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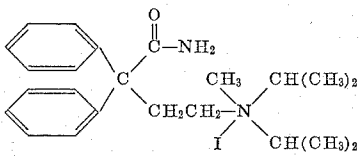
ANTICHOLINERGIC SUBSTITUTED BUTYRAMIDES

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This invention relates to new and useful organic compounds of therapeutic value and to methods for the preparation and therapeutic administration thereof. More particularly, this invention relates to new and useful amino substituted amides which have been found to have highly significant anticholinergic activity.

Speeter, in U.S. Patent 2,823,233, discloses a quaternary amine salt of a substituted butyramide having the formula:

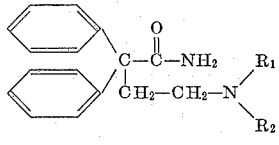


It is significant that, according to Speeter, the quaternary amine salt is necessary for significant therapeutic activity. To date, no tertiary-amino substituted amides have been disclosed having significant parasympathicolytic activity and, in particular, anticholinergic activity.

It is, therefore, an object of this invention to provide tertiary-amino substituted amides having such activity. It is also an object of this invention to provide methods for the preparation and therapeutic administration of said tertiary-amino amides.

These and other objects of this invention are accomplished by providing a 2,2-diphenyl-4-(N-alkyl-t-hydrocarbylamino)-butyramide, wherein the t-hydrocarbyl generally contains 4 to 20 carbon atoms and the alkyl group from 1 to 4 carbon atoms. Preferably, the t-hydrocarbyl substituent is t-butyl or t-amyl. It is most significant that the presence of the t-hydrocarbyl moiety, directly bound to the nitrogen atom of the amino group, is prerequisite to the excellent anticholinergic activity of the novel compounds of this invention. Replacement of the t-hydrocarbyl moiety with, for example, a propyl moiety results in drastically decreased anticholinergic activity.

The anticholinergic butyramides of this invention are more fully represented by the following general formula:



wherein R_1 is a tertiary-hydrocarbon group containing 4 to 20 carbon atoms—preferably, t-butyl or t-amyl—and R_2 is an alkyl group containing 1 to 4 carbon atoms. Although the above formula is set forth in the form of the free base, it is to be understood that the acid addition salts thereof are included within the scope of the present invention. Exemplary of such salts are inorganic acid addition salts, such as the hydrochloride, monohydrosulfate, nitrate, phosphate, hydriodide, and the like, as well as organic acid salts, such as the acetate, maleate, tartrate, malate, pamoate (embinate), napsylate, tosylate, succinate, citrate, benzoate, stearate, and the like.

Another embodiment of this invention is a method for inhibiting gastric secretion which comprises therapeutically administering an effective quantity of the novel compounds of this invention. Such therapeutic administration also results in inhibition of gastric motility and

gastrointestinal smooth muscle innervated by postganglionic cholinergic nerves.

A pharmaceutical composition wherein the improvement comprises a 2,2-diphenyl-4-(N-alkyl-t-hydrocarbylamino)butyramide is the vehicle for administration of the active compounds of this invention. The form of the pharmaceutical composition can be adapted for oral or parenteral administration, oral administration being especially preferred because of the ease and convenience associated therewith. Thus, the pharmaceutical compositions which comprise an embodiment of this invention can be in the form of a compressed tablet or a filled capsule, as well as in the form of a pharmaceutical solution or suspension suitable for oral or intramuscular administration.

Representative of the novel butyramides of this invention are 2,2-diphenyl-4-(N-methyl-t-butylamino)butyramide, 2,2-diphenyl-4-(N-ethyl-t-butylamino)butyramide, 2,2-diphenyl-4-(N-n-propyl-t-butylamino)butyramide, 2,2-diphenyl-4-(N-methyl-t-amylamino)-butyramide, and the like, as well as the corresponding hydrochloride, acetate, and the like acid addition salts of each of the foregoing. Preferred because of exceptional anticholinergic properties is 2,2-diphenyl-4-(N-methyl-t-butylamino)butyramide hydrochloride.

This invention is further represented by the following working examples.

