Anticholinergic Agents. 2.* Absolute Configurations of 2-Methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol and 2-Methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol. Crystal Structures of the Corresponding Mandelates

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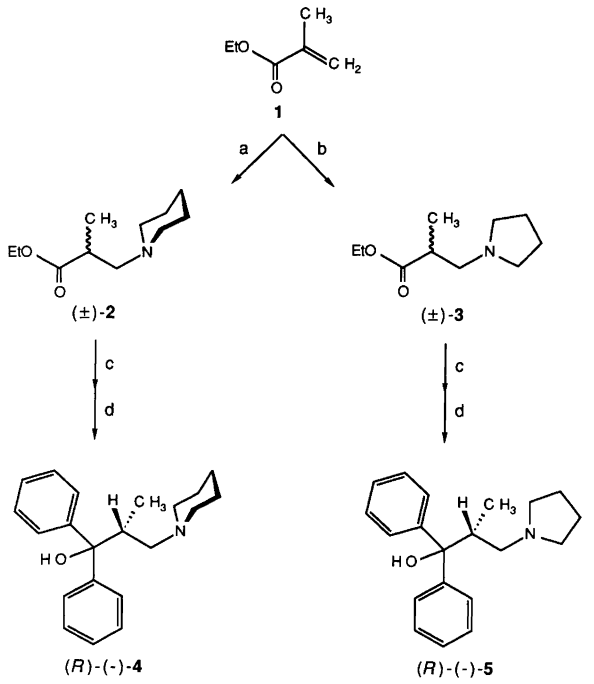
Racemic 2-methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol (**4**) and 2-methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol (**5**) have been synthesized and optically resolved employing (*R*)- and (*S*)-mandelic acid, respectively, as resolving agents. The absolute configurations of the enantiomers of **4** and **5** have been established as (−)-(*R*) and (+)-(*S*) by crystal structure analyses of (−)-(*R*)-2-methyl-1,1-diphenyl-3-(1-piperidinio)-1-propanol (+)-(*S*)-mandelate and (+)-(*S*)-2-methyl-1,1-diphenyl-3-(1-pyrrolidinio)-1-propanol (−)-(*R*)-mandelate. The corresponding methiodides have been prepared.

Muscarinic receptors are currently classified into at least four subtypes.[1–6] This subclassification has been proposed to account for the apparent selectivity of various muscarinic antagonists; e.g. trihexyphenidyl hydrochloride [(±)-1-cyclohexyl-1-phenyl-3-(1-piperidyl)-1-propanol hydrochloride], an anticholinergic drug which has found a place in the treatment of Parkinsonism.[7–9] Recent studies on the stereoselectivity of the enantiomers of trihexyphenidyl hydrochloride and its methiodide at muscarine receptor subtypes revealed high degree of selectivity at M_1-receptors in field-stimulated rabbit vas deferens and at M_2- and M_3-receptors in guinea pig atrium and ileum, respectively.[6] As part of an on-going project on structure–activity relationships of muscarinic antagonists, we have prepared (−)-(*R*)- and (+)-(*S*)-2-methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol [(−)-(*R*)- and (+)-(*S*)-**4**], (−)-(*R*)- and (+)-(*S*)-2-methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol [(−)-(*R*)- and (+)-(*S*)-**5**] and the corresponding methiodides. Syntheses (Scheme 1) of these compounds, and configurational assignments by X-ray diffraction analyses of the corresponding optically active mandelates constitute the subject of the present paper.

Several groups have previously prepared the racemic amino alcohol **4** to obtain information on its spasmolytic, analgesic, and local anaesthetic properties.[10–12] In 1956



Scheme 1. Syntheses of (−)-(*R*)- and (+)-(*S*)-2-methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol [(−)-(*R*)- and (+)-(*S*)-**4**] and (−)-(*R*)- and (+)-(*S*)-2-methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol [(−)-(*R*)- and (+)-(*S*)-**5**]: (a) Piperidine; (b) Pyrrolidine; (c) C_6H_5MgBr; (d). (−)-(*R*)-Mandelic acid [(+)-(*S*)-mandelic acid for the (+)-enantiomers of **4** and **5**].

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Takamatsu and Minaki synthesized the dextrorotatory enantiomer of **4** in a Grignard reaction between 2 equiv. of phenylmagnesium bromide and (+)-2-methyl-1-phenyl-3-(1-piperidyl)-1-propanone.[13] The optical activity reported by these authors is considerably higher than the rotation recorded by us in the same solvent and at the same temperature, $[\alpha]_D^{29} + 38.7°$ versus $[\alpha]_D^{29} + 26.2°$. Our compound was, however, found to be optically pure according to a ^{1}H NMR analysis employing Pirkle's alcohol as a chiral chelating shift reagent.[14,15] The figure reported by Takamatsu and Minaki is thus considered to be erroneous. The absolute configurations of the enantiomers of the amino alcohol **4** have not previously been reported.

