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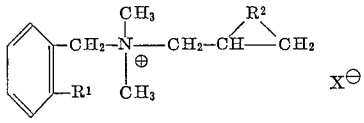
N,N-DIMETHYL-N-(2,3-EPOXYPROPYL)-o-SUBSTITUTED BENZYLAMMONIUM SALTS

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6 Claims. (Cl. 260—348)

This invention relates to certain quaternary amines of therapeutic value in the treatment of depression and more particularly to N,N-dimethyl-N-(2,3-epoxypropyl)-o-substituted benzylammonium salts and N,N-dimethyl-N-(2,3-epithiopropyl)-o-substituted benzylammonium salts. It is the object of the present invention to provide chemical compounds which will serve to counteract psychic depression without stimulating motor activity or appearing to stimulate the central nervous system.

There is provided by the present invention a compound selected from the group having the formula



wherein R^1 is selected from the group consisting of fluoro, chloro, bromo, iodo and lower alkyl, R^2 is sulfur or oxygen but preferably oxygen, and $X^{\ominus}$ represents one equivalent of a nontoxic anion.

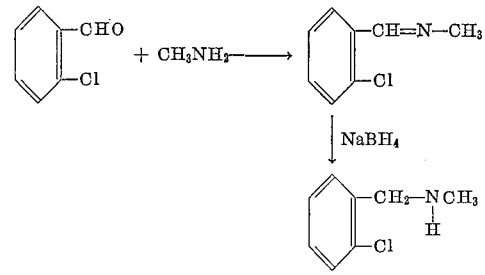
The term lower alkyl as used in the specification and claims includes radicals containing one to six carbon atoms inclusive, e.g. methyl, ethyl, n-propyl, isopropyl, isobutyl, n-amyl, n-hexyl, isohexyl, 2-ethylbutyl, and the like.

The preferred nontoxic anions represented by $X^{\ominus}$ above include the halides (chloride, bromide and iodide), lower alkyl sulfates and the alkyl and aryl sulfonates. Each of these anions is bound by ionic linkage with the positively charged nitrogen atoms. The anion $X^{\ominus}$ is of little consequence in such active compounds since the physiological activity resides in the cation. As prepared, $X^{\ominus}$ may be chloride, bromide, iodide, methanesulfonate, ethanesulfonate, toluenesulfonate or the like. By exchange reactions one of the original variants of $X^{\ominus}$ might be replaced by maleate, succinate, fumarate, tartrate or oleate. The salts obtained through these variations of $X^{\ominus}$ may in some cases have special advantages due to solubility, ease of crystallization, lack of objectionable taste, etc., but these are all subsidiary to the main physiological action which is independent of the character of $X^{\ominus}$. Hence, all variants of $X^{\ominus}$ are considered equivalents.

The compounds of the present invention are useful in the treatment of psychic depression. For example, N,N - dimethyl - (o-chlorobenzyl)-N-(2,3-epoxypropyl)-ammonium iodide administered at doses as low as 10 mgm./kg. p.o. in the mouse given prior to treatment with 5 mgm./kg. reserpine caused the mice to behave normally and prevented the usual sedative effect of reserpine. This is a marked contrast to the results of pretreatment with monoamine oxidase inhibitors before reserpine dosage, as in that instance the mice exhibit great motor stimulation and indeed become so hyperactive that death usually results. The oral lethal dose for fifty percent (50%) of the mice was found to be 1780 mgm./kg. of body weight. Thus the compounds of the present invention exhibit marked antidepressant activity without the motor stimulation of the usual monoamine oxidase inhibitors. By way of further illustration, the ortho-fluorobenzyl and the ortho-methylbenzyl compounds of the present invention had exhibited reserpine reversal at doses as low as 50 and 40 mgm./kg. p.o. respectively.

