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PARASYMPATHICOLYTICALLY ACTIVE ALPHA, ALPHA-DIPHENYL-GAMMA-DIALKYLAMINO-BUTYRAMIDE COMPOUNDS AND MANUFACTURE THEREOF

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This invention relates to certain alpha, alpha-diphenyl-gamma-dialkylamino butyramides and their quaternary ammonium-salts which we have found to be highly potent and highly specific parasympathicolytically active compounds. The compounds of this invention are of especial utility as inhibitors of gastric secretion in man.

It is a principal object of this invention to provide parasympathicolytically active compounds which have the aforesaid utility and which have little or no side effects.

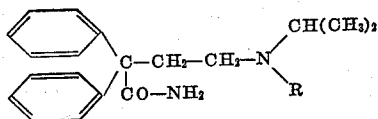
Compounds have heretofore been proposed for the purposes aforesaid but have drawbacks because of the many side effects when administered in man. Thus known compounds heretofore proposed have exhibited side effects as dizziness and orthostatic hypotension at therapeutically active doses which made them unsuitable for human administration. Moreover, these known compounds never exhibited an inhibitory action on histamin-induced gastric secretion in man.

It is another object of this invention to provide parasympathicolytically active compounds which have the aforesaid utility and are more active and lower in toxicity than the said known compounds. The compounds herein disclosed exhibit a large activity and a very low toxicity when administered by the oral route in the prevention of gastric secretion.

The parasympathicolytic activity of alpha, alpha-diphenyl-gamma-dialkylamino butyramides was known (Arch. exp. Pharmacol. u. Pathol. 214, 93 (1951), J. Am. Med. Ass. 151, 798 (1953), and Gastroenterology 23, 199 (1953)). Kirsner et al. (Gastroenterology 23, 199 (1953), and J. Am. Med. Ass. 151, 798 (1953)), found the compounds alpha, alpha-diphenyl-gamma-N-piperidino butyramide and its methiodide to possess strong inhibitory action on gastric secretion. However, owing to side effects these compounds were deemed as unsuitable for therapeutic use.

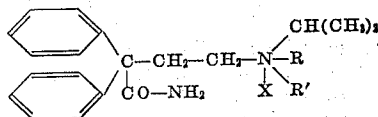
According to this invention, it has been found that the foregoing objectives and advantages are realized by certain new compounds, i.e., compounds selected from the group consisting of alpha, alpha-diphenyl-gamma-alkyl-isopropylamino butyramides and their quaternary ammonium salts.

The alpha, alpha-diphenyl-gamma-alkylisopropylamino butyramides may be represented by the following formula:



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wherein R is alkyl; their quaternary ammonium salts by the formula:



wherein R and R' are alkyl and X is an acidic radical.

A preferred example of the foregoing is alpha, alpha-diphenyl-gamma-diisopropylamino butyramide methiodide, whose parasympathicolytic action is at least two times that of alpha, alpha-diphenyl-gamma-N-piperidino butyramide, which is the strongest active alpha, alpha-diphenyl-gamma-dialkylamino butyramide described up till now. Given orally, the toxicity is exceedingly low, the LD₅₀ (mice) being two to three times as large as for the known alpha, alpha-diphenyl-gamma-dialkyl-amino butyramides. The inhibitory action it exhibits on histamin-induced gastric secretion in man is a property which was not described for any known compounds.

Other examples of preferred alkyl radicals which may be represented by R in the foregoing formulae are methyl and ethyl. R' is preferably represented by methyl, ethyl and isopropyl.

The compounds of this invention may be prepared in any suitable manner. However, it has been found that the preferred method of preparing the compounds is by the hydrolysis of the corresponding nitriles. It also has been found that the nitriles are preferably obtained by one of the following processes:

- (1) By condensing an alkyl isopropyl amine with alpha, alpha-diphenyl-gamma-halogen butyronitrile;
- (2) By condensing alpha, alpha-diphenylacetoneitrile with an alkyl isopropyl aminoethylhalide.

With reference to the methods referred to above, the alkyl groups in the alkyl isopropyl amine or in the alkyl isopropyl aminoethylhalide correspond to those which by virtue of the reactions involved are caused to occur at R and R' in the foregoing formulae.