Example I

t-Butylaminoethanol.—To a solution of 73 g. (1 mole) of t-butylamine in 200 ml. of methanol were added 44 g. (1 mole) of ethylene oxide. The mixture was allowed to stand overnight, and was then heated at reflux temperature for 30 minutes. The reaction product was fractionally distilled, and 67 g. (57 percent of theory) of t-butylaminoethanol were collected; boiling point, 65–75° C. (5 mm. Hg); melting point, 43° C.

2-(N-methyl-t-butylamino)ethanol hydrochloride.—A mixture of 67 g. (0.57 mole) of t-butylaminoethanol, 55 g. of 98 percent formic acid, and 51 g. of 37 percent aqueous formaldehyde was heated under reflux for four hours. The reaction product was acidified with 55 ml. of concentrated hydrochloric acid, and was evaporated to dryness under reduced pressure. The solid residue was crystallized from 100 ml. of isopropyl alcohol, and 81 g. (85 percent of theory) of 2-(N-methyl-t-butylamino)-ethanol hydrochloride were obtained; melting point, 140–142° C.

Analysis.—Calculated for $C_7H_{17}NO \cdot HCl$: C, 50.14; H, 10.82; N, 8.36. Found: C, 49.89; H, 10.91; N, 8.18.

2-(N-methyl-t-butylamino)-1-chloroethane hydrochloride.—A solution of 295 g. (1.76 moles) of 2-(N-methyl-t-butylamino)-ethanol hydrochloride (produced as set forth above) and 600 ml. of chloroform was cooled in an ice bath and 450 g. of thionyl chloride were added. The reaction mixture was stirred for one hour, then heated under reflux for three hours. It was then concentrated under reduced pressure. The residue was recrystallized from an acetone-ether mixture. Total yield of 2-(N-methyl-t-butylamino)-1-chloroethane hydrochloride (first and second crops) was 291 g. (89 percent of theory).

Analysis.—Calculated for $C_7H_{16}ClN \cdot HCl$: C, 45.17; H, 9.21; N, 7.53. Found: C, 45.56; H, 8.91; N, 7.47. The free base, 2-(N-methyl-t-butylamino)-1-chloroethane, was obtained by treating the hydrochloride salt with potassium carbonate.

2,2 - diphenyl-4-(N-methyl-t-butylamino)butyronitrile hydrochloride.—A suspension of 65 g. of sodium amide in 600 ml. of toluene was stirred and heated under reflux. A solution of 300 g. (1.55 moles) of diphenylacetonitrile in 1100 ml. of toluene was added, and the mixture was

heated and stirred for four hours. To the hot suspension of the sodium salt of diphenylacetonitrile obtained thereby was added a solution of 1.56 moles of the free base, 2-(N-methyl-t-butylamino)-1-chloroethane in 500 ml. of toluene. The reaction mixture was refluxed 18 additional hours. It was then cooled and 800 ml. of water were added. The toluene layer was extracted with 1000 ml. of 2 N HCl, then with two 500 ml. portions of 2 N HCl. The aqueous extracts were combined and cooled to 0° C., whereupon a solid precipitated. The solid was collected by filtration, washed with ether and dried, yielding 505 g. (94 percent of theory) of 2,2-diphenyl-4-(N-methyl-t-butylamino)butyronitrile hydrochloride; melting point, 93–97° C. An analytical sample was recrystallized from acetone; melting point, 122–124° C.

Analysis.—Calculated for $C_{21}H_{26}N_2 \cdot HCl$: C, 73.55; H, 7.93; N, 8.17. Found: C, 73.38; H, 7.79; N, 8.24.

2,2-diphenyl-4-(N-methyl-t-butylamino)butyramide.—A solution of 400 g. (1.17 moles) of the above 2,2-diphenyl-4-(N-methyl-t-butylamino)butyronitrile hydrochloride and 715 ml. of 90 percent sulfuric acid was heated on the steam bath for five hours. The reaction mixture was cooled and poured over ice and made basic with ammonium hydroxide. The solid that precipitated was collected by filtration and dissolved in 2.5 liters of chloroform, and this solution was washed with water, dried with potassium carbonate, and concentrated under reduced pressure. The solid residue was recrystallized from methyl ethyl ketone, yielding 283 g. (74.3 percent of theory) of 2,2-diphenyl-4-(N-methyl-t-butylamino) butyramide; melting point, 178–179° C.