The amino alcohol **5** was patented in 1967 as a means of inducing anorexia in obese subjects. It was then prepared by essentially the same methods as employed by us except for that the tartaric acids instead of the mandelic acids were used as resolving agents.[16] More recently Tang *et al.*[17] reported on the dissociative anaesthetic properties of racemic amino alcohol **5**. The enantiomers of **5** have been reported without configurational assignment.

The optical purities of all the enantiomers of 2-methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol (**4**) and 2-methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol (**5**) were assessed by the addition of a chiral solvating agent, (+)-(*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol to the ^{1}H NMR solution according to the method described by Pirkle *et al.*[14,15] The ^{1}H NMR spectra did not reveal detectable amounts of enantiomeric impurities.

Experimental

General methods. Optical rotations were recorded on a Perkin-Elmer 241 instrument. ^{1}H NMR spectra were recorded at 60 MHz on a Jeol PMX-60 instrument, or at 200 MHz on a Varian XL-200 instrument using TMS as an internal reference. ^{13}C NMR spectra were obtained at 50 MHz on a Varian XL-200 instrument. All NMR measurements were carried out in $CDCl_3$ solutions. Melting points were determined on a Büchi melting point apparatus and are uncorrected.

Preparation of methiodides. The methiodides of the amines **4** and **5** were synthesized by refluxing a solution of the amine (0.2 g) and methyl iodide (0.46 g, 3.2 mmol) in acetone (3 ml) for 1 h. The methiodides precipitated on being cooled. The four optically active methiodides were obtained in ca. 85 % yield.

Enantiomeric purity. Addition of Pirkle's alcohol,[14,15] (+)-(*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol, to the ^{1}H NMR solutions of (±)-2-methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol (**4**) and (±)-2-methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol (**5**) in a molar ratio of ca. 16:1 induced spectral non-equivalence of the resonances (doublets) ascribed to the methyl groups of the diastereomeric solvates: (+)-(*S*)-**4**: δ 0.91; (−)-(*R*)-**4**: δ 0.88 and (+)-(*S*)-**5**: δ 0.96; (−)-(*R*)-**5**: δ 0.92.

Detectable amounts of enantiomeric impurities were not observed when Pirkle's alcohol was added to the ^{1}H NMR solutions of the enantiomers of 2-methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol (**4**) and 2-methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol (**5**). Less than 2.5 % of the wrong enantiomer could be detected (ee > 95 %).

(±)-Ethyl 2-methyl-3-(1-piperidyl)propanoate (**2**). Ethyl 2-methylpropenoate (**1**, 5.00 g, 43.9 mmol), piperidine (4.06 g, 47.8 mmol) and acetic acid (0.10 g, 1.7 mmol) were stirred under nitrogen at 70 °C for 17 h. The reaction mixture was cooled, made alkaline with aqueous 1.0 M NaOH (15 ml), and extracted with $CHCl_3$ (20 ml). The organic layer was washed with saturated brine, dried over Na_2SO_4, and distilled. (±)-Ethyl 2-methyl-3-(1-piperidyl) propanoate (**2**) was obtained as a colourless oil (7.19 g, 82 %). B.p.[10] 102–103 °C. ^{1}H NMR (60 MHz): δ 0.93–1.70 (12 H, m), 1.93–2.83 (7 H, m), 4.09 (2 H, q, *J* 7.0 Hz). The corresponding methyl ester has previously been prepared by Bieber[18] in a similar manner.

(±)-Ethyl 2-methyl-3-(1-pyrrolidyl)propanoate (**3**). The synthesis of the amino ester **3** was carried out as described above for **2** except that pyrrolidine (3.48 g, 49.0 mmol) was used instead of piperidine. Yield: 6.79 g (84 %). B.p.[10] 90–91 °C. ^{1}H NMR (60 MHz): δ 1.00–1.45 (6 H, m), 1.50–2.00 (4 H, m), 2.14–2.94 (7 H, m), 4.15 (2 H, q, *J* 7.0 Hz).