With regard to the condensation of an alkyl isopropyl amine with alpha, alpha-diphenyl-gamma-halogen butyronitrile, this condensation gives low yields if it is carried out by boiling the two components under reflux with or without a solvent. It was found that the yields could be considerably improved by carrying out this reaction in a closed system under pressure.

The alpha, alpha-diphenyl-gamma-alkylisopropylamino butyramides can be converted into their quaternary ammonium salts by boiling them under reflux with an alkyl-halide or another alkyl ester. However, if an alpha, alpha-diphenyl-gamma-dialkylamino butyramide is converted into its quaternary ammonium salt by boiling with an isopropyl ester the yields are low. It was found that these yields could be considerably raised by carrying out this quaternisation in a closed vessel under pressure.

The hydrolysis of the nitriles is preferably carried out in the presence of a mineral acid, sulfuric acid normally giving the best results.

The invention will be further explained by reference to the following examples:

Example 1

To a suspension of 7 grams of sodiumamide in 100 ml. of benzene a solution of 33 grams of diphenylacetoneitrile in 80 ml. of benzene was slowly added with stirring, the temperature of the mixture being 30°-35° C. After

all of the diphenyl-acetonitrile had been added the mixture was heated to boiling and boiled under reflux for 45 minutes. After cooling, a solution of 28 grams of diisopropylaminoethylchloride in 40 ml. of xylene is added dropwise, the temperature of the mixture again being 30°-35° C. When this addition has been completed, the mixture is boiled under reflux for a period of three hours. After cooling, washing with water, extraction with hydrochloric acid, alkali-fying with sodium hydroxide, extraction with ether, drying and evaporation of the ether, the remaining oil is distilled in vacuo. 50 grams of an oil with a boiling range of 160°-200° C. at a pressure of 0.5-2.0 mm. mercury are obtained.

20 grams of this alpha,alpha-diphenyl-gamma-diisopropylamino butyronitrile are dissolved in 40 ml. of 90% sulfuric acid and boiled for three hours under reflux. The reaction mixture is poured into ice water and made alkaline with 10 N sodium hydroxide. At first an oil separates, which solidifies at 0° C. The precipitate is filtered, washed with water and recrystallized from aqueous ethanol. The resulting purified product is alpha, alpha-diphenyl-gamma-diisopropylamino butyramide with a melting point of 84° C.

Example 2

19.2 grams of diisopropylamine and 28.6 grams of alpha,alpha - diphenyl - gamma - bromobutyronitrile, dissolved in 60 ml. of xylene are boiled under reflux for a week. Diisopropylammoniumbromide precipitates and is washed with ether after filtration. The ether and the xylene solutions are united and evaporated on a water bath. The remainder is extracted with 3 N hydrochloric acid, the extract made alkaline with 10 N sodium hydroxide and now extracted with ether. After drying and evaporation of the ether the residue is distilled in vacuo. The oil was obtained in a yield of 5 to 10%. The same yields are obtained when the nitrile is boiled for a week with a large excess of diisopropylamine without addition of a solvent. The obtained alpha,alpha-diphenyl-gamma-diisopropylamino butyronitrile is converted to the corresponding amide according to the procedure described above in Example 1. The resulting product was the same as that obtained in Example 1.

Example 3

19.2 grams of diisopropyl amine and 28.5 grams of alpha,alpha - diphenyl - gamma - bromobutyronitrile, dissolved in 60 ml. of xylene are heated for a period of eight hours at a temperature of 120° C. in a sealed tube. The diisopropylammoniumbromide thus formed precipitates and is filtered off and washed with ether. The ether and the xylene solutions are united and evaporated on a water bath. The remainder is extracted with 3 N hydrochloric acid, the extract made alkaline with 10 N sodium hydroxide and now extracted with ether. After drying and evaporation of the ether the residue is distilled in vacuo. The oil is now obtained in a yield of 86%. This alpha,alpha-diphenyl-gamma-diisopropylaminobutyronitrile is converted to the corresponding amide according to the procedure described above in Example 1. The same end-product was obtained.

Example 4

The procedure of Example 1 was followed, except that instead of diisopropylaminoethylchloride 23 grams of methylisopropylaminoethylchloride was used. The nitrile was obtained in a yield of 93%. The resulting product was alpha,alpha-diphenyl-gamma-methylisopropylamino butyramide with a melting point of 152° C.

