Synthesis of Anticholinergic Agents: *N*-Methyl-4-piperidinyl α-Benzoyloxy-α-cyclopentylphenylacetate Salts

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Abstract □ The synthesis of a new anticholinergic agent, *N*-methyl-4-piperidinyl α-benzoyloxy-α-cyclopentylphenylacetate, obtained by reacting *N*-methyl-4-piperidinyl α-cyclopentylmandelate with benzoyl chloride in the presence of methyllithium, is reported. This material may be useful as an antiperspirant.

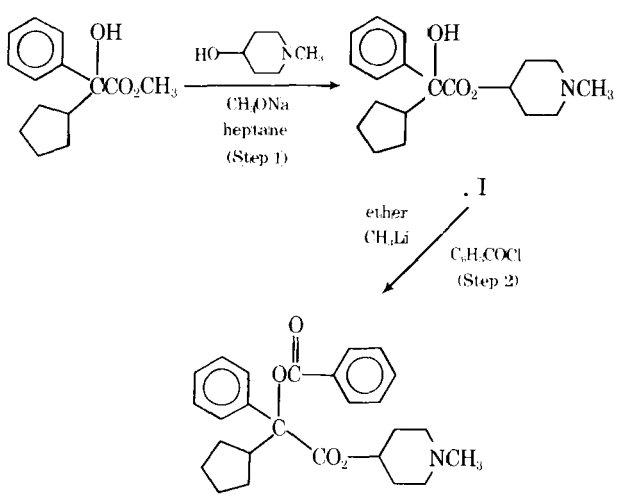
Keyphrases □ *N*-Methyl-4-piperidinyl α-benzoyloxy-α-cyclopentylphenylacetate—synthesized, anticholinergic and antiperspirant activity evaluated □ Anticholinergic activity—*N*-methyl-4-piperidinyl α-benzoyloxy-α-cyclopentylphenylacetate evaluated in rabbit eyes □ Antiperspirant activity—*N*-methyl-4-piperidinyl α-benzoyloxy-α-cyclopentylphenylacetate evaluated in humans

A synthetic substance with local antiperspirant activity that would be effective when applied topically, have low toxicity, and have no systemic effects would be highly desirable.

The effectiveness of anticholinergic drugs, for example, as antiperspirants is well documented (1–3). The benzoyl ester of scopolamine has been used repeatedly on skin at low concentration without measurable systemic effect (1), and 1-methyl-3-pyrrolidyl α-phenylcyclohexaneglycolate methobromide (4) has been found to be valuable for sweat inhibition.

DISCUSSION

N-Methyl-4-piperidinyl α-benzoyloxy-α-cyclopentylphenylacetate (II) was prepared by the reaction of *N*-methyl-4-piperidinyl α-cyclopentylmandelate (I) (5) with benzoyl chloride in the presence of methyllithium at −30°, according to Scheme I.



II

Scheme I

The sequence in Step 1 is not chemically unusual, but it is a convenient and economical route for the synthesis. Step 2, however, does represent a somewhat novel procedure. By the use of low temperature, it was possible to restrict the reaction to the hydroxyl group of the phenylacetate, with only minimum reactivity of the ester group even in the presence of excess methyllithium. Furthermore, when excess benzoyl chloride is added at this low temperature, it destroys the excess methyllithium before the latter can react with the ester group as the reaction temperature is again raised to room temperature. At room temperature, the only reactants remaining are the oxylithium group on the substrate and benzoyl chloride. A previously reported method for introducing an acyl group into a basic ester of similar structure concerned the synthesis of α-acyloxy derivatives of *N*-methyl-4-piperidinyl benzylates (6) and involved a multistep sequence.

The new drug, in the hydrochloride form, was investigated as an anticholinergic antiperspirant. The anticholinergic effect of this compound was determined in rabbit eyes, and its activity was established by measurements of pupil dilation.

The single-dose intraperitoneal LD_{50} in albino mice was 61 mg/kg. The single-dose oral LD_{50} in albino mice was 310 mg/kg.

The test compound was applied topically, up to 160 μg/kg, for 7 consecutive days to human skin without evidence of definite side effects. Further testing with 320- and 640-μg/kg doses also indicated freedom from side effects. ECG's taken before and after application of the two highest doses showed no detectable effects.