(±)-2-Methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol (**4**). The racemic amino alcohol **4** was prepared in a Grignard reaction between 2 equiv. of phenylmagnesium bromide and the amino ester **2** essentially as described by Nazarov and Kazaryan.[11] The amino alcohol (±)-**4**, recrystallized from *n*-hexane, was obtained in 63 % yield. R_f 0.56 (SiO_2, *n*-hexane–ethyl acetate–dimethylethylamine 90:10:2). M.p. 122 °C, lit.[10] m.p. 115 °C, lit.[12] m.p. 120–121 °C, lit.[11] m.p. 122–122.5 °C. ^{1}H NMR (200 MHz): δ 0.93 (3 H, d, *J* 7.1 Hz), 1.36–1.63 (7 H, m), 2.22–2.38 (6 H, m), 2.87–3.00 (1 H, m), 7.16–7.48 (10 H, m); ^{13}C NMR (50 MHz): δ 16.1, 24.2, 26.4, 37.5, 55.9, 62.5, 82.2, 126.7, 127.0, 127.4, 127.6, 127.9, 128.6, 146.2, 148.3.

(−)-(R)-2-Methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol [*(−)-(R)-4*]. The racemic amino alcohol **4** (4.90 g, 15.9 mmol) and (+)-(*S*)-mandelic acid (2.41 g, 15.9 mmol) were dissolved in refluxing ethyl acetate (49 ml). Crystals appeared almost immediately when the reaction mixture was cooled. The crystals were harvested after 12 h at room temperature and washed with cold ethyl acetate. {Note: on prolonged (24 h) standing at room temperature the other diastereomeric salt started to crystallize}. The salt was recrystallized four times from decreasing volumes of ethyl acetate–ethanol (2:1). Yield: 0.54 g (15 %). M.p. 171 °C, $[\alpha]_D^{20} + 54.3°$ (*c* 1.5, MeOH). The salt was dissolved in aqueous 1 M NaOH and extracted with diethyl ether

(3×15 ml). The solution was dried over Na_2SO_4 and concentrated to dryness to furnish (−)-(*R*)-**4** (0.30 g, overall 12 %). M.p. 136 °C. $[\alpha]_D^{20} - 27.9°$ (*c* 1.5, MeOH). (+)-(*R*)-2-methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol hydrochloride [(+)-(*R*)-**4** HCl]: m.p. 235 °C (decomp.); $[\alpha]_D^{20} + 40.8°$ (*c* 1.5, MeOH).

(+)-(S)-2-Methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol [*(+)-(S)-***4**]. The mother liquors of the first two crystallizations of (−)-(*R*)-2-methyl-1,1-diphenyl-3-(1-piperidinio)-1-propanol (+)-(*S*)-mandelate [(−)-(*R*)-**4** (+)-(*S*)-mandelate] were concentrated to dryness, redissolved in 1 M NaOH and extracted with diethyl ether (3×15 ml). The solvent was removed *in vacuo*. The residue (2.31 g, 7.5 mmol) and (−)-(*R*)-mandelic acid (1.14 g, 7.5 mmol) were dissolved in refluxing ethyl acetate–ethanol (2:1; 30 ml). The crystalline salt was recrystallized thrice from decreasing amounts of ethyl acetate–ethanol (2:1). Yield: 0.99 g (28 %). M.p. 171 °C, $[\alpha]_D^{20} - 57.0°$ (*c* 1.5, MeOH). The amino alcohol (+)-(*S*)-**4** (0.69 g, overall 28 %) was obtained from the mandelate salt in the usual manner. M.p. 136 °C. lit.[13] m.p. 135–136 °C; $[\alpha]_D^{20} + 26.6°$, $[\alpha]_D^{29} + 26.2°$ (*c* 1.5, MeOH), lit.[13] $[\alpha]_D^{29} + 38.7°$ (*c* 1.5, MeOH). (−)-(*S*)-2-methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol hydrochloride [(−)-(*S*)-**4** HCl]: m.p. 235 °C (decomp.), lit.[13] m.p. 225–226 °C (decomp.); $[\alpha]_D^{20} - 41.2°$ (*c* 1.5, MeOH), $[\alpha]_D^{32} - 49.5°$ (*c* 2.55, H_2O), lit.[13] $[\alpha]_D^{32} - 52.0°$ (*c* 2.55, H_2O).

(+)-(R)-2-Methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol methiodide [*(+)-(R)-***4** *methiodide*]. M.p. 226–227 °C; $[\alpha]_D^{20} - 52.3°$ (*c* 1.5, MeOH).

(−)-(S)-2-Methyl-1,1-diphenyl-3-(1-piperidyl)-1-propanol methiodide [*(−)-(S)-***4** *methiodide*]. M.p. 227–228 °C; $[\alpha]_D^{20} - 52.9°$ (*c* 1.5, MeOH).