Analysis.—Calculated for $C_{21}H_{28}N_2O$: C, 77.73; H, 8.70; N, 8.63. Found: C, 77.37; H, 8.70; N, 8.63.

2,2 - diphenyl-4-(N-methyl-t-butylamino)butyramide hydrochloride.—A suspension of 109 g. of 2,2-diphenyl-4-(N-methyl-t-butylamino)butyramide in 700 ml. of isopropyl alcohol was stirred and HCl gas was added until the solids went into solution. The solution was then filtered and diluted with 500 ml. of ether. After standing overnight, the solid that had precipitated was collected by filtration and recrystallized from isopropyl alcohol, yielding 105 g. (87 percent of theory) of 2,2-diphenyl-4-(N-methyl-t-butylamino)butyramide hydrochloride; melting point, 235–236° C.

Example II

2-(N-ethyl-t-butylamino)ethanol.—A solution of 115 g. (1.14 moles) of N-ethyl-t-butylamine, 75 ml. of ethylene oxide, and 200 ml. of methanol was heated in a pressure reactor for 18 hours at 65° C. The reaction mixture was then distilled to obtain 137 g. (83 percent of theory) of 2-(N-ethyl-t-butylamino)ethanol; boiling point, 72–75° C. (7 mm.), N_D^{25} 1.4425.

Analysis.—Calculated for $C_8H_{19}NO$: N, 9.64. Found: N, 9.69.

2 - (N-ethyl-t-butylamino)-1-chloroethane hydrochloride.—A solution of 9.5 g. (0.065 mole) of 2-(N-ethyl-t-butylamino)-ethanol in 35 ml. of chloroform was made acidic by passing in HCl gas. The solution was then cooled in an ice bath and 20 ml. of thionyl chloride were added dropwise. After being stirred for two hours, the solution was heated under reflux for two hours. It was then concentrated and the residue was recrystallized from acetone-ether, yielding 8.8 g. (68 percent of theory) of 2-(N-ethyl-t-butylamino)-1-chloroethane hydrochloride; melting point, 166–173° C.

Analysis.—Calculated for $C_8H_{18} \cdot ClN \cdot HCl$: N, 7.00. Found: N, 7.01. This salt was neutralized to the free base by treating with potassium carbonate solution.

2,2-diphenyl-4-(N-ethyl-t-butylamino)butyramide.— A suspension of 1.7 g. of sodium amide in 50 ml. of toluene was stirred and heated under reflux and a solution of 9 g. of diphenylacetonitrile in 100 ml. of toluene was added. After heating under reflux for an additional four hours, a solution of the above-prepared 2-(N-ethyl-t-butylamino)-1-chloroethane in 100 ml. of benzene was added, and the reaction mixture was stirred and heated under reflux for 18 hours. The reaction mixture was then cooled and diluted with 50 ml. of water. The organic layer was washed with 100 ml. of 1 N hydrochloric acid. The resulting aqueous acid layer was separated, made basic, and then washed with two 50 ml. portions of benzene. The benzene solution was dried with potassium carbonate and concentrated to yield 9 g. of crude 2,2-diphenyl-4-(N-ethyl-t-butylamino)butyronitrile. Without purification, the nitrile was dissolved in 55 ml. of 90 percent sulfuric acid and heated on a steam bath for four hours. After being cooled, the solution was poured over ice and made basic with ammonium hydroxide. The basic solution was extracted with two 100 ml. portions of chloroform. The chloroform extracts were combined and dried with potassium carbonate, then concentrated under reduced pressure. A solid crystallized from the concentrate on standing and was recrystallized from cyclohexane and isopropanol-water to yield 4.4 g. (29 percent of theory) of 2,2-diphenyl-4-(N-ethyl-t-butylamino)butyramide; melting point, 107–109° C.

