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ANTIDEPRESSANT COMPOSITIONS

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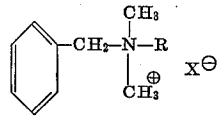
2 Claims. (Cl. 167—65)

This invention relates to compositions and a method for treatment and more particularly to quaternary ammonium salts of N,N-dimethylbenzylamines as active ingredients and a method for treatment of psychic depression.

The therapeutic compositions of the present invention comprise a quaternary salt of certain N,N-dimethylbenzylamines as an essential active ingredient in combination with a pharmacologically acceptable anion. The compositions of the present invention possess valuable therapeutic utility as antidepressants and it is the object of the present invention to provide a novel method of counteracting mental depression and apathy without stimulating motor activity.

The therapeutic ingredient is, in the preferred form of the present invention, a quaternary ammonium salt of an N,N-dimethylbenzylamine which can be represented by the following formula:



wherein R is a member of the group 2,3-epoxypropyl, 2,3-epithiopropyl or 2,3-dihydroxypropyl, and $X^{\ominus}$ is a nontoxic anion.

The nontoxic anions which would be pharmaceutically acceptable include the halides (chloride, bromide and iodide), (lower)alkyl sulfates, the alkyl and aryl sulfonates, phosphate, maleate, fumarate, succinate, tartrate, oxalate and citrate and other ones known to the art. By exchange reactions one of the original variants of $X^{\ominus}$ may be replaced with another. 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 variations of $X^{\ominus}$ are considered equivalent.

The compounds of the present invention may be embodied in any of the known pharmaceutical forms for oral, subcutaneous, intramuscular or intravenous administration. Preferably, the compounds are prepared in solid compositions for oral administration in unit dosage form as tablets, capsules, pills, granules or powders. Solutions, emulsions or suspensions of the compounds of the present invention may be prepared for oral administration. Sterile suspensions or solutions are required for parenteral use and isotonic preparations may also be desirable for injection use.

The term unit dosage form as used in the specification and claims means a physically distinct entity suitable as a unitary dosage for administration, each unit containing a pre-determined quantity of a compound of the present invention. The quantity of the compound contained in the unit dosage form is directly dependant upon the considerations which are well known in the art of compounding a pharmaceutically active material for therapeutic use. The characteristics of the active compound, the particular

therapeutic effect to be achieved, the route of administration and the mechanism of the action of the material in the host are important considerations in determining the quantity of the active compound included in the unit dosage form. Examples of suitable oral unit dosage forms are capsules, pills, tablets, cachets and powder packets for solid compositions, and teaspoonfuls, dropperfuls, ampoules and vials for liquid oral dosage forms.

The tablets or pills can be laminated or otherwise compounded to provide for time release action of the active compound. For example, the tablet or pill can comprise an inner portion constituting one unit dose and an outer portion constituting another unit dose, the outer portion being in the form of an envelope encompassing the inner portion. The two portions can be separated by an enteric layer which serves to delay the release of the active compound contained in the inner portion by resisting disintegration in the stomach thereby allowing it to pass intact into the intestine where the enteric layer is destroyed releasing the active compound in the inner portion. Such an enteric layer may consist of any number of known substances such as polymeric acids or mixtures thereof, cellulose acetate, cetyl alcohol, shellac and the like.

In the preferred embodiment of this invention, N-benzyl-N,N-dimethyl-N-(2,3-epoxypropyl)-ammonium iodide was mixed with conventional tableting ingredients such as corn starch, lactose, sucrose, stearic acid, sorbitol, talc and functionally similar materials acceptable as pharmaceutical carriers and binders. The solid unit dosage form would contain N-benzyl-N,N-dimethyl-N-(2,3-epoxypropyl)-ammonium iodide in an amount of at least 10 mg. and would be administered at a time rate designed to achieve the desired pharmacological result.

Examples of oral liquid dosage forms include aqueous solutions and aqueous or oil suspensions and emulsions wherein the product is dissolved or dispersed in a pharmaceutically acceptable carrier or vehicle. Flavoring agents may be added to increase the palatability of the dosage form. Examples of vehicles are cottonseed oil, sesame oil, peanut oil and the like and acceptable dispersing agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, dextran, methyl cellulose and the like.

The unit dosage forms containing the compounds of the present invention can include other pharmacologically active compounds such as sedatives, including phenobarbital, barbital and like barbiturates, vitamins, hormones, hypotensive and ataractic agents.