(±)-2-Methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol (**5**). The racemic amino alcohol **5** was obtained in 68 % yield in a Grignard reaction between 2 equiv. of phenylmagnesium bromide and the amino ester **3** essentially as described by Veldkamp.[16] R_f 0.40 (SiO_2, *n*-hexane–ethyl acetate–dimethylethylamine 90:10:2). M.p. 118–120 °C, lit.[16] 118–119 °C. ^{1}H NMR (200 MHz): δ 1.01 (3 H, d, *J* 7.1 Hz), 1.71–1.78 (5 H, m), 2.43–2.66 (6 H, m), 2.69–2.81 (1 H, m), 7.13–7.56 (10 H, m); ^{13}C NMR (50 MHz): δ 15.8, 23.9, 38.9, 55.7, 59.7, 82.1, 126.6, 126.8, 126.85, 126.9, 128.1, 128.6, 146.4, 148.9.

(−)-(R)-2-Methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol [*(−)-(R)-***5**]. The racemic amino alcohol **5** (5.00 g, 16.9 mmol) was resolved employing (+)-(*S*)- and (−)-(*R*)-mandelic acid as described above for the amino alcohol **4**. (+)-(*S*)-Mandelic acid furnished (−)-(*R*)-**5** (0.98 g, 39 %). M.p. 137–139 °C, lit.[16] m.p. 135–137.5 °C; $[\alpha]_D^{20} - 8.8°$ (*c* 1.5, MeOH), lit.[16] $[\alpha]_D^{25} - 38.9 \pm 0.5°$ (*c* 1.1808, $CHCl_3$). (+)-(*R*)-2-Methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol hydrochloride [(+)-(*R*)-**5** HCl): m.p. 235 °C (decomp.), lit.[16] m.p. 235–236 °C (decomp.); $[\alpha]_D^{20} + 39.6°$ (*c* 1.5, MeOH), lit.[16] $[\alpha]_D^{25} + 39 \pm 1°$ (*c* 0.701, MeOH).

(+)-(S)-2-Methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol [*(+)-(S)-***5**]. Yield: 1.13 g (45 %). M.p. 137 °C, lit.[16] m.p. 135–137.5 °C; $[\alpha]_D^{20} + 9.3°$ (*c* 1.5, MeOH), lit.[16] $[\alpha]_D^{25} + 38.1 \pm 0.5°$ (*c* 1.2336, $CHCl_3$). (−)-(*S*)-2-Methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol hydrochloride [(−)-(*S*)-**5** HCl]: m.p. 235 °C (decomp.), lit.[16] m.p. 234–235.5 °C; $[\alpha]_D^{20} - 40.1°$ (*c* 1.5, MeOH), lit.[16] $[\alpha]_D^{25} - 41 \pm 1°$ (*c* 0.6442, MeOH).

(+)-(R)-2-Methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol methiodide [*(+)-(R)-***5** *methiodide*]. M.p. 226 °C; $[\alpha]_D^{20} + 69.7°$ (*c* 1.5, MeOH).

(−)-(S)-2-Methyl-1,1-diphenyl-3-(1-pyrrolidyl)-1-propanol methiodide [*(−)-(S)-***5** *methiodide*]. M.p. 226–227 °C; $[\alpha]_D^{20} - 69.9°$ (*c* 1.5, MeOH).

Table 1. Final fractional coordinates and equivalent temperature factors with estimated standard deviations for non-hydrogen atoms in (−)-(*R*)-2-methyl-1,1-diphenyl-3-(1-piperidinio)-1-propanol (+)-(*S*)-mandelate [(−)-(*R*)-**4** (+)-(*S*)-mandelate].

