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N-SUBSTITUTED-BETA HALO-ETHYL AMINES

James F. Kerwin and Glenn E. Ullyot, Philadelphia, Pa., assignors to Smith, Kline & French Laboratories, Philadelphia, Pa., a corporation of Pennsylvania

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6 Claims. (Cl. 260—570.9)

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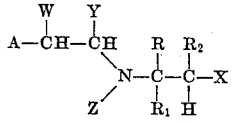
This invention relates to certain new chemical compounds, more particularly certain new halogen-containing amines and organic and inorganic salts thereof. The new chemical compounds according to this invention have utility as physiologically active agents and, more particularly, have adrenolytic or sympathicolytic activity.

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



in which:

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.

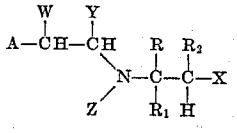
Y is a member of the group consisting of alkyl groups having less than eight carbon atoms.

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

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

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

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

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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_1 and R_2 are members of the group consisting of hydrogen and alkyl groups such that the sum of the carbon atoms in R, R_1 and R_2 does not exceed six.

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

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 A, W, Y, Z, R, R_1, R_2 and X, they will be as given above.

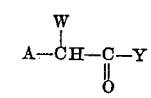
The compounds in accordance with this invention and as identified by the above structural formula may be prepared variously by one of three general methods, from the following general description of which procedure for the preparation of the several compounds will be apparent to those skilled in the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

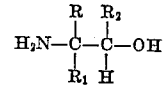
The organic and inorganic salts contemplated by this invention include by way of example salts of the bases formed with organic acids such, for example, as tartaric, succinic, glycolic, camphorsulfonic, etc. and inorganic acids such as, for example, sulfamic, hydrochloric, hydrobromic, sulfuric, phosphoric,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

METHOD A

A mixture of an aldehyde or ketone of the type

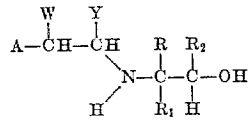


and an amino alcohol of the type:



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:



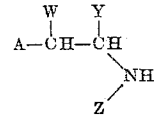
If desired, the aldehyde or ketone and amino alcohol may be first reacted to form an aldimine or ketimine and such catalytically reduced. However, proceeding as first outlined above will generally be most convenient.

The amino alcohol so produced is then 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.

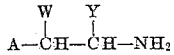
Finally, the hydroxyl group of the amino alcohol is replaced by a halogen radical X in the general formula given above by reacting the amino alcohol with a halogenating agent such as, for example, with thionyl chloride, thionyl bromide, hydrochloric, or hydrobromic acid. The product will be obtained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

METHOD B

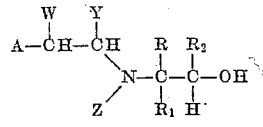
A mixture of aldehyde and ketone of the type indicated in connection with Method A above and a primary amine of the type Z—NH_2 are catalytically reduced to form a secondary amine of the type



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



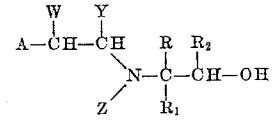
The secondary amine so produced is then reacted with an alkylene halohydrin, such as ethylene bromhydrin, 1-bromo-2-propanol, or the like, or with an alkylene oxide, such as ethylene oxide, propylene oxide, or the like, to form an amino alcohol having the structure:



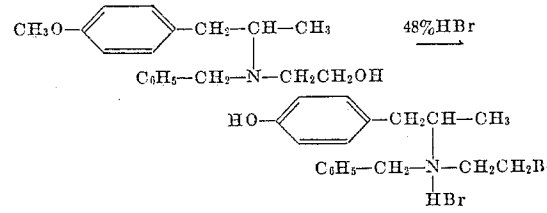
and the amino alcohol is finally treated with a halogenating agent as in Method A above for replacement of the hydroxyl group by a halogen group as X in the general formula given above.

METHOD C

Compounds containing one or more hydroxyl groups attached to an aromatic nucleus in groups A, Y or Z can be obtained from the corresponding methoxy containing β-hydroxyethylamines of the general formula



by heating a methoxy-containing compound of the above type with a hydrohalide acid, such as concentrated hydrobromic acid. The methoxy grouping is converted into a hydroxy group and, simultaneously, the aliphatic hydroxy group is replaced by halogen to form a β-haloethylamine. The reaction according to this method will be made apparent by the following example:

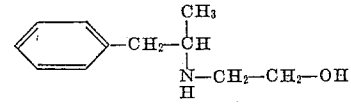


The following examples will be illustrative of the various types of compounds and of specific compounds in accordance with this invention and procedure for their preparation and will, it is believed, serve to make fully apparent all of the compounds embraced by the general formula given above and the 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.

