

## UNITED STATES PATENT OFFICE

2,597,247

## N-SUBSTITUTED AMINO-ETHANOLS

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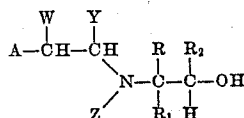
No Drawing. Application August 2, 1948,  
Serial No. 42,148

5 Claims. (Cl. 260—570.8)

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This invention relates to certain new chemical compounds, more particularly certain new amino alcohols and organic and inorganic salts thereof. The new chemical compounds according to this invention have utility as intermediates for the production of compounds useful as physiologically active agents and which, 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:

A is a member of the group consisting of aryl, substituted aryl, cyclohexyl, cyclopentyl and aralkyl groups.

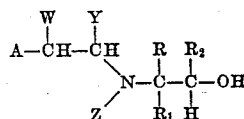
W is a member of the group consisting of hydrogen and alkyl groups containing not more than six carbon atoms.

Y is a member of the group consisting of alkyl groups having less than eight carbon atoms.

Z is a member of the group consisting of aralkyl, substituted aralkyl, aryl and substituted aryl groups.

R, R<sub>1</sub> and R<sub>2</sub> are members of the group consisting of hydrogen and alkyl groups such that the sum of the carbon atoms in R, R<sub>1</sub> and R<sub>2</sub> does not exceed six; and organic and inorganic salts thereof.

More particularly, preferential compounds according to this invention will have the following structure:



in which:

A is a member of the group consisting of aryl, substituted aryl in which the substitution is chosen from the group consisting of alkyl groups containing not more than 4 carbon atoms, a hydroxy group, alkoxy groups containing not more than 4 carbon atoms, chlorine, bromine, fluorine, amino, acylamino containing not more than 4 carbon atoms, alkylamino containing not more than 8 carbon atoms, cyclohexyl and aralkyl in which the alkyl part does not contain more than 4 carbon atoms.

W is a member of the group consisting of

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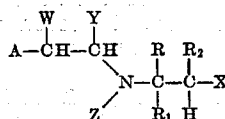
hydrogen and an alkyl group containing not more than 3 carbon atoms.

Y is a member of the group consisting of alkyl containing not more than 4 carbon atoms.

Z is a member of the group consisting of aralkyl containing not more than 4 carbon atoms in the alkyl portion, substituted aralkyl in which the substitution is chosen from the group consisting of alkyl groups containing not more than 4 carbon atoms, a hydroxy group, alkoxy groups containing not more than 4 carbon atoms, chlorine, bromine, fluorine, amino, acylamino containing not more than 4 carbon atoms, alkylamino containing not more than 8 carbon atoms.

R, R<sub>1</sub> and R<sub>2</sub> are members of the group consisting of hydrogen and alkyl groups such that the sum of the carbon atoms in R, R<sub>1</sub> and R<sub>2</sub> does not exceed six; and organic and inorganic salts of said compounds.

The compounds according to this invention will be useful as intermediates for the preparation of compounds having physiological properties, such, for example, as halogenated amines having the following structure:



in which:

A is a member of the group consisting of aryl, substituted aryl, cyclohexyl, cyclopentyl, and aralkyl groups.

W is a member of the group consisting of hydrogen and alkyl groups containing not more than six carbon atoms.

Y is a member of the group consisting of alkyl groups having less than eight carbon atoms.

Z is a member of the group consisting of aralkyl, substituted aralkyl, aryl and substituted aryl groups.

R, R<sub>1</sub> and R<sub>2</sub> are members of the group consisting of hydrogen and alkyl groups such that the sum of the carbon atoms in R, R<sub>1</sub> and R<sub>2</sub> does not exceed six.

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

And organic and inorganic salts of said compounds.

When in the several formulae given herein-  
after in connection with description of procedure  
for the preparation of compounds according to  
this invention and as illustrative of specific com-  
pounds according to this invention, the radicals

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are indicated by the symbols A, W, Y, Z, R, R<sub>1</sub>, R<sub>2</sub> and X, they will be as given above.