Atom	*x*	*y*	*z*	U_{eq}/Å$^{2\,a}$
O1	0.9914(3)	0.0190(2)	0.5179(2)	0.040
O2	1.0980(3)	0.3504(2)	0.3551(2)	0.043
O3	1.2770(3)	0.3879(2)	0.4258(2)	0.050
O4	1.2164(4)	0.5655(2)	0.4217(2)	0.061
N1	1.1778(3)	0.1755(2)	0.3368(2)	0.034
C1	1.2120(4)	−0.0420(3)	0.5054(2)	0.037
C2	1.1500(5)	−0.1244(3)	0.4898(3)	0.051
C3	1.2245(6)	−0.2014(3)	0.4700(3)	0.064
C4	1.3601(6)	−0.1969(4)	0.4635(3)	0.065
C5	1.4239(5)	−0.1155(4)	0.4781(3)	0.065
C6	1.3513(4)	−0.0384(3)	0.4987(3)	0.051
C7	1.1552(4)	0.0594(3)	0.6169(2)	0.036
C8	1.2724(4)	0.1006(3)	0.6432(2)	0.043
C9	1.2923(5)	0.1171(3)	0.7228(3)	0.051
C10	1.1958(5)	0.0921(3)	0.7766(2)	0.053
C11	1.0814(5)	0.0498(3)	0.7516(2)	0.052
C12	1.0610(4)	0.0328(3)	0.6720(2)	0.043
C13	1.1298(4)	0.0416(3)	0.5307(2)	0.032
C14	1.0832(5)	0.2110(3)	0.5083(2)	0.050
C15	1.1631(4)	0.1281(3)	0.4810(2)	0.036
C16	1.1320(4)	0.1060(3)	0.3958(2)	0.040
C17	1.3282(4)	0.1837(3)	0.3329(2)	0.046
C18	1.3697(5)	0.2494(3)	0.2687(3)	0.058
C19	1.3129(6)	0.2214(3)	0.1894(3)	0.072
C20	1.1626(6)	0.2116(3)	0.1940(2)	0.067
C21	1.1204(5)	0.1476(3)	0.2596(2)	0.054
C22	1.1676(5)	0.4762(3)	0.2206(3)	0.055
C23	1.2038(6)	0.4981(4)	0.1448(3)	0.069
C24	1.2660(6)	0.5799(4)	0.1299(3)	0.072
C25	1.2924(6)	0.6375(4)	0.1899(4)	0.079
C26	1.2590(5)	0.6140(3)	0.2670(3)	0.061
C27	1.1957(4)	0.5325(3)	0.2827(2)	0.042
C28	1.1532(4)	0.5083(3)	0.3559(3)	0.045
C29	1.1790(4)	0.4068(3)	0.3839(2)	0.036

$^a U_{eq} = (U_{11} + U_{22} + U_{33})/3$.

Table 2. Bond distances (Å) and bond angles (°) with estimated standard deviations for (−)-(*R*)-2-methyl-1,1-diphenyl-3-(1-piperidinio)-1-propanol (+)-(*S*)-mandelate [(−)-(*R*)-**4** (+)-(*S*)-mandelate].

Distance		Distance	
O1–C13	1.433(5)	O2–C29	1.255(5)
O3–C29	1.243(6)	O4–C28	1.419(6)
N1–C16	1.506(5)	N1–C17	1.503(6)
N1–C21	1.499(6)	C1–C2	1.381(6)
C1–C6	1.391(6)	C1–C13	1.535(6)
C2–C3	1.393(7)	C3–C4	1.356(9)
C4–C5	1.373(8)	C5–C6	1.386(8)
C7–C8	1.390(6)	C7–C12	1.388(6)
C7–C13	1.523(6)	C8–C9	1.401(6)
C9–C10	1.380(7)	C10–C11	1.365(7)
C11–C12	1.402(6)	C13–C15	1.562(6)
C14–C15	1.524(6)	C15–C16	1.529(6)
C17–C18	1.519(7)	C18–C19	1.530(7)
C19–C20	1.505(9)	C20–C21	1.525(7)
C22–C23	1.389(7)	C22–C27	1.376(6)
C23–C24	1.371(8)	C24–C25	1.358(8)
C25–C26	1.407(8)	C26–C29	1.376(6)
C27–C28	1.532(7)	C28–C29	1.539(6)
Angle		**Angle**	
C16–N1–C17	112.7(3)	C16–N1–C21	107.2(3)
C17–N1–C21	111.2(3)	C2–C1–C6	117.5(4)
C2–C1–C13	120.9(4)	C6–C1–C13	121.6(4)
C1–C2–C3	121.1(5)	C2–C3–C4	120.7(5)
C3–C4–C5	119.2(5)	C4–C5–C6	120.9(5)
C1–C6–C5	120.6(5)	C8–C7–C12	117.8(4)
C8–C7–C13	122.0(4)	C12–C7–C13	120.2(4)
C7–C8–C9	120.7(4)	C8–C9–C10	120.5(5)
C9–C10–C11	119.4(4)	C10–C11–C12	120.5(5)
C7–C12–C11	121.1(4)	O1–C13–C1	106.6(3)
O1–C13–C7	110.3(3)	O1–C13–C15	107.9(3)
C1–C13–C7	108.8(3)	C1–C13–C15	112.3(3)
C7–C13–C15	110.8(3)	C13–C15–C14	111.6(4)
C13–C15–C16	107.9(3)	C14–C15–C16	110.9(4)
N1–C16–C15	116.1(4)	N1–C17–C18	110.7(4)
C17–C18–C19	112.0(4)	C18–C19–C20	110.3(5)
C19–C20–C21	111.8(5)	N1–C21–C20	112.3(4)
C23–C22–C27	122.3(5)	C22–C23–C24	119.6(5)
C23–C24–C25	119.3(5)	C24–C25–C26	121.1(5)
C25–C26–C27	120.3(5)	C22–C27–C26	117.5(4)
C22–C27–C28	121.8(4)	C26–C27–C28	120.6(4)
O4–C28–C27	111.7(4)	O4–C28–C29	111.2(4)
C27–C28–C29	111.3(4)	O2–C29–O3	125.8(4)
O2–C29–C28	116.7(4)	O3–C29–C28	117.5(4)