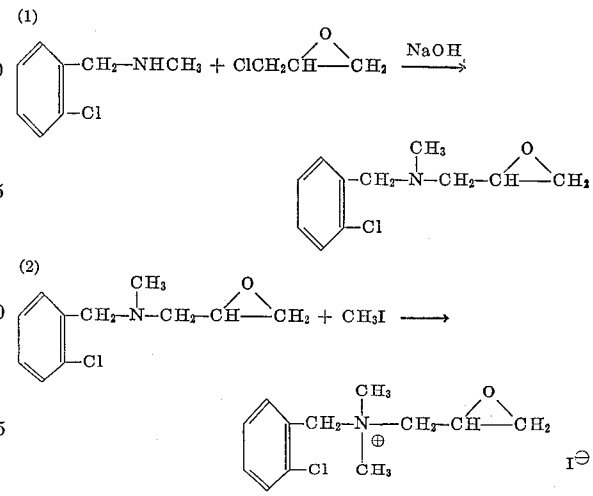
The compounds of the present invention are prepared by reacting epichlorohydrin with an N-methyl ortho-substituted benzylamine followed by reaction with sodium hydroxide to obtain a tertiary amine reaction product and then quaternizing the amine with an alkylating agent having the general formula CH_3X where X is any therapeutically acceptable anion. If desirable, X may then be replaced with any other therapeutically acceptable anion through ion exchange reactions known in the art.

The secondary amines used as starting agents in the preparation of the compounds of the present invention may be prepared from the appropriate substituted benzaldehyde by reaction with methylamine and reduction of the reaction product to the secondary amine. Such procedures are reported in The Preparation of Amines by Reductive Alkylation by W. S. Emerson, Organic Reactions, vol. 4, p. 174, John Wiley & Sons, Inc., 1948 and in J. H. Billman and A. C. Diesing, J. Org. Chem., 22, 1068 (1957) and may be illustrated by the following equations, using o-chlorobenzaldehyde for the preparation of N-methyl-o-chlorobenzylamine:



Alternately, the appropriately substituted benzoic acid chloride or equivalent may be reacted with methylamine to obtain an N-methyl amide which may be treated with a reducing agent such as lithium aluminum hydride to give the desired N-methyl-o-substituted benzylamine. This procedure is reported in Reductions by Lithium Aluminum Hydride by W. G. Brown in Organic Reactions, vol. 6, p. 469, John Wiley & Sons, Inc., 1951.

The preparation of the compounds of the present invention may be illustrated by the following equations using epichlorohydrin and o-chloro-N-methylbenzylamine and methyl iodide as the reagents for illustrative purposes:



The resulting quaternary ammonium salts are useful as pharmaceuticals. More specifically, compounds of this invention are antidepressants which are not monoamine oxidase inhibitors.

The N,N-dimethyl-N-(2,3-epoxypropyl)-N-benzylammonium salts substituted at the ortho position with bromine, iodine or a lower-alkyl radical may be prepared by substituting the appropriate secondary amine as a reagent in the procedure of Examples 1 through 3.

The compounds of the present invention may be synthesized by reaction of N-(2,3-epoxypropyl)-dimethylamine with an appropriately o-substituted benzyl halide, etc. or by the reaction of a methyl halide, etc. with an appropriately o-substituted N-benzyl-N-2,3-epoxypropyl-N-methylamine.

The 2,3-epithiopropyl substituted compounds may be prepared instead of the preferred epoxypropyl compounds by the addition of the following step to the procedure of Examples 1 through 4, to wit, after the preparation of the tertiary amine and before quaternization, the tertiary amine is reacted with potassium thiocyanate and methanol to give the desired N-methyl-N-(2,3-epithiopropyl)-o-substituted benzylamine which is then quaternized to the desired salt.

The following examples are given to illustrate the scope of this invention without limiting it thereto.

Example 1

N-methyl-o-chlorobenzylamine (15.56 g., 0.1 mole) and 0.3 ml. of water was added to epichlorohydrin (9.25 g., 0.1 mole) dropwise with stirring and cooling (ice bath). The mixture was stirred overnight in the melting ice bath. The mixture was then cooled in ice and a cold solution of sodium hydroxide (4.8 g., 0.12 mole) in 8 ml. of water was adder over 15 minutes with stirring. After the addition was complete, the ice bath was removed and stirring was continued at room tempearture for 20 minutes. The resulting mixture was then added to 25 ml. of water and extracted with five 50-ml. portions of ether. The combined ether extracts were then dried over anhydrous sodium sulfate, filtered and concentrated to a light yellow oil. Distillation of this oil at 0.1 mm. Hg, main fraction distilling at 71–72° C. yielded 9.03 g. of N-methyl-N-(2,3-epoxypropyl)-o-chlorobenzylamine as an oil. The quaternary ammonim iodide salt was then prepared by adding methyl iodide (11.4 g., 0.081 mole) dropwise to a stirred, cooled (ice bath) solution of N-methyl-N-(2,3-epoxypropyl)-o-chlorobenzylamine (9.0 g., 0.051 mole) in 30 ml. of acetonitrile. After the addition was complete, the ice bath was removed and the mixture was stored at 25° C. for eight hours. The mixture was then poured into 100 ml. of ether and kept overnight at 5° C. An oil resulted which was separated from the ether and dried in high vacuum. It crystallized after four days. It was triturated with ether and dried in high vacuum yielding N,N-dimethyl-N-(o-chlorobenzyl)-N-(2,3-epoxypropyl)-ammonium iodide, 4.88 g., M.P. 95° C.