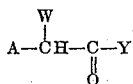
The compounds in accordance with this invention and as identified by the above structural formula may be prepared variously by one of two general methods, from the following general description of which procedure for the preparation of the several compounds will be apparent to those skilled in the art.

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.

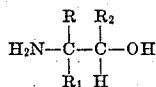
The organic and inorganic salts contemplated by this invention include, by way of example, salts formed with organic acids such, for example, as tartaric, succinic, glycolic, camphor-sulfonic, etc. and with inorganic acids such as, for example, sulfamic, hydrochloric, hydrobromic, sulfuric, phosphoric,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

## METHOD A

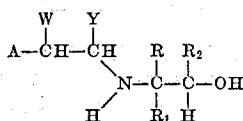
A mixture of a ketone of the type



and an amino alcohol of the type:



is reduced with hydrogen in the presence of a suitable hydrogenation catalyst, as, for example, platinum, palladium or Raney nickel with the production of an amino alcohol having the formula:



If desired, the ketone and amino alcohol may be first reacted to form a ketimine and such catalytically reduced. However, proceeding as first outlined above will generally be most convenient.

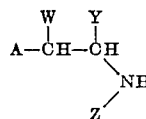
The amino alcohol so produced is reacted with a halogenated compound corresponding to the radical Z in the general formula above, such, for example, as benzyl chloride, which will introduce the group Z shown in the general formula above. The reaction will be accomplished by heating together the secondary amine and the alkylating agent, the temperature employed depending upon the reactivity of the halide chosen. In most cases, the reaction is conveniently carried out in alcohol solution in the presence of an acid binding agent such as potassium carbonate.

When used as an intermediate for the production of the halogen containing amine indicated above, the hydroxyl group of the amino alcohol is replaced by a halogen radical X in the general formula given above by reacting the amino alcohol with a halogenating agent such as, for example, with thionyl chloride, thionyl bromide, hydrochloric, or hydrobromic acid. The product will be obtained in the form of its hydrohalide salt.

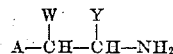
## METHOD B

A mixture of a ketone of the type indicated in connection with Method A above and a primary amine of the type Z—NH<sub>2</sub> are catalytically reduced to form a secondary amine of the type

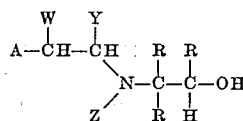
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The same secondary amine can be prepared by reduction of an aldehyde or ketone in which the group Z is included, such as benzaldehyde or benzyl methyl ketone, etc., in the presence of a primary amine of the type



The secondary amine so produced is then reacted with an alkylene halohydrin, such as ethylene bromhydrin, 1-bromo-2-propanol, or the like, or with an alkylene oxide, such as ethylene oxide, propylene oxide, or the like, to form an amino alcohol having the structure:



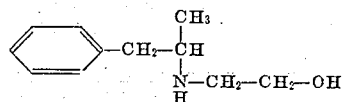
When used as an intermediate the amino alcohol is treated as above for replacement of the hydroxyl group by a halogen group as X in the general formula given above.

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 elements of the general structure common to all of them.

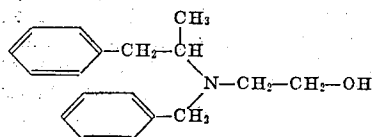
## Example 1

N - (β - phenylisopropyl) - N - benzylaminoethanol will be prepared by Method A 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 alcohol, the remainder was distilled in vacuo and the fraction boiling at 118–122°/3 mm. has the formula:



**Step 2.**—Six hundred grams of β-phenylisopropylaminoethanol, 416 g. of benzyl chloride, 238 g. of anhydrous potassium carbonate and 1000 cc. of alcohol are stirred and refluxed for six hours. Water is added to the reaction mixture and the organic material extracted into ether. Distillation yielded N-(β-phenylisopropyl)-N-benzyl aminoethanol, a colorless oil boiling at 161–169°/1 mm., corresponding to the formula:

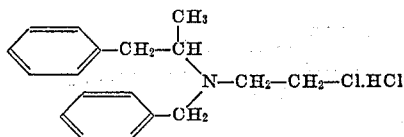


To form a salt of this base, it is added to aqueous hydrochloric acid to give the hydrochloride salt, melting at 201.5–203.5° C. Similarly, any

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organic or inorganic acid salt may be prepared.

The above compound will be used as an intermediate for the preparation of a halogenated amine salt as follows: A solution of 17 g. of the hydrochloride salt, N-( $\beta$ -phenylisopropyl)-N-benzyl-aminoethanol hydrochloride, and 13 g. of thionyl chloride in 100 cc. of chloroform is heated at 50–60° for an hour. Removal of the solvent and recrystallization of the residue from alcohol and ether gives N-( $\beta$ -phenylisopropyl)-N-benzyl- $\beta$ -chloroethylamine hydrochloride, a solid, M. P. 144–147° C. corresponding to the formula:

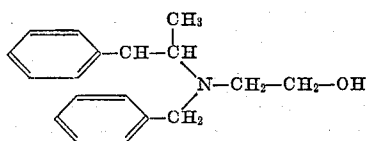


Example 2

N-( $\beta$ -phenylisopropyl)-N-benzylaminoethanol will be prepared by Method B above as follows:

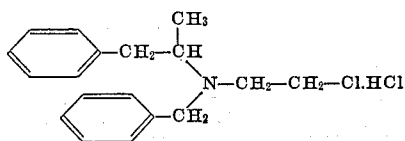
**Step 1.**—Fifty-three grams of benzaldehyde and 67 g. of  $\beta$ -phenylisopropylamine are mixed, the water formed in the reaction is separated and the residue hydrogenated in alcohol solution in the presence of platinum catalyst. Catalyst and solvent are removed and the product, N-benzyl- $\beta$ -phenylisopropylamine, distilled, B. P. 190–195° C./22 mm.

**Step 2.**—Eighty-five grams of N-benzyl- $\beta$ -phenylisopropylamine, 24 g. of ethylene bromohydrin and 100 cc. of toluene are refluxed for four hours. The reaction mixture is filtered and the filtrate distilled. The fraction boiling at 178–182° C. at 2 mm. corresponds to the formula:



This base may be converted to a salt. Thus, added to aqueous hydrochloric, it will give the hydrochloride salt melting at 201–204° C., or added to other organic or inorganic acids will give the salt corresponding to the acid selected.

As illustrative of use of the above compound as an intermediate, a solution of 17 g. of the hydrochloric salt, N-( $\beta$ -phenylisopropyl)-N-benzyl-aminoethanol hydrochloride, and 13 g. of thionyl chloride in 100 cc. of chloroform is heated at 50–60° for an hour. Removal of the solvent and recrystallization of the residue from alcohol and ether gives N-( $\beta$ -phenylisopropyl)-N-benzyl- $\beta$ -chloroethylamine hydrochloride, a solid, M. P. 144–147° C. corresponding to the formula:



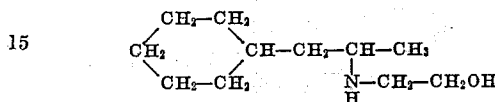
Following the above procedure using optically active  $\beta$ -phenylisopropylamine, the product compound will be optically active. Thus, where the d-isomer of  $\beta$ -phenylisopropylamine is used in step 1, dextrorotatory N-( $\beta$ -phenylisopropyl)-N-benzylaminoethanol, M. P. 137–139° C.,  $[\alpha]_D^{20} = +34.4$  ( $C = 8.00$  in ethanol) is formed as the end product.