Results and Discussion

X-Ray crystal structure investigations of the title compounds were undertaken to establish their absolute configurations.

*(−)-(*R*)-2-Methyl-1,1-diphenyl-3-(1-piperidinio)-1-propanol (+)-(*S*)-mandelate* [*(−)-(*R*)-**4** (+)-(*S*)-mandelate*]. The crystals of (−)-2-methyl-1,1-diphenyl-3-(1-piperidinio)-1-propanol (+)-(*S*)-mandelate [(−)-**4** (+)-(*S*)-mandelate], $C_{29}H_{35}NO_4$ belong to the orthorhombic system with space group $P2_12_12_1$, cell dimensions $a = 9.951(2)$, $b = 14.645(2)$, $c = 17.163(2)$ Å and $Z = 4$ ($D_x = 1.24$ g cm^{-3}). Using $2\Theta_{max} = 50°$ and MoK_α radiation, and choosing an observed–unobserved cut-off at $2.5\sigma(I)$, a total of 2084 observed reflections were recorded on an automatic diffractometer at room temperature. No correction for absorption or secondary extinction was applied (crystal size: 0.4×0.4×0.4 mm). The structure was solved by direct methods[19] and refined by full-matrix least-squares techniques.[20] Weights in least squares were calculated from the standard deviations in intensities, $\sigma(I)$, taken as $\sigma(I) = [C_1 + (0.02C_2)^2]^{1/2}$, where C_1 is the total number of counts and C_2 the net count. Anisotropic temperature factors were used for non-hydrogen atoms. The maximum r.m.s. amplitudes of thermal vibration range from 0.19 to 0.35 Å. Hydrogen atom positions were calculated and refined with isotropic temperature factors. The final R value was 4.3 % ($R_w = 4.5$ %) for 2084 observed reflections. Final fractional coordinates with estimated standard deviations for the non-hydrogen atoms are listed in Table 1. Bond distances and bond angles, with estimated standard deviations are given in Table 2. Fig. 1 is a perspective drawing of the molecule showing the numbering of atoms and the absolute configuration of the amino alcohol as (−)-(*R*) since the absolute configuration of the mandelate moiety is known.

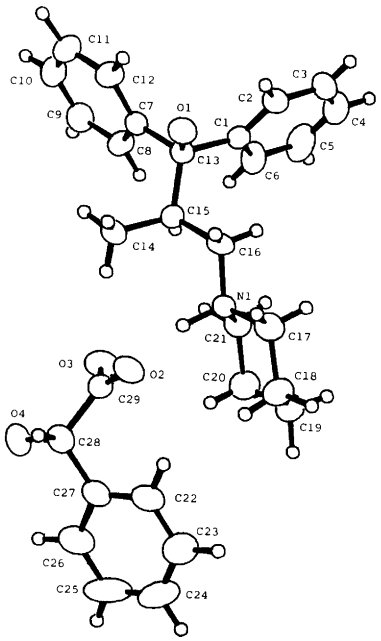

Fig. 1. Perspective drawing of (−)-(*R*)-2-methyl-1,1-diphenyl-3-(1-piperidinio)-1-propanol (+)-(*S*)-mandelate [(−)-(*R*)-**4** (+)-(*S*)-mandelate] showing the numbering of atoms and absolute configuration.

*(+)-(*S*)-2-Methyl-1,1-diphenyl-3-(1-pyrrolidinio)-1-propanol (−)-(*R*)-mandelate* [*(+)-(*S*)-**5** (−)-(*R*)-mandelate*]. The crystals of (+)-2-methyl-1,1-diphenyl-3-(1-pyrrolidinio)-1-propanol (−)-(*R*)-mandelate [(+)-**5** (−)-(*R*)-mandelate], $C_{28}H_{33}NO_4$ belong to the orthorhombic system with space group $P2_12_12_1$, cell dimensions $a = 9.908(3)$, $b = 14.572(5)$,

Table 3. Final fractional coordinates and equivalent temperature factors with estimated standard deviations for non-hydrogen atoms in (+)-(*S*)-2-methyl-1,1-diphenyl-3-(1-pyrrolidinio)-1-propanol (−)-(*R*)-mandelate [(−)-(*S*)-**5** (−)-(*R*)-mandelate].

