(*R*)-(−)-1,1-Diphenyl-3-piperidinobutan-1-ol, an Anticholinergic Agent. The Crystal Structure of (*R*)-(−)-1,1-Diphenyl-3-piperidiniobutan-1-ol (*R,R*)-tartrate

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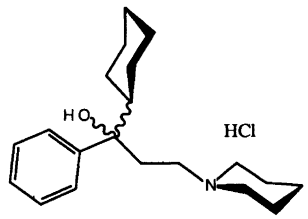
Racemic 1,1-diphenyl-3-piperidinobutan-1-ol has been prepared and optically resolved employing (*R,R*)- and (*S,S*)-tartaric acid, respectively, as the resolving agents. The absolute configurations of the enantiomers have been established as (*R*)-(−) and (*S*)-(+) by a crystal structure analysis of (*R*)-(−)-1,1-diphenyl-3-piperidiniobutan-1-ol (*R,R*)-tartrate.

Muscarinic receptors are currently classified into at least four subtypes.[1–6] This sub-classification has been proposed to account for the apparent selectivity of various muscarinic antagonists; e.g. trihexyphenidyl hydrochloride (**1**), an anticholinergic drug which has found a place in the treatment of Parkinsonism.[7–9] As part of an on-going project on structure–activity relationships of muscarinic antagonists, we have prepared (*R*)-(−)- and (*S*)-(+)-1,1-diphenyl-3-piperidinobutan-1-ol (**2**). Kasuya has reported the atropine-like effect of the (+)-enantiomer of these amino alcohols (**2**) to be considerably higher than that of the (−)-isomer.[10] These results, however, appear to be at variance with those of Kjær and Petersen who failed to observe significant spasmolytic or analgesic effects of racemic **2** in animal experiments.[11]



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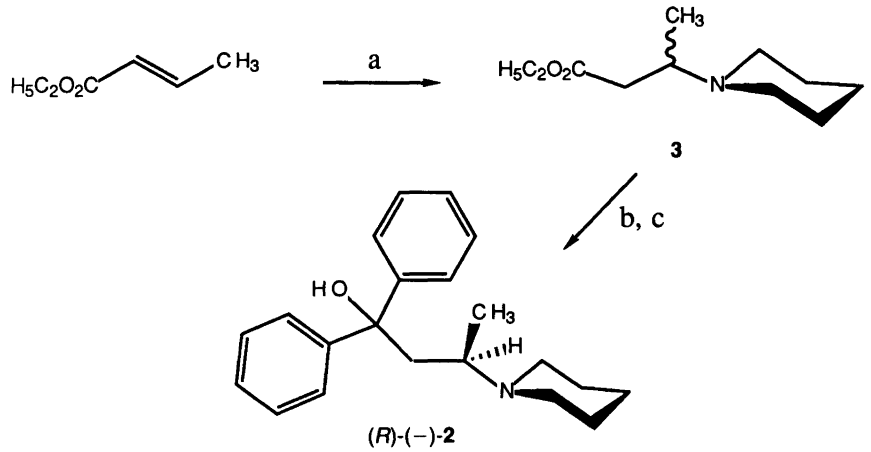
Racemic amino alcohol (±)-**2** has previously been obtained employing somewhat different routes.[11,12] The present synthesis was performed by treating piperidine with ethyl 2-butenoate in a Michael addition to give the amino



Scheme 1. Synthesis of (*R*)-(−)-1,1-diphenyl-3-piperidinobutan-1-ol [(*R*)-(−)-**2**]. *Reagents:* a, piperidine; b, C_6H_5MgBr; c, (*R,R*)-tartaric acid.

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ester **3**[13] which was subsequently treated with two equivalents of phenylmagnesium bromide in a Grignard-type reaction to furnish the amino alcohol (±)-**2**. Optical resolution of **2** employing (*R,R*)- and (*S,S*)-tartaric acid as the resolving agents was carried out essentially as described by Kasuya[14] (cf. Scheme 1).

The enantiomeric purity of (*R*)-(−)-1,1-diphenyl-3-piperidinobutan-1-ol [(*R*)-(−)-**2**] was assessed by the addition of a chiral solvating agent, (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's alcohol) to the ^{1}H NMR solution according to the method described by Pirkle *et al.*[15,16] The ^{1}H NMR spectrum did not reveal detectable amounts of (*S*)-(+)-1,1-diphenyl-3-piperidinobutan-1-ol [(*S*)-(+)-**2**].