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## Example 3

N-( $\beta$ -cyclohexylisopropyl)-N-benzylaminoethanol will be prepared by Method A above as follows:

**Step 1.**—Seventy grams of cyclohexylacetone are added to 30 g. of ethanolamine in 75 cc. of alcohol and the solution shaken with hydrogen in the presence of platinum catalyst. The solution is filtered from the catalyst, the alcohol removed and the residue distilled in vacuo. The fraction boiling at 154–158°/20 mm.,  $\beta$ -cyclohexylisopropylaminoethanol, has the formula:



**Step 2.**—A mixture of 114 g. of  $\beta$ -cyclohexylisopropylaminoethanol, 78 g. of benzyl chloride, 69 g. of anhydrous potassium carbonate and 100 cc. of alcohol are stirred and refluxed for six hours. The reaction mixture is diluted with water and extracted with ether. The ether solution is dried and distilled; the product, N-( $\beta$ -cyclohexylisopropyl)-N-benzylaminoethanol, boils at 170–179°/4 mm.

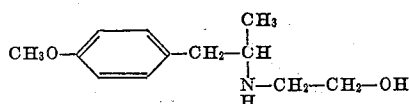
The distillate is converted into a salt by the addition of an acid, for example, hydrochloric, which gives it hydrochloride salt which melts at 121.5–123° C.

Using the above compound as an intermediate, twenty-eight grams of N-( $\beta$ -cyclohexylisopropyl)-N-benzylaminoethanol hydrochloride are added to 21 g. of thionyl chloride in 50 cc. of chloroform and the solution heated to 55–60° for an hour. The solvent is removed and the product, N-( $\beta$ -cyclohexylisopropyl)-N-benzyl- $\beta$ -chloroethylamine hydrochloride, recrystallized from a mixture of alcohol and ether, M. P. 145–147° C.

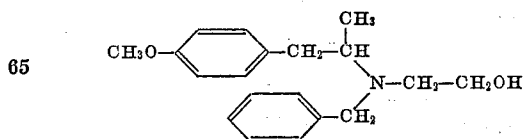
## Example 4

N-(p-methoxyphenylisopropyl)-N-benzylaminoethanol will be prepared by Method A above as follows:

**Step 1.**—A mixture of 82 g. of p-methoxyphenylacetone and 31 g. of ethanolamine is reduced as in Example 1 above to obtain p-methoxyphenylisopropylaminoethanol, an oil boiling at 154–157°/2 mm. and having the formula:



**Step 2.**—105 g. of p-methoxyphenylisopropylaminoethanol with 63 g. of benzyl chloride are then reacted in the presence of potassium carbonate as described in Example 1 above to obtain N-(p-methoxyphenylisopropyl)-N-benzylaminoethanol, an oil boiling at 190–195°/1 mm. and corresponding to the formula:

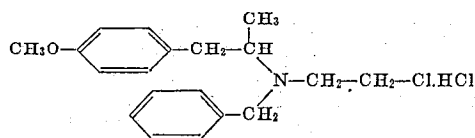


The hydrochloride prepared from the distillate melts at 143–144°.

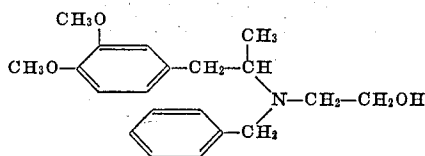
Using the above compound as an intermediate, 50 g. of N-(p-methoxyphenylisopropyl)-N-benzylaminoethanol hydrochloride, 36 g. of thionyl chloride and 100 cc. of chloroform are heated at 50–55° for an hour. After removal of the solvent

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and recrystallization of the residue, the N-(p-methoxyphenylisopropyl) - N - benzyl -  $\beta$  - chloroethylamine hydrochloride, a white solid, melts at 122-123° C. and corresponds to the formula:

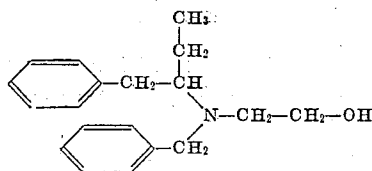


Example 5



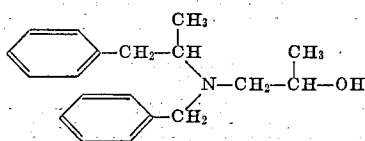
This compound will be prepared by the procedure described in Example 4 above using 3,4-dimethoxyphenylacetone in place of p-methoxyphenylacetone in step 1.