Atom	*x*	*y*	*z*	U_{eq}/Å$^{2\,a}$
O1	0.5162(2)	0.0185(2)	0.4795(1)	0.042
O2	1.2919(3)	0.5620(2)	0.5831(1)	0.063
O3	0.2246(2)	0.3840(2)	0.5806(1)	0.053
O4	0.4002(2)	0.3453(1)	0.6544(1)	0.048
N1	0.3231(3)	0.1709(2)	0.6635(1)	0.039
C1	0.3493(6)	0.0607(4)	0.3822(3)	0.035
C2	0.4426(7)	0.0358(5)	0.3259(4)	0.048
C3	0.4204(7)	0.0540(5)	0.2463(4)	0.055
C4	0.3031(7)	0.0967(5)	0.2227(4)	0.056
C5	0.2087(7)	0.1213(5)	0.2779(4)	0.052
C6	0.2310(7)	0.1029(4)	0.3579(4)	0.044
C7	0.2962(6)	−0.0441(4)	0.4928(3)	0.039
C8	0.1560(8)	−0.0422(5)	0.4973(4)	0.057
C9	0.0828(8)	−0.1188(6)	0.5174(5)	0.069
C10	0.1472(9)	−0.2004(6)	0.5322(5)	0.070
C11	0.2859(9)	−0.2046(5)	0.5300(5)	0.068
C12	0.3582(7)	−0.1261(5)	0.5089(4)	0.052
C13	0.3764(6)	0.0407(4)	0.4682(3)	0.035
C14	0.4230(7)	0.2112(4)	0.4941(4)	0.051
C15	0.3441(3)	0.1261(2)	0.5205(2)	0.037
C16	0.3753(4)	0.1022(2)	0.6051(2)	0.041
C17	0.1729(4)	0.1782(3)	0.6686(2)	0.050
C18	0.1482(5)	0.2170(3)	0.7495(3)	0.079
C19	0.2707(5)	0.1975(3)	0.7978(2)	0.077
C20	0.3704(6)	0.1497(4)	0.7453(3)	0.057
C21	0.3022(5)	0.5293(3)	0.7246(3)	0.043
C22	0.2397(6)	0.6125(4)	0.7381(3)	0.059
C23	0.1991(7)	0.6374(4)	0.8132(4)	0.069
C24	0.2176(7)	0.5799(4)	0.8748(4)	0.067
C25	0.2812(7)	0.4960(4)	0.8626(4)	0.067
C26	0.3241(6)	0.4712(4)	0.7880(3)	0.054
C27	0.3499(5)	0.5041(3)	0.6420(3)	0.044
C28	0.3214(5)	0.4025(3)	0.6238(3)	0.039

$^{a}U_{eq} = (U_{11} + U_{22} + U_{33})/3$.

Table 4. Bond distances (Å) and bond angles (°) with estimated standard deviations for (+)-(*S*)-2-methyl-1,1-diphenyl-3-(1-pyrrolidinio)-1-propanol (−)-(*R*)-mandelate [(+)-(*S*)-**5** (−)-(*R*)-mandelate].