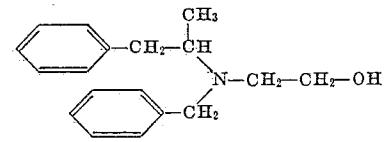
Example 1

N-(β-phenylisopropyl)-N-benzyl-β-chlorethylamine hydrochloride 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:



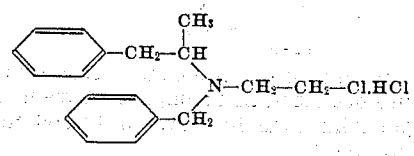
Step 2.—Six hundred grams of β-phenylisopropylaminoethanol, 416 g. of benzyl chloride, 238 g. of anhydrous potassium carbonate and 1000 cc. of alcohol are stirred and refluxed for six hours. Water is added to the reaction mixture and the organic material extracted into ether. Distillation yielded N-(β-phenylisopropyl)-N-benzyl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



This base is added to aqueous hydrochloric acid to give the hydrochloride salt melting at 201.5–203.5° C.

Step 3.—A solution of 17 g. of the hydrochloride salt, N-(β-phenylisopropyl)-N-benzylaminoethanol 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-(β-phenylisopropyl)-N-benzyl-β-chlorethylamine hydrochloride, a solid, M. P. 144–147° C. corresponding to the formula:

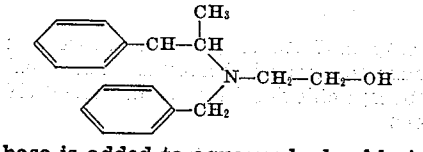


Example 2

N-(β-phenylisopropyl)-N-benzyl-β-chlorethylamine hydrochloride will be prepared by Method B above as follows:

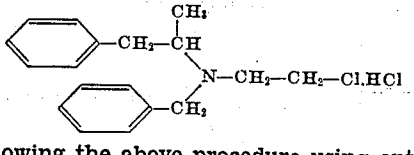
Step 1.—Fifty-three grams of benzaldehyde and 67 g. of β-phenylisopropylamine are mixed, the water formed in the reaction is separated and the residue hydrogenated in alcohol solution in the presence of platinum catalyst. Catalyst and solvent are removed and the product, N-benzyl-β-phenylisopropylamine,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

Step 2.—Eighty-five grams of N-benzyl-β-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 is added to aqueous hydrochloric acid to give the hydrochloride salt melting at 201–204° C.

Step 3.—A solution of 17 g. of the hydrochloric salt, N-(β-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-(β-phenylisopropyl)-N-benzyl-β-chlorethylamine hydrochloride, a solid, M. P. 144–147° C. corresponding to the formula:

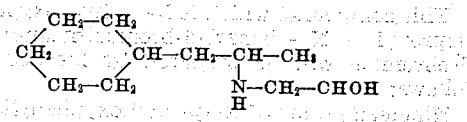


Following the above procedure using optically active β-phenylisopropylamine, the product compound will be optically active. Thus, where the d-isomer of β-phenylisopropylamine is used in Step 1, dextrorotatory N-(β-phenylisopropyl)-N-benzyl-β-chlorethylamine hydrochloride, M. P. 131.5–133° C., $[\alpha]_D^{20}=+37.9$ (C=8.00 in ethanol), is formed as the end product.

Example 3

N-(β-cyclohexylisopropyl)-N-benzyl-β-chlorethylamine hydrochloride 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., β-cyclohexylisopropylaminoethanol, has the formula:



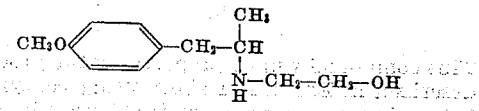
Step 2.—A mixture of 114 g. of β-cyclohexylisopropylaminoethanol, 78 g. of benzyl chloride, 69 g. of anhydrous potassium carbonate and 100 cc. of alcohol are stirred and refluxed for six hours. The reaction mixture is diluted with water and extracted with ether. The ether solution is dried and distilled; the product, N-(β-cyclohexylisopropyl)-N-benzylaminoethanol, boils at 170–179°/4 mm. The distillate is converted into its hydrochloride salt which melts at 121.5–123° C.

