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QUATERNARY AMMONIUM SALTS OF 2,2-DIPHENYL - 4,4 - DIMETHYL - 4 - PYRROLIDINO-BUTYRAMIDE

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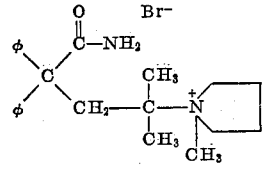
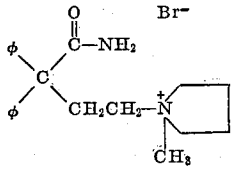
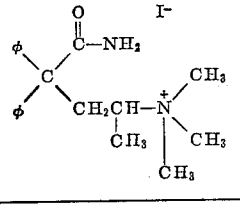
5 Claims. (Cl. 260—326.3)

The present invention relates to novel organic compounds and is more particularly concerned with the novel 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyronitrile free base, 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide free base, 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide acid addition salts, and 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide lower-alkyl quaternary ammonium salts.

The 2,2-diphenyl-4,4-dimethyl - 4 - pyrrolidinobutyronitrile free base, 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide free base, and 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide acid addition salts are useful intermediates for the preparation of the pharmacologically active 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide lower-alkyl quaternary ammonium salts.

The quaternary ammonium salts of the present invention possess excellent anticholinergic activity (i.e., antispasmodic and antisecretory activity). This is in contrast to the combination of properties shown by quaternary ammonium salts of closely related unsubstituted amides (i.e., primary amides) which lack the 4,4-dimethyl side chain. For example, some related compounds which lack the 4,4-dimethyl side chain show poor antispasmodic activity combined with mediocre antisecretory activity while others show poor antispasmodic activity

TABLE I

Compound	Anticholinergic Activity	
	Antispasmodic Index	Antisecretory Activity
	3.0	84 percent at 0.25 mg./kg.
Related Compounds		
A. 	1.0	50 percent at 0.2 mg./kg.
B. 	0.08	50 percent at 5.0 mg./kg.

combined with poor antisecretory activity. Thus the quaternary ammonium salts of the present invention are desirable where excellent anticholinergic activity is desired.

The data given in Table I are illustrative of the differentiating effects noted above. The antispasmodic index was determined by intravenous administration to Thiry-Vella dogs and equated to atropine equals 1.0 (low values mean low activity). The antisecretory activity was determined intravenously in rats and is given as the ED in mg./kg.—the effective dose necessary to reduce gastric secretion by the percentage indicated in the table.

The data in Table I show that 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide methobromide possesses excellent anticholinergic activity which would not be expected from the properties of closely related compounds. The importance of the 4,4-dimethyl side chain is clearly evident from the fact that compound B which contains a 4-methyl side chain and compound A which contains no side chain are clearly inferior antispasmodic agents. Compound B in addition shows poor antisecretory activity. Thus the quaternary ammonium salts of the present invention are particularly desirable where strong anticholinergic activity is desired.

The compounds of the present invention can be prepared by reacting diphenylacetonitrile with 2-methyl-2-pyrrolidinopropyl chloride in the presence of an alkali metal amide, advantageously lithium amide, to produce 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyronitrile free base. This free base is hydrolyzed to produce 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide free base according to the procedure of Cheney et al., J. Org. Chem. 17, 771 (1952). The latter free base (amide) can be purified by conversion to an acid addition salt such as the hydrochloride, sulfate, hydrobromide, phosphate, lactate, acetate, citrate, and the like, and the acid addition salt can be reconverted to the purified free base. The desired 2,2-diphenyl-4,4-dimethyl -4- pyrrolidinobutyramide lower-alkyl quaternary ammonium salts are thereupon produced by reacting the free base in an inert solvent such as methyl ethyl ketone or benzene with a quaternary ammonium salt-producing compound such as methyl chloride, methyl iodide, ethyl bromide, methyl bromide, methyl p-toluenesulfonate, butyl iodide, ethyl sulfate, ethyl iodide, and the like.