Distance		Distance	
O1–C13	1.435(7)	O2–C27	1.424(6)
O3–C28	1.240(6)	O4–C28	1.256(6)
N1–C16	1.506(5)	N1–C17	1.495(5)
N1–C20	1.505(7)	C1–C2	1.383(9)
C1–C6	1.387(9)	C1–C13	1.521(9)
C2–C3	1.403(10)	C3–C4	1.378(11)
C4–C5	1.376(10)	C5–C6	1.409(9)
C7–C8	1.391(10)	C7–C12	1.371(10)
C7–C13	1.529(9)	C8–C9	1.375(12)
C9–C10	1.373(13)	C10–C11	1.376(13)
C11–C12	1.397(11)	C13–C15	1.564(7)
C14–C15	1.533(8)	C15–C16	1.518(5)
C17–C18	1.514(6)	C18–C19	1.495(7)
C19–C20	1.505(8)	C21–C22	1.380(8)
C21–C26	1.392(8)	C21–C27	1.533(7)
C22–C23	1.391(9)	C23–C24	1.357(9)
C24–C25	1.392(10)	C25–C26	1.391(9)
C27–C28	1.539(7)		
Angle		**Angle**	
C16–N1–C17	115.3(3)	C16–N1–C20	111.8(3)
C17–N1–C20	105.7(4)	C2–C1–C6	118.2(6)
C2–C1–C13	120.2(6)	C6–C1–C13	121.6(6)
C1–C2–C3	121.3(7)	C2–C3–C4	120.1(7)
C3–C4–C5	119.4(7)	C4–C5–C6	120.5(7)
C1–C6–C5	120.5(6)	C8–C7–C12	117.0(7)
C8–C7–C13	121.2(6)	C12–C7–C13	121.8(6)
C7–C8–C9	121.6(8)	C8–C9–C10	120.3(8)
C9–C10–C11	119.8(8)	C10–C11–C12	118.9(8)
C7–C12–C11	122.4(7)	O1–C13–C1	110.1(5)
O1–C13–C7	106.4(5)	O1–C13–C15	107.5(4)
C1–C13–C7	109.1(5)	C1–C13–C15	111.2(5)
C7–C13–C15	112.4(5)	C13–C15–C14	111.8(4)
C13–C15–C16	108.5(4)	C14–C15–C16	111.2(4)
N1–C16–C15	114.1(3)	N1–C17–C18	103.9(3)
C17–C18–C19	107.5(4)	C18–C19–C20	107.0(4)
N1–C20–C19	104.7(4)	C22–C21–C26	118.3(5)
C22–C21–C27	120.2(5)	C26–C21–C27	121.5(5)
C21–C22–C23	120.9(6)	C22–C23–C24	120.9(6)
C23–C24–C25	119.2(6)	C24–C25–C26	120.2(6)
C21–C26–C25	120.5(6)	O2–C27–C21	112.0(4)
O2–C27–C28	110.8(4)	C21–C27–C28	111.1(4)
O3–C28–O4	125.7(5)	O3–C28–C27	118.1(5)
O4–C28–C27	116.1(4)		

$c = 17.075(4)$ Å and $Z = 4$ ($D_x = 1.24$ g cm^{-3}). Using $2\Theta_{max} = 50°$ and MoK_α radiation, and choosing an observed–unobserved cutoff at $2.5\sigma(I)$, a total of 1913 observed reflections were recorded on an automatic diffractometer at room temperature. No correction for absorption or secondary extinction was applied (crystal size: 0.4×0.3×0.3 mm). The structure was solved by direct methods[19] and refined by full-matrix least-squares techniques.[20] Weights in least squares were calculated from the standard deviations in intensities, $\sigma(I)$, taken as $\sigma(I) = [C_1 + (0.02C_2)^2]^{1/2}$, where C_1 is the total number of counts and C_2 the net count. Anisotropic temperature factors were used for non-hydrogen atoms. The maximum r.m.s. amplitudes of thermal vibration range from 0.20 to 0.35 Å. Hydrogen atom positions were calculated and refined with isotropic temperature factors. The final R value was 4.6 % ($R_w = 4.5$ %) for 1913 observed reflections. Final fractional coordinates with estimated standard deviations for the non-hydrogen atoms are listed in Table 3. Bond distances and bond angles, with estimated standard deviations are given in Table 4. Fig. 2 is a perspective drawing of the molecule showing the numbering of atoms. Furthermore, the figure reveals the absolute configuration of the amino alcohol as (+)-(*S*) since the absolute configuration of the mandelate is known.

Lists of thermal parameters, hydrogen atom parameters, and observed and calculated structure factors are available from P. Groth on request.

The potency and selectivity of the individual enantiomers of the amino alcohols **4** and **5** at muscarinic receptor subtypes will be reported elsewhere.

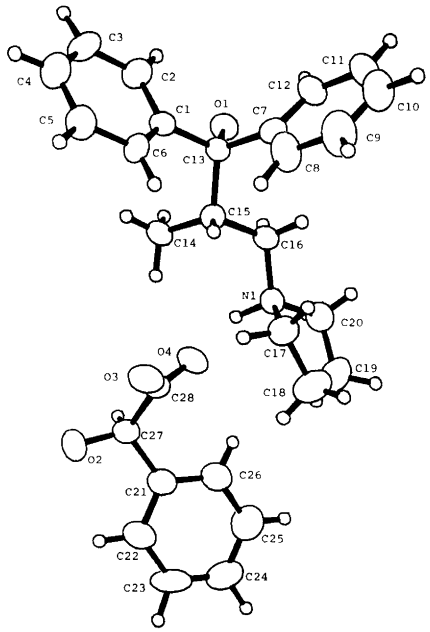

Fig. 2. Perspective drawing of (+)-(*S*)-2-methyl-1,1-diphenyl-3-(1-pyrrolidinio)-1-propanol (−)-(*R*)-mandelate [(+)-(*S*)-**5** (−)-(*R*)-mandelate] showing the numbering of atoms and absolute configuration.

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