Example 6



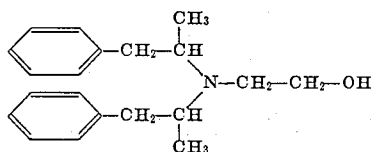
This compound will be prepared by the procedure described in Example 1 above using benzyl ethyl ketone in place of benzyl methyl ketone in step 1.

Example 7



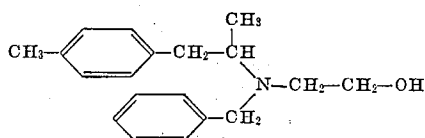
This compound will be prepared by the procedure described in connection with Example 1 above using isopropanolamine in place of ethanolamine in step 1.

Example 8



This compound will be prepared by the procedure described in Example 2 above using benzyl methyl ketone and  $\beta$ -phenylisopropylamine in step 1. The hydrochloride salt melts at 158.5-160° C.

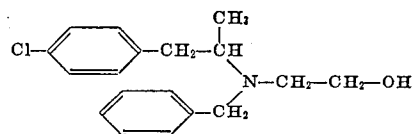
Example 9



This compound will be prepared according to the procedure described in Example 1 above using p-methylphenylacetone in place of benzyl methyl ketone in step 1.

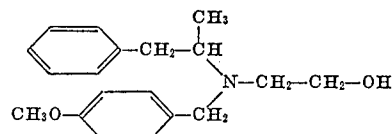
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Example 10



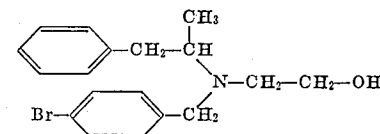
This compound will be prepared according to the procedure described in Example 1 above using p-chlorophenylacetone in place of benzyl methyl ketone in step 1.

Example 11



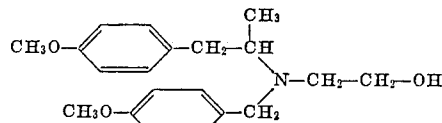
This compound will be prepared according to the procedure described in Example 1 above using p-methoxybenzyl chloride in place of benzyl chloride in step 2.

Example 12



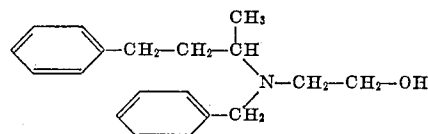
This compound will be prepared according to the procedure described in Example 1 above using p-bromobenzyl chloride in place of benzyl chloride in step 2.

Example 13



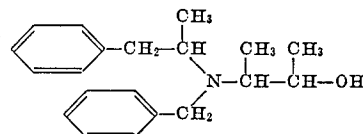
This compound will be prepared according to the procedure described in Example 4 above using p-methoxybenzyl chloride in place of benzyl chloride in step 2.

Example 14



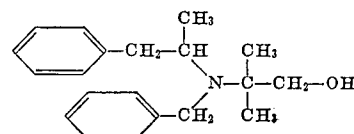
This compound will be prepared according to the procedure described in Example 1 above using benzylacetone in place of benzylmethyl ketone in step 1.

Example 15



This compound will be prepared according to the procedure described in Example 1 above using 3-amino-2-butanol in place of ethanolamine in step 1.