Step 3.—Twenty-eight grams of N-(β-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-(β-cyclohexylisopropyl)-N-benzyl-β-chlorethylamine hydrochloride, recrystallized from a mixture of alcohol and ether, M. P. 145–147° C.

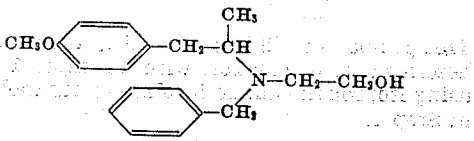
Example 4

N-(p-methoxyphenylisopropyl)-N-benzyl-β-chlorethylamine hydrochloride 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:

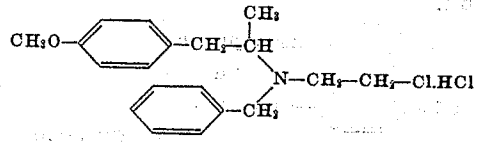


Step 2.—105 g. of p-methoxyphenylisopropylaminoethanol with 63 g. of benzyl chloride are then reacted in the presence of potassium carbonate as described in Example 1 above to obtain N-(p-methoxyphenylisopropyl)-N-benzylaminoethanol, an oil boiling at 190–195°/1 mm. and corresponding to the formula:

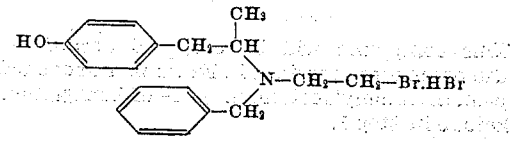


The hydrochloride prepared from the distillate melts at 143–144°.

Step 3.—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 and recrystallization of the residue, the N-(p-methoxyphenylisopropyl)-N-benzyl-β-chlorethylamine hydrochloride, a white solid, melts at 122–123° C. and corresponds to the formula:



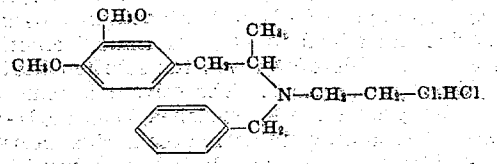
Example 5



This compound, which is N-(p-hydroxyphenylisopropyl) - N - benzyl-β-bromoethylamine hydrobromide will be prepared by Method C as follows:

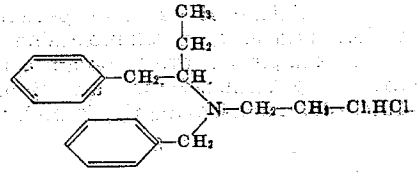
Nineteen grams of N-(p-methoxyphenylisopropyl)-N-benzylaminoethanol, prepared as described in Example 4, is heated with 35 ml. of 48% hydrobromic acid and 0.5 ml. of hypophosphorus acid at 100–110° C. for an hour and then at 126° C. for five hours. The excess acid is distilled in vacuo and the residue is recrystallized from a mixture of alcohol and ether. The N-(p-hydroxyphenylisopropyl)-N-benzyl-β - bromoethylamine hydrobromide so obtained melts at 178.5–181.5° C.

Example 6



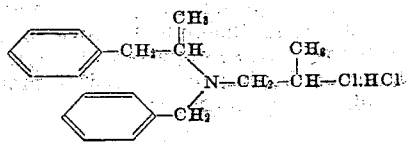
This compound will be prepared by the procedure described in Example 4 above using 3,4-dimethoxyphenylacetone in place of p-methoxyphenylacetone in Step 1.

Example 7



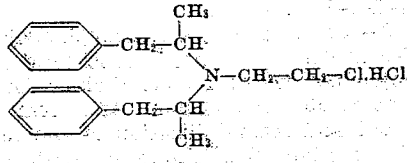
This compound will be prepared by the procedure described in Example 1 above using benzyl ethyl ketone in place of benzyl methyl ketone in Step 1.

Example 8



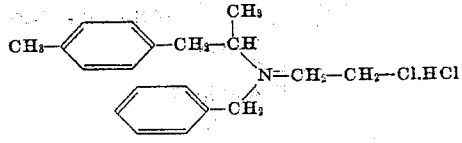
This compound will be prepared by the procedure described in connection with Example 1 above using isopropanolamine in place of ethanolamine in Step 1.