The compounds of the present invention may be prepared from the appropriate methylamine by reaction with epichlorohydrin and sodium hydroxide thereby obtaining a tertiary amine reaction product which is then quaternized with an alkylating agent such as a methyl halide to give the desired quaternary ammonium salt. The following equations illustrate the procedure for preparation of N-benzyl-N-(2,3-epoxypropyl)-N-methylamine using benzaldehyde, methylamine and epichlorohydrin as reagents for illustrative purposes and the subsequent quaternization of that compound with methyl iodide to obtain N - benzyl - N,N - dimethyl-N-(2,3-epoxypropyl)-ammonium iodide.

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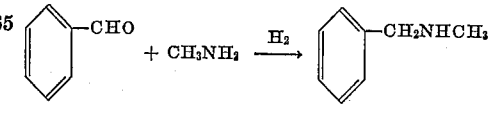

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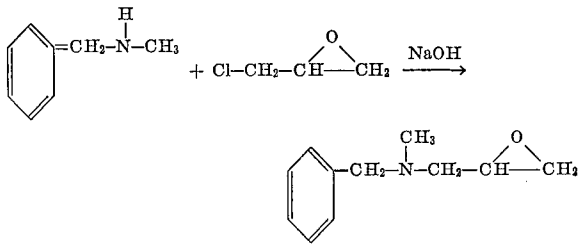

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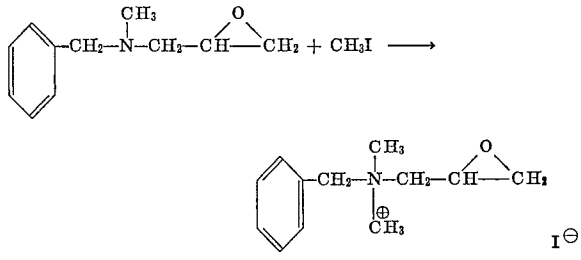


Table I illustrates the therapeutic utility of the compounds of the present invention for the treatment of depression of the central nervous system. For example, N-benzyl-N,N-dimethyl-N - (2,3 - epoxypropyl) - ammonium iodide administered to mice at doses as low as 10 mgm./kg. p.o. prior to treatment with 5 mgm./kg. reserpine prevented the usual sedative effect of reserpine. An oral dosage of 1682 mgm./kg. proved lethal to fifty percent of the mice. When mice are pretreated with monoamine oxidase inhibitors before reserpine dosage, the mice exhibit great motor stimulation. Treatment with the compounds of the present invention is advantageous in that they exhibit marked antidepressant activity without the motor stimulation of the usual monoamine oxidase inhibitors.

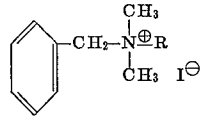
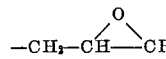
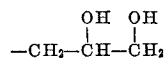
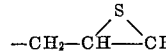


TABLE I

R	Minimum Effective Dose, mgm./kg. p.o.	Dose Lethal to 50%, mgm./kg.
	10	1682
	10	----------
	50	2000

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

Example 1

The epichlorohydrin (41.6 g., 0.45 mole) was added dropwise, with stirring and cooling (ice bath), N-methylbenzylamine (54.0 g., 0.44 mole) and 1.3 ml. of water. The mixture was stirred in the melting ice bath overnight. The mixture was then cooled again in ice and, with continued stirring, a solution of sodium hydroxide (21.2 g., 0.53 mole) in 35 ml. of water was added dropwise over 20 minutes. After the addition was complete, the ice bath was removed and stirring was continued for 20 minutes.

The resulting mixture was then poured into 75 ml. of water, the layers were separated, and the aqueous layer was extracted with five 100-ml. portions of ether. The combined organic layer and ether extracts were then dried over anhydrous sodium sulfate and concentrated under reduced pressure to a pale yellow oil. Distillation of this oil yielded 32.4 g. of colorless N-benzyl-N-(2,3-epoxypropyl)-N-methylamine, B.P. 64°/0.3 mm.

Analysis.—Calculated for $C_{11}H_{15}NO$: C, 74.53; H, 8.53; N, 7.90. Found: C, 74.55; H, 8.52; N, 7.88.