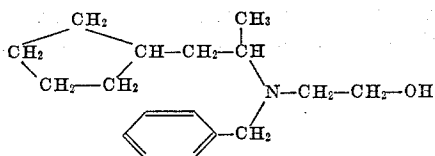
Example 16



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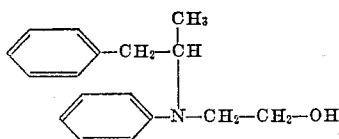
This compound will be prepared according to the procedure described in Example 1 above using 2-amino-2-methyl-1-propanol in place of ethanolamine in step 1.

## Example 17



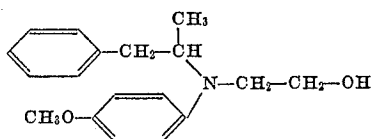
This compound will be prepared according to the procedure described in Example 1 above using cyclopentylacetone in place of benzyl methyl ketone in step 1.

## Example 18



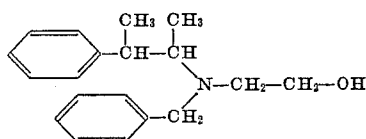
This compound will be prepared according to the procedure described in Example 2 above using benzyl methyl ketone and aniline in step 1.

## Example 19



This compound will be prepared according to the procedure described in Example 2 above using benzyl methyl ketone and p-anisidine in step 1 and reacting with ethylene bromohydrin in step 2.

## Example 20



This compound will be prepared according to the procedure described in Example 1 above using  $\beta$ -methyl- $\beta$ -phenylacetone in place of benzyl methyl ketone in step 1.

In the foregoing examples aminoethanols and aminoethanol hydrochlorides 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 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.

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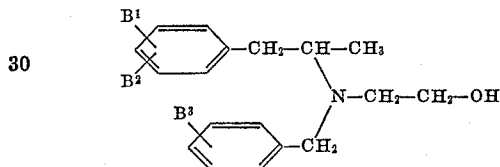
Specific examples of aminoethanols and of organic and inorganic salts thereof and of those organic and inorganic salts specifically mentioned herein will be had by reference to the structural formulae given herein by substituting therein the several specific substituents given in connection with the 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.

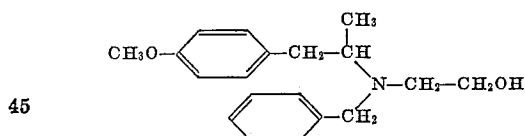
What we claim and desire to protect by Letters Patent is:

1. Compounds having the formula:

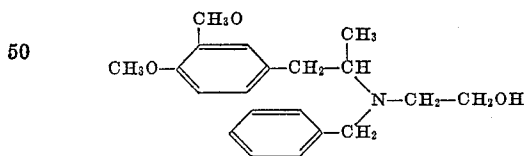


in which B<sup>1</sup>, B<sup>2</sup> and B<sup>3</sup> are members of the group consisting of hydrogen and methoxy, the substituents for B<sup>1</sup>, B<sup>2</sup> and B<sup>3</sup>, respectively, being so selected that the total number of carbon atoms included therein will be from 1 to 3 in number.

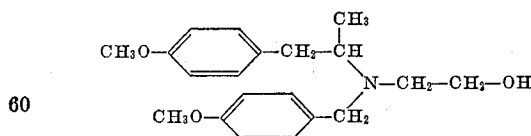
2. The compound having the formula:



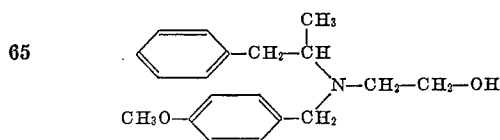
3. The compound having the formula:



4. The compound having the formula:



5. The compound having the formula:



JAMES F. KERWIN.  
GLENN E. ULLYOT.

**11****REFERENCES CITED**

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

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| 695,217 |
| 536,881 |

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| Great Britain | May 26, 1932  |
| Germany       | Aug. 20, 1940 |
| Great Britain | May 30, 1941  |