Configurational assignments of the enantiomers of 1,1-diphenyl-3-piperidinobutan-1-ol (**2**) by an X-ray diffraction analysis of the (*R,R*)-tartrate of the (−)-enantiomer constitute the subject of the present paper.

Experimental

General methods. Optical rotations and mass spectra were recorded on Perkin–Elmer 241, and Micromass 7070F instruments, respectively. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 76 MHz, respectively, on a Varian XL-300 instrument using $SiMe_4$, or the central solvent peaks (^{13}C) of $CDCl_3$ (δ 77.16) or CD_3OD (δ 49.04) as internal references.

(±)-Ethyl 3-piperidinobutanoate[13] (**3**). The amino ester **3** was prepared essentially as described by Nazarov and Kruglikova[13] except for the addition of catalytic amounts of ethanoic acid which reduced the reaction time from ca. 6 days to ca. 1 day. MS: *m/z* (%): 199 (M^+, 2), 184 (7), 156 (3), 112 (100); ^{1}H NMR ($CDCl_3$): δ 1.05 (3 H, d, *J* 6.6 Hz), 1.26 (3 H, t, *J* 7.1 Hz), 1.39–1.45 (2 H, m), 1.5–1.6 (4 H, m), 2.21 (1 H, dd, *J* 8.4 and 14.2 Hz), 2.45 (4 H, m), 2.57 (1 H, dd, *J* 5.9 and 14.2 Hz), 3.12 (1 H, m), 4.13 (2 H, q, *J* 7.1 Hz); ^{13}C NMR ($CDCl_3$): δ 14.4, 15.2, 24.9, 26.5, 38.3, 49.5, 57.2, 60.3, 173.0.

(±)-1,1-Diphenyl-3-piperidinobutan-1-ol [(±)-2]. The racemic amino alcohol **2** was prepared in a Grignard reaction as described by Kjær and Petersen.[11] The product was, however, purified by chromatography on silica gel rather than crystallization of the HBr salt. ^{1}H NMR ($CDCl_3$): δ 0.89 (3 H, d, *J* 6.71 Hz), 1.35–1.7 (6 H, m), 2.1–2.25 (3 H, m), 2.37 (1 H, m), 2.55–2.65 (3 H, m), 7.1–7.5 (10 H, m), 9.1 (1 H, br s); ^{13}C NMR ($CDCl_3$): δ 13.1 (CH_3), 24.6 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 42.0 (CH_2), 57.5 (CH), 78.4, 125.6, 126.1, 126.4, 128.0, 128.1, 148.5, 148.9.

(R)-(−)-1,1-Diphenyl-3-piperidinobutan-1-ol [(R)-(−)-2]. The amino alcohol (*R*)-(−)-**2** was obtained as described by Kasuya[14] employing (*R,R*)-tartaric acid as the resolving agent. (*R*)-(−)-**2** (*R,R*)-tartrate: $[\alpha]_D^{20}$ −35.6° (*c* 0.340, MeOH); m.p. 195–198 °C (decomp.); lit.[14] $[\alpha]_D^{16}$ −38.2° (MeOH); m.p. 206 °C. (*R*)-(−)-**2**: $[\alpha]_D^{20}$ −55.2° (*c* 1.84, EtOH); m.p. 96 °C; ^{1}H and ^{13}C NMR spectra agreed with those of (±)-**2**; lit.[14] $[\alpha]_D^{20}$ −64.6° (EtOH); m.p. 96 °C. (*R*)-(−)-**2**·hydrochloride: $[\alpha]_{578}^{20}$ −51.6 (*c* 1.82, MeOH); m.p. 237.5 °C (decomp.); ^{1}H and ^{13}C NMR spectra were in agreement with those expected for **2**·hydrochloride; lit.[14] $[\alpha]_D^{18}$ −53.1° (MeOH); m.p. 234 °C.