Example 5

The procedure of Example 2 was followed, except that instead of diisopropylamine 15.8 grams of methyl isopropylamine was used. The nitrile was obtained in a yield of 10%. The resulting product was the same as obtained in Example 4.

Example 6

The procedure of Example 3 was followed, except that instead of diisopropylamine 15.8 grams of methyl isopropyl amine was used. The nitrile was obtained in a yield of 89%. The resulting product was the same as obtained in Example 4.

Example 7

The procedure of Example 1 was followed, except that instead of diisopropylaminoethylchloride 25.6 grams of ethyl isopropyl aminoethylchloride was used. The nitrile was obtained in a yield of 89%. The resulting product was alpha,alpha-diphenyl-gamma-ethylisopropylamino butyramide with a melting point of 115° C.

Example 8

The procedure of Example 2 was followed, except that instead of diisopropylamine 18.5 grams of ethyl isopropyl amine was used. The nitrile was obtained in a yield of 5%. The resulting product was the same as obtained in Example 7.

Example 9

The procedure of Example 3 was followed, except that instead of diisopropylamine 18.5 grams of ethyl isopropyl amine was used. The nitrile was obtained in a yield of 87%. The resulting product was the same as obtained in Example 7.

Example 10

8 grams of alpha,alpha-diphenyl-gamma-diisopropylamino butyramide and 15 ml. of methyl iodide, dissolved in 50 ml. of isopropanol are boiled under reflux for a period of 5 to 10 hours. Thereafter the solvent and the excess methyl iodide are evaporated in vacuo and the residue is washed several times with boiling ethyl acetate. The resulting product was alpha,alpha-diphenyl-gamma-diisopropylmethylammonium butyramide iodide.

Example 11

The procedure of Example 10 was followed, except that instead of methyl iodide dimethyl sulfate was used. The resulting product was alpha,alpha-diphenyl-gamma-diisopropylmethylammonium butyramide sulfate.

Example 12

The procedure of Example 10 was followed, except that instead of alpha,alpha-diphenyl-gamma-diisopropylamino butyramide and methyl iodide alpha,alpha-diphenyl-gamma-methylisopropylamino butyramide and methyl bromide was used. The resulting product was alpha,alpha-diphenyl-gamma-dimethylisopropylammonium butyramide bromide.

Example 13

The procedure of Example 10 was followed, except that instead of alpha,alpha-diphenyl-gamma-diisopropylamino butyramide and methyl iodide alpha,alpha-diphenyl-gamma-ethylisopropylamino butyramide and methyl bromide was used. The resulting product was alpha,alpha-diphenyl-gamma-methyl-ethylisopropylammonium butyramide bromide.

Example 14

5 grams of alpha,alpha-diphenyl-gamma-dimethylamino butyramide, 15 ml. of isopropyl bromide and 40 ml. of isopropanol are heated for 6 hours at 110° C. in a closed vessel. Thereafter the solvent and the excess of isopropyl bromide are evaporated in vacuo and the residue is washed several times with boiling ethyl acetate. The resulting product is the same as obtained in Example 12.

Example 15

The procedure of Example 14 was followed, except that instead of alpha,alpha-diphenyl-gamma-dimethylamino butyramide alpha,alpha-diphenyl-gamma-methylethylami-

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no butyramide was used. The resulting product is the same as obtained in Example 13.

The amides obtained can be used on account of their strongly pronounced parasympatholytic activity as therapeutic agents, e.g., for inhibition of gastric secretion, on the one hand, and as intermediates for further syntheses on the other.

In order for the preferred properties to be obtained the number of carbon atoms in the alkyl radicals should not be in excess of four.

We claim:

1. In a method comprising reacting an alpha,alpha-diphenyl-gamma-alkyl isopropylamino butyramide with an alkyl ester of a mineral acid to form a quaternary ammonium salt of said butyramide containing a non-toxic mineral acid radical and recovering said quaternary ammonium salt, the step of effecting the reaction at a temperature at least of the order of 110° C. to 120° C. in a closed system under pressure.

2. In a method comprising reacting an alpha,alpha-diphenyl-gamma-alkyl isopropylamino butyramide with an alkyl ester of a mineral acid to form a quaternary ammonium salt of said butyramide containing a non-toxic

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mineral acid radical and recovering said quaternary ammonium salt, the improvement which consists of effecting the reaction at an elevated temperature, in a closed system at superatmospheric pressure.

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