Analysis.—Calculated for $C_{12}H_{22}NOClI$: C, 40.75; H, 4.85; N, 3.96. Found: C, 41.00; H, 5.02; N, 3.99.

Example 2

N-methyl-o-fluorobenzylamine (13.9 g., 0.1 mole) and 0.3 ml. of water was added slowly over a period of 15 minutes to mechanically stirred, cooled epichlorohydrin (9.25 g., 0.1 mole). The entire mixture was stirred overnight in a melting ice bath. The mixture was then cooled in ice and with mechanical stirring, a cold solution of sodium hydroxide (4.8 g., 0.12 mole), in 8 ml. of water was added dropwise over a period of 15 minutes. Then the ice bath was removed and the mixture was stirred for an additional 20 minutes. The mixture was then added to 25 ml. of water and extracted three times with 100-ml. portions of ether. The ether extracts were combined, dried over anhydrous sodium sulfate, filtered and concentrated to an oil. The oil was then distilled at 0.3 mm. Hg, the main fraction distilling at 65° C. The oil was distilled again at 0.025 mm. Hg, the main fraction distilling at 45.5° C. yielding 7:51 g. of N-methyl-N-(2,3-epoxypropyl)-o-fluorobenzylamine as an oil. Methyl iodide (6.38 g., 0.045 mole) was added slowly to a magnetically stirred cooled solution of N-methyl-N-(2,3-epoxypropyl)-o-fluorobenzylamine (6.51 g., 0.02 mole) in 30 ml. of acetonitrile. The ice bath was removed and the solution was stirred for three hours at room temperature. Ether was then added to the solution until it became cloudy and the entire mixture was kept overnight at 5° C. The crystals were removed by filtration and dried under reduced pressure yielding N,N-dimethyl-N-(2,3-epoxypropyl)-N-(o-fluorobenzyl)-ammonium iodide, 5.0 g.

Analysis.—Calculated for $C_{12}H_{22}NOFI$: C, 42.85; H, 5.16; N, 4.16. Found: C, 42.30; H, 5.20; N, 3.94.

Example 3

N-methyl-o-methylbenzylamine (20.0 g., 0.15 mole) and 0.45 ml. of water was added slowly to epichlorohydrin (13.87 g., 0.15 mole) with stirring and cooling (ice bath). The mixture was stirred in the melting ice bath overnight. The mixture was then cooled in ice and a cold solution of sodium hydroxide (7.2 g., 0.18 mole) in 12 ml. of water was added slowly. After the addition was complete, the ice bath was removed and stirring was continued for an additional 20 minutes. The resulting mixture was then added to 37.5 ml. of water and extracted with three 100-ml. portions of ether. The ether extracts were combined, dried over anhydrous sodium sulfate, filtered and concentrated to an oil. Distillation of this oil at 0.05 mm. Hg, yielded 8.43 g. of N-methyl-N-(2,3-epoxypropyl)-o-methylbenzylamine distilling at 73° C. as an oil. The quaternary ammonium-p-toluenesulfonate salt was then prepared by slowly adding methyl-p-toluenesulfonate (4.65 g., 0.025 mole) to a stirred cooled (ice bath) solution of N-methyl-N-(2,3-epoxypropyl)-o-methylbenzylamine (4.55 g., 0.025 mole in 25 ml. of acetonitrile. The ice bath was removed and the solution was stirred for three hours. Ether was added until the cloud-point was reached and the mixture was kept overnight at 4° C. Crystals resulted which were removed by filtration and dried under reduced pressure. Recrystallization from acetonitrile-ether yielded 1.7 g. of N-methyl-N-(2,3-epoxypropyl)-o-methylbenzylammonium p-toluenesulfonate, M.P. 109° C.