(S)-(+)-1,1-diphenyl-3-piperidinobutan-1-ol [(S)-(+)-2]. The amino alcohol (*S*)-(+)-**2** was obtained employing (*S,S*)-tartaric acid rather than by crystallization of the corresponding (*R,R*)-tartrate from propanone as described by Kasuya.[14] (*S*)-(+)-**2** (*S,S*)-tartrate: $[\alpha]_{578}^{20}$ +36.5° (*c* 0.406, MeOH); m.p. 195–198 °C (decomp.). (*S*)-(+)-**2**: $[\alpha]_D^{20}$ +58.2° (*c* 1.53, EtOH); m.p. 96 °C; ^{1}H and ^{13}C NMR spectra agreed with those of (±)-**2**; lit.[14] $[\alpha]_D^{20}$ +53.5° (EtOH); m.p. 96 °C. (*S*)-(+)-**2**·hydrochloride: $[\alpha]_D^{20}$ +45.4° (*c* 1.71, MeOH); m.p. 231 °C (decomp.); ^{1}H and ^{13}C NMR spectra were in agreement with those expected for **2**·hydrochloride; lit.[14] $[\alpha]_D^{18}$ +52.1° (MeOH); m.p. 234 °C.

Enantiomeric purity. Addition of Pirkle's alcohol,[15,16] (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, to the ^{1}H NMR solution of a 3:2 mixture of (*R*)-(−)-1,1-diphenyl-3-piperidinobutan-1-ol [(*R*)-(−)-**2**] and (*S*)-(+)-1,1-diphenyl-3-piperidinobutan-1-ol [(*S*)-(+)-**2**] induced spectral nonequivalence of the resonances (doublets) ascribed to the CH_3 groups of the two diastereomeric solvates: (*S*)-(+)-**2**: δ 0.75; (*R*)-(−)-**2**: δ 0.83. Molar ratio Pirkle's alcohol: [(*R*)-(−)-**2** + (*S*)−(+)-**2**] = 1:1.

The enantiomeric purity of (*R*)-(−)-1,1-diphenyl-3-piperidinobutan-1-ol [(*R*)-(−)-**2**] was assessed by the addition of Pirkle's alcohol to the ^{1}H NMR solution ($CDCl_3$). (*S*)-(+)-1,1-diphenyl-3-piperidinobutan-1-ol [(*S*)-(+)-**2**] could not be detected.

Results and discussion

The crystals of (−)-1,1-diphenyl-3-piperidiniobutan-1-ol (*R,R*)-tartrate, $C_{26}H_{33}NO_7$, belong to the triclinic system with space group *P*1, cell dimensions $a = 5.930(1)$, $b = 10.095(2)$, $c = 10.946(2)$ Å, $\alpha = 70.69(2)$, $\beta = 81.62(2)$, $\gamma = 89.86(2)°$ and $Z = 1$ ($D_x = 1.24$ 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 889 observed reflections were recorded on an automatic diffractometer at room temperature. No correction for absorption or secondary extinction was applied (crystal size 0.2×0.2×0.1 mm). The structure was solved by direct methods[17] and refined by full-matrix least-squares techniques.[18] 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 are in the range 0.24–0.43 Å. Hydrogen atom positions were calculated and

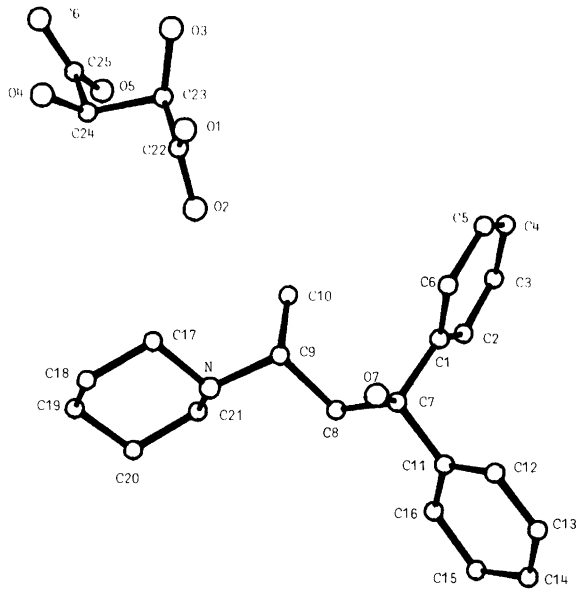

Fig. 1. Perspective drawing of (*R*)-(−)-1,1-diphenyl-3-piperidiniobutan-1-ol (*R,R*)-tartrate [(*R*)-(−)-**2** (*R,R*)-tartrate] showing the numbering of atoms.

Table 1. Final fractional coordinates and equivalent temperature factors with estimated standard deviations for non-hydrogen atoms.