Example 9



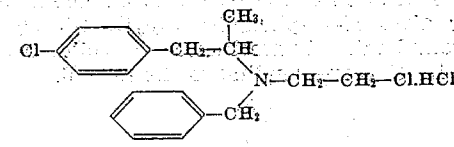
This compound will be prepared by the procedure described in Example 2 above using benzyl methyl ketone and β-phenylisopropylamine in Step 1.

Example 10



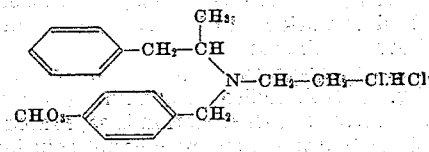
This compound will be prepared according to the procedure described in Example 1 above using p-methylphenylacetone in place of benzyl methyl ketone in Step 1.

Example 11



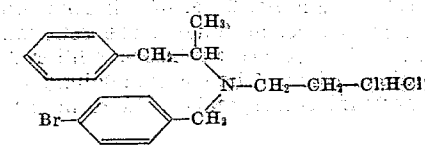
This compound will be prepared according to the procedure described in Example 1 above using p-chlorophenylacetone in place of benzyl methyl ketone in Step 1.

Example 12



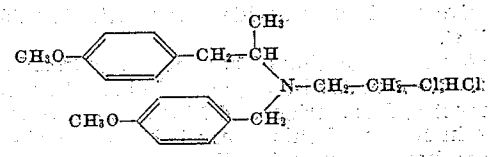
This compound will be prepared according to the procedure described in Example 1 above using p-methoxybenzyl chloride in place of benzyl chloride in Step 2.

Example 13



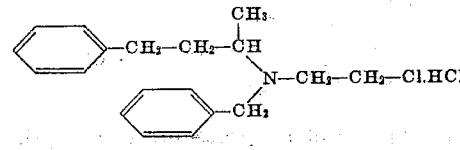
This compound will be prepared according to the procedure described in Example 1 above using p-bromobenzyl chloride in place of benzyl chloride in Step 2.

Example 14



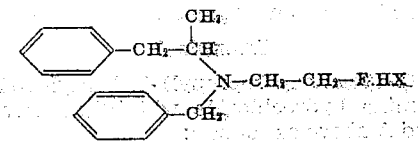
This compound will be prepared according to the procedure described in Example 4 above using p-methoxybenzyl chloride in place of benzyl chloride in Step 2.

Example 15



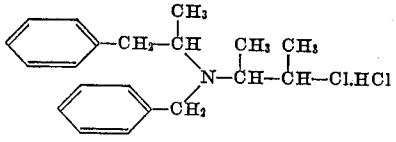
This compound will be prepared according to the procedure described in Example 1 above using benzylacetone in place of benzylmethyl ketone in Step 1.

Example 16



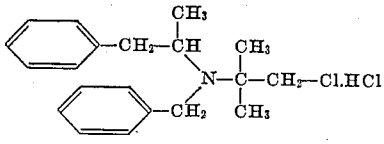
This compound will be prepared by heating N-benzyl-β-phenylisopropylamine, which is obtained as described in Example 2, with β-fluoroethyl bromide in a manner similar to that described in Step 2 of Example 2. In this instance the β-fluorethylamine is obtained directly by distillation in vacuo or by isolation in the form of a hydrohalide salt.

Example 17



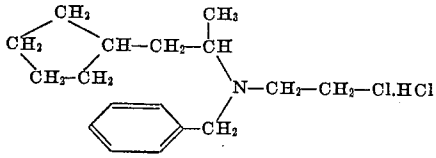
This compound will be prepared according to the procedure described in Example 1 above using 3-amino-2-butanol in place of ethanolamine in Step 1.

Example 18



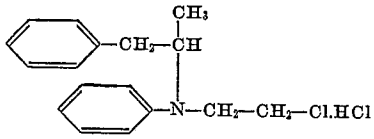
This compound will be prepared according to the procedure described in Example 1 above using 2-amino-2-methyl-1-propanol in place of ethanolamine in Step 1.

Example 19



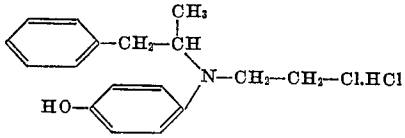
This compound will be prepared according to the procedure described in Example 1 above using cyclopentylacetone in place of benzyl methyl ketone in Step 1.

