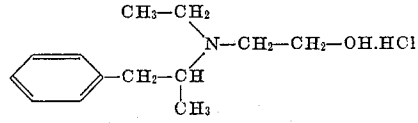
N - ethyl - N-(γ-phenylpropyl)-aminoethanol hydrobromide having the following formula:



will be prepared by general Method A above, reacting ethylaminoethanol (known compound) with γ-phenylpropyl bromide in step 2, which will give the amino alcohol. The above salt will be formed from the amino alcohol and dry hydrogen bromide in ether solution, and reacting the amino alcohol salt with thionyl bromide will give a halogen containing amine salt.

Example 6

N-(β-phenylisopropyl) - N - ethylaminoethanol hydrochloride having the following formula:



will be prepared by general Method C as follows:

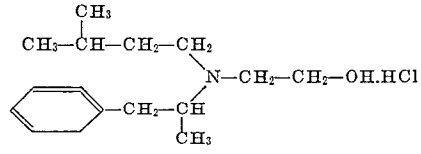
Step 1.—N-(β-phenylisopropyl)-aminoethanol is prepared as described in Example 2.

Step 2.—A mixture of 85 g. of N-(β-phenylisopropyl)-aminoethanol, 85 g. of ethyl iodide, 36 g. of anhydrous potassium carbonate and 100 ml. of alcohol is stirred and refluxed for four hours. The reaction mixture is diluted with water, the organic material extracted into ether and distilled. Forty-five grams of oil, comprising N-(β-phenylisopropyl)-N-ethylaminoethanol, is collected at 110° at 1 mm. and may be converted to the hydrochloride salt in ether solution. After recrystallization from alcohol and ether, the hydrochloride salt of N-(β-phenylisopropyl)-N-ethylaminoethanol melts at 110–112° C.

Using the above hydrochloride salt for production of a halogen containing amine salt, forty-six grams of the above hydrochloride, 35 g. of thionyl chloride and 150 ml. of chloroform is heated at 50° for two hours. The solvent is distilled in vacuo and the residue is recrystallized from alcohol and ether. The N-(β-phenylisopropyl)-N-ethyl-β-chloroethylamine hydrochloride so obtained melts at 160–160.5° C.

Example 7

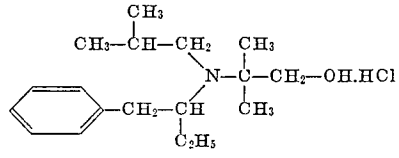
N - (isoamyl) - N - (β - phenylisopropyl) - aminoethanol hydrochloride having the following formula:



will be prepared by general Method B, reducing isovaleraldehyde and β-phenylisopropylamine in step 1, reacting with ethylene bromohydrin in step 2, which will give the amino alcohol. Reacting with hydrogen chloride will give the above salt of the alcohol.

Example 8

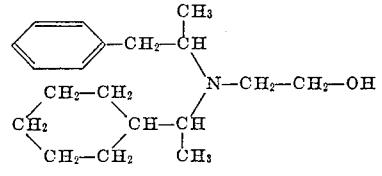
N - (isobutyl) - N - (1 - phenyl - 2 - butyl) - 2-amino-2-methylpropanol hydrochloride having the following formula:



will be prepared by general Method C, reducing a mixture of benzyl ethyl ketone and 2-amino-2-methyl-1-propanol in step 1, alkylating with isobutyl bromide in step 2, which will give the amino alcohol, and reacting with hydrogen chloride to obtain the above salt.

Example 9

N - (α - cyclohexylethyl) - N - (β - phenylisopropyl) -aminoethanol having the following formula:



will be prepared by general Method B, reducing a solution of methyl cyclohexyl ketone and β-phenylisopropylamine in step 1, alkylating the product with ethylene bromohydrin in step 2, which gives the amino alcohol. Reacting with thionyl chloride will give a halogen containing amine salt.

In the foregoing examples aminoethanols, aminoethanol hydrochlorides and hydrobromides according to this invention have been exemplified. It will, however, be understood that all of the several aminoethanols embraced within the scope of this invention as defined by the general formula given herein will be readily prepared by the general methods herein described as exemplified by the specific examples given herein and such, we believe, will be evident to those skilled in chemistry. Further, it will be understood that organic and inorganic salts of the several aminoethanols, as well as those more specifically mentioned herein, will be formed as generally described herein and as specifically described for the production of hydrochlorides and hydrobromides and such, we believe, will be obvious to anyone skilled in chemistry, it being made apparent from the foregoing disclosure that the several aminoethanols will react with organic and inorganic acids generally under known procedure.

It will be appreciated with reference to the foregoing examples that the aminoethanol product may be recovered in step 2 as the free base or in the form of a salt.

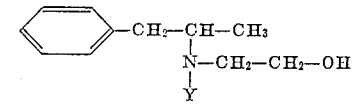
Special examples of aminoethanols and of organic and inorganic salts thereof and of those organic and inorganic salts specifically mentioned herein will be had by reference to the structural formulae given herein by substituting therein the several specific substituents given in connection with the general formula and, in the case of organic and inorganic salts of the aminoethanols, by the addition of the radical of any organic or inorganic acid to the amino group.

The compounds contemplated by this invention will be variously optically inactive or optically active and it will be understood that the optically active and optically inactive forms of the compounds contemplated by this invention are all included within the scope of this invention.

As has been indicated, the starting material for the preparation of any given compound having the structure contemplated by this invention will be found among known compounds or, the structure being obvious from the foregoing disclosure with reference to any given compound, will be readily prepared by known methods.

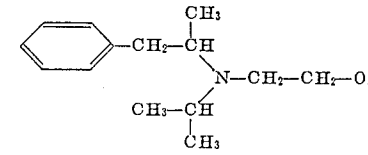
What we claim and desire to protect by Letters Patent is:

1. Compounds having the formula:

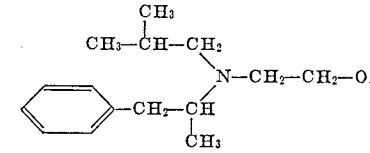


in which Y is a member of the group consisting of an allyl group and alkyl groups having not in excess of five carbon atoms and salts of said compounds.

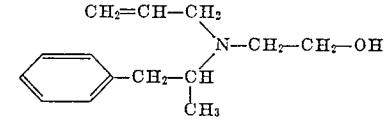
2. The compound having the formula:



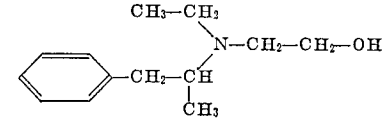
3. The compound having the formula:



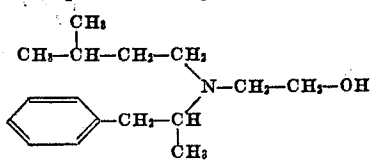
4. The compound having the formula:



5. The compound having the formula:



6. The compound having the formula:



JAMES F. KERWIN.
GLENN E. ULLYOT.

REFERENCES CITED

The following references are of record in the file of this patent:

UNITED STATES PATENTS

Number	Name	Date
2,229,187	Peyer	Jan. 21, 1941

FOREIGN PATENTS

Number	Country	Date
538,456	Germany	Nov. 13, 1931
718,398	France	Jan. 23, 1932
373,440	Great Britain	May 26, 1932
695,217	Germany	Aug. 20, 1940
536,881	Great Britain	May 30, 1941