The standard antiperspirant back test was conducted on volunteers with concentrations of the test material of up to 4% in a 75% alcoholic solution. The substance was demonstrated to be significantly effective in reducing perspiration.

EXPERIMENTAL

***N*-Methyl-4-piperidinyl α-Benzoyloxy-α-cyclopentylphenylacetate Hydrochloride Hydrobromide (III)**—Methyl α-cyclopentylmandelate (233 g), *N*-methyl-4-piperidinol (115 g), heptane (bp 94–95°) (1540 ml), and sodium methoxide (9.1 g) were slowly distilled until the methanol–heptane azeotrope no longer passed over, as shown by the take-off temperature reaching and staying at 94° (3 hr). The mixture was then cooled, poured into 1 liter of water, and shaken vigorously. The heptane phase was separated and washed with successive portions of water until neutral and then dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum.

The concentrate was dissolved in 1 liter of dry methylene chloride, and hydrochloric acid was passed in at 0° with external cooling until the solution was saturated. The solution was then concentrated under vacuum to remove the excess acid, and the concentrate was redissolved in 1300 ml of warm methylene chloride. Approximately 2000 ml of acetone was then added, and the solvent was boiled off until crystals began to appear. The mixture was allowed to cool slowly to 25° and was then stored overnight at 3° to complete precipitation of the product. The precipitate was collected by filtration, washed with cold acetone (−10°; 3 × 200 ml), and dried under vacuum.

The combined filtrate and washings were concentrated to 500 ml under partial vacuum. The mixture was allowed to cool slowly and then was refrigerated overnight. On the next day, it was filtered, and the product was washed with cold acetone (−10°; 3 × 70 ml). The product was dried under vacuum, and 279 g was obtained (mp 221–223°). The entire yield was placed in a 3-liter flask containing 1 liter of 25% aqueous potassium carbonate and 1 liter of pentane.

This mixture was stirred mechanically at high speed until the suspended hydrochloride dissolved (4 hr). The pentane layer was separated, dried over potassium carbonate, filtered, and concentrated under vacuum. The concentrate was transferred to a 5-liter three-necked flask with benzene (250 ml), and then benzene was boiled off under vacuum, thus assuring anhydrous conditions. Anhydrous ether (3 liters) was then added, and the mixture was stirred until solution was complete.

The solution was then cooled to −35°, and 477 ml of methyllithium (1.8 *M* in ether) was added dropwise with rapid stirring. The temperature was maintained at −30° with a dry ice–acetone bath throughout the addition (2–3 hr). Benzoyl chloride (209 ml) was then added at −30°, and the mixture was stirred an additional 15 min at this temperature. The cooling bath was removed, and the mixture was stirred until it reached 25° and then was allowed to stand overnight.

The mixture was next cooled to 0°, and 800 ml of water was added slowly with rapid stirring. Then the ether was removed under vacuum, and 1 liter of methylene chloride was added. This phase was then separated, dried over magnesium sulfate, filtered, and concentrated again to 1 liter.

Hydrogen chloride gas was passed into the methylene chloride solution at 0° until the solution was saturated. The excess hydrogen chloride and the solvent were then removed under vacuum. One liter of anhydrous ether was then added to the syrup, and the mixture was stirred mechanically. Crystallization soon began. After 2 hr of stirring, the mixture was filtered; the product was washed with ether (3 × 300 ml) and dried under vacuum. The yield was 387.4 g, mp 180–184°. When recrystallized from methylene chloride–ether, the material melted at 185–187°.

Anal.—Calc. for $C_{26}H_{31}NO_4$·73% HBr·27% HCl: C, 63.63; H, 6.57; Br, 11.89; Cl, 1.95; N, 2.86; O, 13.05. Found: C, 63.48; H, 6.66; Br, 11.81; Cl, 1.86; N, 2.80; O, 12.88.

The mixed salt formation was probably due to the generation of bromide from lithium bromide present as a stabilizer in the methyllithium solution.

***N*-Methyl-4-piperidinyl α-Benzoyloxy-α-cyclopentylphenylacetate (II)**—Compound III (10 g) was slurried in 100 ml of ether and 100 ml of 10% aqueous sodium bicarbonate. As soon as two clear phases formed, the mixture was transferred to a separator; the ethereal phase was separated and dried over anhydrous magnesium sulfate. Evaporation of the ether gave an almost quantitative yield of a highly viscous oil. The material was eluted with chloroform–methanol (4:1) through a 22.2 × 2-cm silica gel column.