The starting 2-methyl-2-pyrrolidinopropyl chloride can be readily prepared from its hydrochloride which in turn can be prepared by reacting 2-methyl-2-pyrrolidinopropanol [Moffett, J. Org. Chem. 14, 862 (1949)] with gaseous hydrogen chloride and thionyl chloride.

The following example is illustrative of the process and products of the present invention, but is not to be construed as limiting.

Example.—Preparation of 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide methobromide

A. 2-METHYL-2-PYRROLIDINOPROPYL CHLORIDE HYDROCHLORIDE

Hydrogen chloride gas was passed into a solution of 104 grams (0.728 mole) of 2-methyl-2-pyrrolidinopropanol (Moffett, supra) in 500 milliliters of benzene with stirring and cooling by an ice bath until the solution tested strongly acidic. While being cooled by the ice bath, 65 milliliters of thionyl chloride was slowly added with stirring. The mixture was then gently heated under reflux for two hours during which sulfur dioxide and hydrogen chloride were evolved. Part of the solvent was removed by distillation under reduced pressure whereupon the product, 2-methyl-2-pyrrolidinopropyl chloride hydrochloride, crystallized. The product was collected, washed with benzene and ether, dried, and recrystallized from a mixture of ethanol and ethyl acetate. The yield

was 138 grams and the product, 2-methyl-2-pyrrolidinopropyl chloride hydrochloride, had a melting point of 145 to 147 degrees centigrade.

Analysis.—Calculated for $C_8H_{17}Cl_2N$: C, 48.49; H, 8.65; N, 7.07; Cl, 35.79. Found: C, 48.79; H, 8.74; N, 6.78; Cl, 35.58.

B. 2,2-DIPHENYL-4,4-DIMETHYL-4-PYRROLIDINOBUTYRONITRILE FREE BASE

In a three liter, 3-necked flask equipped with stirrer, reflux condenser, and dropping funnel 127.5 grams (0.66 mole) of diphenylacetonitrile was added to a slurry of 17.5 grams (0.76 mole) of lithium amide in one liter of toluene and the mixture was heated under reflux for four hours. Then 130 grams (0.66 mole) of 2-methyl-2-pyrrolidinopropyl chloride hydrochloride was converted to the free base by treatment with fifty percent sodium hydroxide solution, the free base was extracted with 500 milliliters of toluene and the toluene extract was dried over potassium carbonate. The dried toluene extract was slowly added to the aforesaid slurry. After heating under reflux for eighteen hours, the mixture was cooled, washed with 500 milliliters of water, and then extracted with 500 milliliters of six percent hydrochloric acid. The acid extract was washed with ether, made alkaline by adding 250 milliliters of twenty percent sodium hydroxide solution, and the mixture was extracted with 500 milliliters of benzene. After drying over anhydrous sodium sulfate the benzene was removed by distillation under reduced pressure, and the dark, viscous residue was distilled under vacuum. The product, 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyronitrile free base, weighed 140 grams; it had a boiling point of 174 to 176 degrees centigrade at 0.03 millimeter of mercury and $n_D^{25}=1.5681$.

Analysis.—Calculated for $C_{22}H_{26}N_2$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.23; H, 7.99; N, 9.46.

C. 2,2-DIPHENYL-4,4-DIMETHYL-4-PYRROLIDINOBUTYRAMIDE FREE BASE

A solution of 90 milliliters of 98 percent sulfuric acid and nine milliliters of water was added to fifty grams (0.157 mole) of 2,2-diphenyl-4,4-dimethyl-4- pyrrolidinobutyronitrile free base, Part B, in a 500-milliliter, 3-necked flask equipped with stirrer and reflux condenser and the mixture was heated on a steam bath for sixteen hours. The viscous solution was poured over cracked ice and made basic by the addition of 800 milliliters of concentrated ammonium hydroxide. The oil was extracted with benzene, the benzene solution was dried over anhydrous sodium sulfate, and the benzene was distilled under reduced pressure to produce 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide free base as an oil.