Example 20



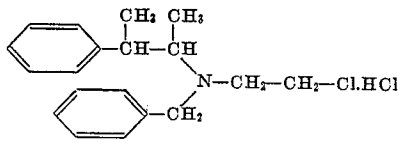
This compound will be prepared according to the procedure described in Example 2 above using benzyl methyl ketone and aniline in Step 1.

Example 21



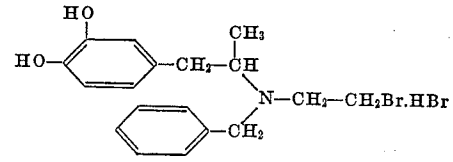
This compound will be prepared according to the procedure described in Example 2 above using benzyl methyl ketone and p-anisidine in Step 1 and effecting demethylation as described in connection with procedure in accordance with the Method C above.

Example 22



This compound will be prepared according to the procedure described in Example 1 above using β-methyl-β-phenylacetone in place of benzyl methyl ketone in Step 1.

Example 23



This compound will be prepared by treating N - (3,4 - dimethoxyphenylisopropyl) -N-benzyl-aminoethanol, the intermediate obtained in the preparation of Example 6, with concentrated hydrobromic acid according to general Method C.

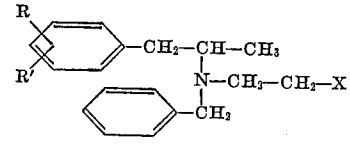
In the foregoing examples hydrochlorides and hydrobromides are exemplified. However, it will be understood that the foregoing examples will illustrate other organic and inorganic salts by the substitution in the several formulae for the HCl or HBr group of the desired acid group.

The foregoing examples illustrate the salts contemplated by this invention. The bases contemplated by this invention will be formed by interacting the salts with one molecular equivalent of a strong alkali, such as sodium hydroxide, potassium hydroxide, lithium hydroxide, or the like, in aqueous solution, say, for example, a 10%–40% solution. The foregoing examples will serve to illustrate the structure of the bases contemplated by this invention with elimination of the acid group from the formulae. It will be appreciated that the salts contemplated by this invention may be prepared by neutralizing the bases with the desired acid.

The compounds contemplated by this invention will be various optically inactive or optically active.

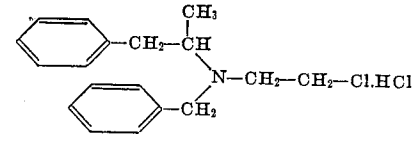
What we claim and desire to protect by Letters Patent is:

1. A compound having the structure

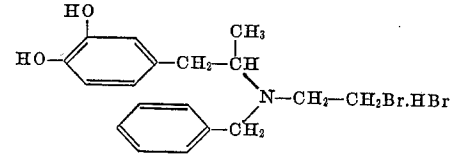


in which R and R' are members of the group consisting of hydrogen, alkyl groups containing not more than 4 carbon atoms, a methoxy group, a hydroxy group, fluorine, chlorine and bromine and X is a member of the group consisting of chlorine and bromine; and acid addition salts of said compounds.

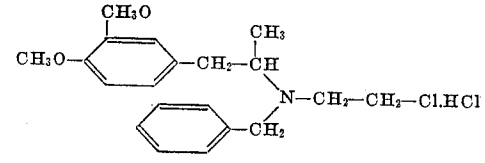
2. A compound having the following structure



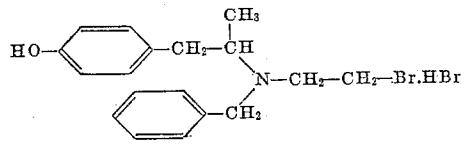
3. A compound having the structure



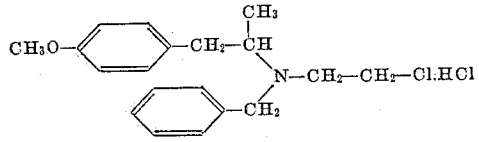
4. A compound having the structure



5. A compound having the structure



6. A compound having the structure



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
1,949,247	Eisleb	Feb. 27, 1934
2,006,114	Rosenmund et al.	June 25, 1935
2,276,618	Kulz	Mar. 17, 1942

FOREIGN PATENTS

Number	Country	Date
536,881	Great Britain	May 30, 1941

OTHER REFERENCES

Blicke et al.: "J. Am. Chem. Soc.," vol. 61, pp. 771–773 (1931).

Kulz et al.: "Ber. deut. Chem.," vol. 72, 2161–2767 (1939).

Nickerson et al.: Federation Proceedings, vol. 5, pp. 194–195 (1946).