Anal.—Calc. for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32; O, 15.18. Found: C, 73.83; H, 7.42; N, 3.40; O, 15.02.

***N*-Methyl-4-piperidinyl α-Benzoyloxy-α-cyclopentylphenylacetate Hydrochloride (IV)**—The free base (8.3 g), obtained as described, was dissolved in 200 ml of methylene chloride and 100 ml of ether. Gaseous hydrogen chloride was introduced at 0–10° until the solution was saturated. The solvent and the excess acid were removed under reduced pressure, and the viscous residue was covered with anhydrous ether. After a few hours, the ether was decanted, and the syrup was recovered with ether. After 24 hr, the crystallization was complete. The yield was 8 g. When recrystallized three times from methylene chloride–ether, the white crystalline material melted at 162.5–164°.

Anal.—Calc. for $C_{26}H_{32}ClNO_4$: C, 68.18; H, 7.04; Cl, 7.74; N, 3.05. Found: C, 67.87; H, 6.97; Cl, 7.53; N, 3.23.

***N*-Methyl-4-piperidinyl α-Benzoyloxy-α-cyclopentylphenylacetate Methiodide (V)**—Compound IV (5 g) was dissolved in 30 ml of water. Then 50 ml of ether was added, and the mixture was neutralized slowly with 10% aqueous potassium carbonate. The ethereal phase was then separated, dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was dissolved in 10 ml of anhydrous acetone, and 2 g of methyl iodide was added. The solution was refluxed for 4 hr. After cooling, ether was added to precipitate the product. Five grams of material was thus obtained. It was recrystallized from methanol–ether, mp 133–137°.

Anal.—Calc. for $C_{27}H_{34}INO_4$: C, 57.55; H, 6.08; N, 2.50. Found: C, 57.68; H, 6.27; N, 2.42.

***N*-Methyl-4-piperidinyl α-Benzoyloxy-α-cyclopentylphenylacetate Hydrobromide (VI)**—The free base obtained from 10 g of III was dissolved in 200 ml of methylene chloride–ether (1:1). Gaseous hydrogen bromide was passed through the solution until a strong acid reaction was obtained. The solvent was then evaporated under reduced pressure, and the viscous residue was covered with anhydrous ether for 2 days. The oil solidified upon standing after addition of some methylene chloride. The product was collected and crystallized with 30 ml of methylene chloride and 60 ml of ether. The 4.6 g of product was recrystallized twice from methylene chloride–ether, mp 185–186.5°.

Anal.—Calc. for $C_{26}H_{32}BrNO_4$: C, 62.15; H, 6.42; N, 2.78. Found: C, 61.56; H, 6.50; N, 2.87.

The IR spectra were determined from mineral oil mulls. Compounds III, IV, and VI exhibited a characteristic ammonium absorption at 2360–3640 cm^{-1}; in II–IV and VI, the carbonyl stretching vibration occurred at 1735–1750 cm^{-1} and the aromatic C=C absorption was observed at 1595–1600 cm^{-1}. None of the benzoylated materials showed absorption in the hydroxy region.

NMR spectra were obtained in a deuterated chloroform–tetramethylsiloxane system. Compounds III, IV, and VI exhibited peaks at δ 1.4–1.8, 2–2.2, 2.2–2.5, 3–3.4, 5–5.3, 7.2–7.8, and 8–8.4 ppm. The nine protons of the cyclopentyl ring occurred as a singlet at 1.6 ppm, the three *N*-methyl group protons were observed as a doublet at 2.4 ppm, and the aromatic protons occurred as a multiplet at 7.2–7.8 ppm. Compound II gave a similar spectrum with peaks in the same shift region as observed for the salts.

TLC, developed with a chloroform–methanol–acetic acid system, showed main spots at R_f 0.45, 0.44, 0.44, and 0.46 for II, III, IV, and VI, respectively. The mixed salt, III, was further identified by mass spectrometry. A parent peak at *m/e* 421.5 corresponding to the molecular weight of its base, II, was observed. The same retention time was noted for II–IV and VI by GLC. The methiodide salt, V, synthesized from II, was identified only by elemental analysis.

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