D. 2,2-DIPHENYL-4,4-DIMETHYL-4-PYRROLIDINOBUTYRAMIDE HYDROCHLORIDE

The 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide free base was dissolved in ethyl acetate and a slight excess of ethanolic hydrogen hydrochloride added to precipitate an oily product which slowly solidified. The solid was recrystallized from an isopropanol-methanol mixture to yield 35 grams of 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide hydrochloride which melted at 220 to 224 degrees centigrade.

Analysis.—Calculated for $C_{22}H_{29}ClN_2O$: C, 70.85; H, 7.84; N, 7.51; Cl, 9.51. Found: C, 71.62; H, 7.70; N, 7.59; Cl, 9.65.

Following the procedure of Part D, above other acid addition salts such as 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide sulfate, 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide hydrobromide, 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide acetate, 2,2-diphenyl-4,4 - dimethyl - 4 - pyrrolidinobutyramide citrate, 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide phosphate, 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide lactate, and the like, can be produced by substituting the corresponding acid for hydrogen chloride.

Purified 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide free base can be produced by mixing 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide hydrochloride with an excess of aqueous sodium hydroxide solution, extracting the mixture with benzene, drying the benzene solution with an hydrous sodium sulfate, separating the benzene solution by decantation, and removing the benzene by distillation.

E. 2,2-DIPHENYL-4,4-DIMETHYL-4-PYRROLIDINOBUTYRAMIDE METHOBROMIDE

Twenty grams (0.21 mole) of methyl bromide was added to a solution of 6.5 grams (0.019 mole) of 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide free base in 125 milliliters of methyl ethyl ketone in a 500-milliliter, single-necked, round-bottomed flask and the mixture kept stoppered for 48 hours at about 25 degrees centigrade. The mixture was filtered and the recovered crystals were recrystallized from ethanol to yield 2,2-diphenyl-4,4-dimethyl - 4 - pyrrolidinobutyramide methobromide which melted at 167 to 168 degrees centigrade.

Analysis.—Calculated for $C_{23}H_{31}BrN_2O$: C, 64.03; H, 7.24; N, 6.49; Br, 18.52. Found: C, 63.87; H, 7.24; N, 6.24; Br, 18.73.

Following the procedure of Part E, above, other lower-alkyl quaternary ammonium salts such as 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide ethobromide, 2,2-diphenyl-4,4-dimethyl - 4 - pyrrolidinobutyramide methochloride, 2,2 - diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide ethosulfate, 2,2 - diphenyl - 4,4 - dimethyl - 4 - pyrrolidinobutyramide methiodide, 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide ethiodide, 2,2-diphenyl-4,4- dimethyl - 4 - pyrrolidinobutyramide methyl p-toluenesulfonate, 2,2-diphenyl-4,4-dimethyl-4-pyrrolidinobutyramide butyl iodide, and the like can be produced by substituting the corresponding lower-alkyl quaternary ammonium salt-producing compound for methyl bromide.

It is to be understood that the invention is not to be limited to the exact details of operation or exact compounds shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the scope of the appended claims.

We claim:

1. 2,2 - diphenyl - 4,4 - dimethyl - 4 - pyrrolidinobutyramide free base.

2. 2,2 - diphenyl - 4,4 - dimethyl - 4 - pyrrolidinobutyramide acid addition salts.

3. 2,2 - diphenyl - 4,4 - dimethyl - 4 - pyrrolidinobutyramide hydrochloride.

4. 2,2 - diphenyl - 4,4 - dimethyl - 4 - pyrrolidinobutyramide lower-alkyl quaternary ammonium salts.

5. 2,2 - diphenyl - 4,4 - dimethyl - 4 - pyrrolidinobutyramide methobromide.

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