2,2-diphenyl-4-(N-ethyl-t-butylamino)butyramide hydrochloride.—The hydrochloride salt was prepared by dissolving the free base in isopropanol, adding HCl gas until the solids dissolved, and then diluting with ether. The white crystalline solid which formed was recrystallized from isopropanol to yield 2,2-diphenyl-4-(N-ethyl-t-butylamino)butyramide hydrochloride in 75 percent yield; melting point, 229–231° C.

The acid addition salts of the aminobutyramides of this invention are readily prepared by methods fully set forth in the prior art. For example, if a solid acid is to be employed in forming the acid addition salt, an equivalent of this acid, either as such or in solution, is added to a solution containing an equivalent of the aminobutyramide. If the acid addition salt thus formed is insoluble in the reaction solvent, the salt is isolated by filtration or centrifugation. On the other hand, if the salt is soluble in the reaction medium, it can be isolated by evaporation of the volatile constituents. When a gaseous acid, as, for example, hydrogen chloride, is employed, it is possible to use an excess of the acid since the excess can be readily removed by volatilization.

Among the acids which form acid addition salts with the aminobutyramides of this invention are inorganic acids including hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydriodic acid, and the like, as well as organic acids including acetic acid, maleic acid, citric acid, tartaric acid, malic acid, pamoic acid, naphthalensulfonic acid, p-toluene-sulfonic acid, succinic acid, benzoic acid, stearic acid, and the like.

In general, the compounds of this invention may be prepared by the hydrolysis of the corresponding nitriles. These nitriles are prepared, for example, by condensing an alkyl-t-butylamine with a 2,2-diphenyl-4-halobutyronitrile; or a 2,2-diphenylacetonitrile can be condensed with an alkyl-t-butylaminoethyl halide (prepared, for example, by the method of Slotta and Behnisch, Ber. 68, 754 (1935)). In general, the techniques and information set forth in J. Organic Chemistry, vol. 17, pages 770–777 (1952), can be employed in the preparation of the novel butyramides of this invention.

Examples I and II set forth the preferred methods for the preparation of the compounds of this invention. Thus, employing the procedure of Example II—with the exception that 1.14 moles of N-n-propyl-t-butylamine are employed in place of the N-ethyl-t-butylamine utilized therein—2,2 - diphenyl - 4 - (N-n-propyl-t-butylamino) butyramide is prepared. Likewise, 2,2-diphenyl-4-(N-n-butyl-t-butylamino)butyramide is prepared, employing the procedure of Example II, with the exception that 1.14

moles of N-n-butyl-t-butylamine are utilized in place of the N-ethyl-t-butylamine.

In some cases, one or both of the phenyl groups at the 2 carbon position of the butyramides of this invention can be substituted with such groups as halo (i.e., chloro, bromo, iodo, fluoro) or alkyl containing 1 to 4 carbon atoms. However, it is generally preferred that the phenyl substituents of the novel compounds of this invention be unsubstituted.

Although the preparation of the novel amides of this invention has been illustrated by butyramides wherein the t-hydrocarbyl moiety directly bound to the nitrogen atom of the amino group is t-butyl, it is to be clearly understood that any t-hydrocarbyl group containing 4 to 20 carbon atoms and, preferably, 4 to 8 carbon atoms, can be employed. Illustrative of such hydrocarbyl groups are t-octyl [2(2,4,4-trimethylpentyl)], triphenylmethyl, 2(2-methylnonadecyl), and the like.

The term "hydrocarbyl" as employed herein signifies a hydrocarbon moiety bound to the nitrogen atom of the amino group of the amides of this invention through a tertiary carbon atom.

We claim:

1. 2,2-diphenyl-4-(N-n-alkyl-t-hydrocarbylamino) - butyramide wherein n-alkyl has from 1 to 4 carbon atoms and t-hydrocarbyl is a saturated C_4–C_8 tertiary hydrocarbon radical.

2. An acid addition salt of a compound of claim 1 with a pharmaceutically acceptable acid.

3. 2,2-diphenyl-4-(N-methyl-t-butylamino)butyramide.

4. 2,2-diphenyl-4-(N-ethyl-t-butylamino)butyramide.

5. 2,2-diphenyl-4-(N-methyl-t-amylamino)butyramide.

6. 2,2 - diphenyl-4-(N-methyl-t-butylamino)butyramide hydrochloride.

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