Analysis.—Calculated for $C_{20}H_{27}NO_4S$: C, 63.63; H, 7.21; N. 3.72. Found: C, 63.40; H, 7.33; N, 3.72.

Example 4

A mixture of N-methyl-N-(2,3-epoxypropyl)-o-chlorobenzylamine (31.75 g., 0.15 mole) and potassium thiocyanate (21.86 g., 0.225 mole) in 75 ml. of methanol was refluxed for one hour. The mixture was then cooled to 25° C., added to 200 ml. of water and extracted three times with 100 ml. portions of ether. The ether extracts were combined, dried over sodium sulfate, filtered and concentrated to an oil which was distilled at 0.05 mm. Hg, yielding 11.5 g. of N-methyl-N-(2,3-epithiopropyl)-o-chlorobenzylamine, B.P. 90°–94° C.

Analysis.—Calculated for $C_{11}H_{14}NSCl$: C, 58.00; H, 6.19; N, 6.15; S, 14.08; Cl, 15.57. Found: C, 58.25; H, 6.23; N, 6.59; S, 13.60; Cl, 15.58.

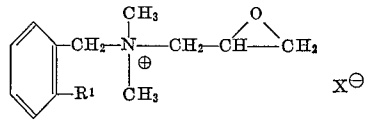
To N - methyl-N-(2,3-epithiopropyl)-o-chlorobenzylamine (9.99 g., 0.044 mole) in 40 ml. of freshly distilled acetonitrile was added p-methyltoluene sulfonate (9.87 g., 0.053 mole). The mixture was allowed to stand at 25° C. for two hours. Ether was then added to the mixture until crystallization began and it was kept at 25° C. for 24 hours and then at 4° C. for 24 hours. The crystals were removed by filtration, dried under reduced pressure and recrystallized from ethanol yielding N,N-dimethyl-N-(2,3-epithiopropyl)-N-o-chlorobenzylammonium p-toluene sulfonate, M.P. 109–192° C.

Analysis.—Calculated for $C_{19}H_{24}NO_3S_2Cl$: C, 55.12; H, 5.84; N, 3.38. Found: C, 55.25; H, 5.82; N, 3.37.

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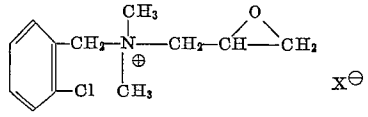
What I claim is:

1. A quaternary ammonium salt having the formula



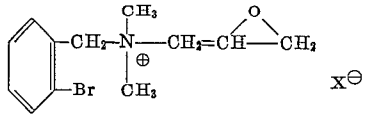
wherein R^1 is a member selected from the group consisting of fluoro, chloro, bromo, iodo and lower alkyl and $X^{\ominus}$ is a therapeutically acceptable anion.

2. A quaternary ammonium salt having the formula



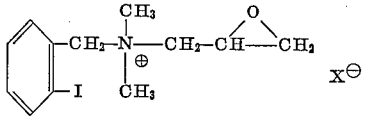
wherein $X^{\ominus}$ is a therapeutically acceptable anion.

3. A quaternary ammonium salt having the formula



wherein $X^{\ominus}$ is a therapeutically acceptable anion.

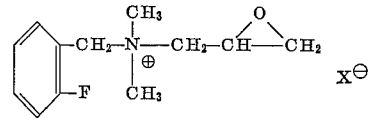
4. A quaternary ammonium salt having the formula



wherein $X^{\ominus}$ is a therapeutically acceptable anion.

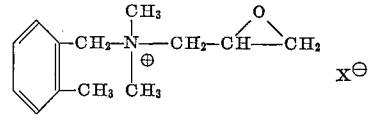
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5. A quaternary ammonium salt having the formula



wherein $X^{\ominus}$ is a therapeutically acceptable anion.

6. A quaternary ammonium salt having the formula



wherein $X^{\ominus}$ is a therapeutically acceptable anion.

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