To a stirred, cooled (ice bath) solution of N-benzyl-N-(2,3-epoxypropyl)-N-methylamine (9.0 g., 0.051 mole) in 75 ml. of acetonitrile was added dropwise methyl iodide (9.5 g., 0.15 mole) during 20 minutes. After the addition was complete, the ice bath was removed and the mixture was stored at room temperature overnight. The reaction mixture was then diluted with 200 ml. of ether and, after seeding and cooling, the crystalline precipitate was removed by filtration. Reprecipitation from acetonitrile with ether yielded 14.9 g. of N-benzyl-N,N-dimethyl-N-(2,3-epoxypropyl)-ammonium iodide in the form of colorless crystals, M.P. 97–99° C.

Analysis.—Calculated for $C_{12}H_{18}INO$: C, 45.2; H, 5.69; N, 4.39. Found: C, 45.20; H, 5.65; N, 4.29.

Example 2

N-benzylamine (12.1 g., 0.10 mole) was added to a solution of glycidol (6.36 ml., 0.10 mole) during a period of five minutes. The resulting solution was stored for 24 hours at 25° C. and then concentrated under reduced pressure to a pale yellow oil. This oil was dissolved in 55 ml. of acetone and methyl iodide was added dropwise over a period of five minutes. The reaction mixture was kept at about 25° C. with an ice bath during the addition and stored at 25° C. for 24 hours. The reaction mixture was then poured into 250 ml. of ether and stored for two days at 5° C. The oil was then isolated by decantation and dried under high vacuum, treated with 200 ml. of warm acetone and stirred at 5° C. overnight. Crystalline product was removed by filtration, treated with boiling acetone and the solid removed by filtration and washed with acetone and dried yielding 13.0 g. of N - benzyl-N-(2,3-dihydroxypropyl)-N,N-dimethylammonium iodide, M.P. 124–125° C.

Analysis.—Calculated for $C_{12}H_{20}NO_2I$: C, 42.8; H, 5.98; N, 4.16. Found: C, 42.80; H, 5.92; N, 4.22.

Example 3

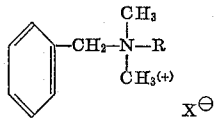
Potassium thiocyanate (11.25 g., 0.115 mole) was added to a solution of N-benzyl-N-(2,3-epoxypropyl)-N-methylamine in 30 ml. of methanol and the mixture refluxed for one hour. It was then cooled, poured into 221 ml. of water and this mixture was extracted three times with 100 ml. portions of chloroform. The extracts were combined, dried over sodium sulfate and concentrated to a yellow oil. This oil was then distilled under reduced pressure, the product distilling at 78–80° C. at 0.2 mm. of pressure yielding 3.41 g. of N-methyl-N-(2,3,-epithiopropyl)benzylamine.

Methyl p-toluene sulfonate (7.07 g., 0.038 mole) was added dropwise with stirring to a solution of N-methyl-N-(2,3-epithiopropyl)benzylamine in 25 ml. of freshly distilled acetonitrile. The mixture was allowed to stand at 25° C. for 2½ hours. A small amount of ether (2 ml.) was added causing precipitation of a white crystalline solid. The mixture was stored overnight at 4° C. and then the solid was removed by filtration, washed with acetonitrile and dried under reduced pressure. The material was recrystallized from ethanol yielding 8.12 g. of N-benzyl-N,N-dimethyl-N-(2,3-epithiopropyl)ammonium p-toluene sulfonate, M.P. 204–205° C.

Analysis.—Calculated for $C_{19}H_{25}NO_3S_2$: C, 60.12; H, 6.64; N, 3.69. Found: C, 59.95; H, 6.53; N, 3.96.

What I claim is:

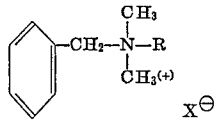
1. A pharmaceutical composition comprising a pharmaceutical carrier and an antidepressant amount of a compound having the formula



wherein R is a member selected from the group 2,3-epoxypropyl, 2,3-dihydroxypropyl, or 2,3-epithiopropyl, and $X^{\ominus}$ is a pharmaceutically acceptable nontoxic anion.

2. A pharmaceutical composition in unit dosage form

comprising a pharmaceutical carrier and at least 10 mg. of a compound having the formula



wherein R is a member selected from the group 2,3-epoxypropyl, 2,3-dihydroxypropyl, or 2,3-epithiopropyl, and $X^{\ominus}$ is a pharmaceutically acceptable nontoxic anion.

References Cited

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