Atom	*z*	*y*	*z*	U_{eq}[a]
O1	0.732(6)	0.472(3)	0.224(4)	0.107
O2	1.052(6)	0.362(4)	0.217(4)	0.073
O3	0.792(6)	0.109(3)	0.286(3)	0.054
O4	0.796(6)	0.248(4)	0.015(4)	0.058
O5	0.232(6)	0.144(3)	0.184(4)	0.055
O6	0.501(6)	0.038(3)	0.086(3)	0.064
O7	0.629(6)	0.839(3)	0.442(4)	0.035
N	0.255(6)	0.777(3)	0.192(4)	0.040
C1	0.341(6)	0.945(4)	0.558(4)	0.049
C2	0.495(7)	0.980(4)	0.621(4)	0.069
C3	0.461(7)	1.094(4)	0.667(4)	0.104
C4	0.279(8)	1.172(4)	0.645(4)	0.091
C5	0.111(6)	1.141(4)	0.579(4)	0.076
C6	0.157(7)	1.023(4)	0.533(4)	0.072
C7	0.395(6)	0.823(4)	0.505(4)	0.045
C8	0.230(6)	0.820(4)	0.411(4)	0.051
C9	0.311(6)	0.716(4)	0.334(4)	0.056
C10	0.187(7)	0.572(4)	0.402(4)	0.078
C11	0.360(7)	0.686(4)	0.626(4)	0.047
C12	0.154(6)	0.648(4)	0.703(4)	0.052
C13	0.109(6)	0.524(4)	0.801(4)	0.064
C14	0.291(7)	0.437(4)	0.830(4)	0.069
C15	0.498(7)	0.470(4)	0.759(4)	0.078
C16	0.539(7)	0.599(4)	0.651(4)	0.065
C17	0.013(7)	0.797(4)	0.181(4)	0.047
C18	−0.003(6)	0.879(4)	0.037(4)	0.058
C19	0.100(7)	0.802(4)	−0.053(4)	0.063
C20	0.347(7)	0.773(4)	−0.036(4)	0.075
C21	0.358(6)	0.693(4)	0.107(4)	0.052
C22	0.842(7)	0.365(4)	0.219(4)	0.061
C23	0.685(6)	0.234(4)	0.241(4)	0.059
C24	0.607(7)	0.253(4)	0.104(4)	0.051
C25	0.428(7)	0.136(4)	0.124(4)	0.037

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

Table 2. Bond distances (Å) and bond angles (°) with estimated standard deviations.

Distance		Distance	
O1–C22	1.28(6)	O2–C22	1.25(6)
O3–C23	1.38(6)	O4–C24	1.38(6)
O5–C25	1.26(6)	O6–C25	1.25(6)
O7–C7	1.44(6)	N–C9	1.55(6)
N–C17	1.47(6)	N–C3	1.52(6)
C1–C2	1.34(6)	C1–C6	1.35(6)
C1–C7	1.54(6)	C2–C3	1.39(6)
C3–C4	1.34(7)	C4–C5	1.41(6)
C5–C6	1.45(6)	C7–C8	1.53(6)
C7–C11	1.56(6)	C8–C9	1.59(6)
C9–C10	1.53(6)	C11–C12	1.35(6)
C11–C16	1.38(6)	C12–C13	1.35(6)
C13–C14	1.40(6)	C14–C15	1.34(6)
C15–C16	1.44(6)	C17–C18	1.53(6)
C18–C19	1.51(6)	C19–C20	1.52(7)
C20–C21	1.52(6)	C22–C23	1.55(6)
C23–C24	1.58(6)	C24–C25	1.53(6)

Angle		Angle	
C9–N–C17	116.0(31)	C9–N–C21	111.3(9)
C17–N–C21	110.4(30)	C2–C1–C6	120.4(36)
C2–C1–C7	116.9(33)	C6–C1–C7	122.5(34)
C1–C2–C3	119.7(37)	C2–C3–C4	121.8(40)
C3–C4–C5	121.0(37)	C4–C5–C6	114.7(33)
C1–C6–C5	122.4(36)	O7–C7–C1	109.9(31)
O7–C7–C8	111.7(32)	O7–C7–C11	109.8(31)
C1–C7–C8	109.2(30)	C1–C7–C11	106.1(31)
C8–C7–C11	110.0(30)	C7–C8–C9	110.3(30)
N–C9–C8	108.8(29)	N–C9–C10	109.4(30)
C8–C9–C10	109.9(31)	C7–C11–C12	121.5(34)
C7–C11–C16	118.8(34)	C12–C11–C16	119.7(36)
C11–C12–C13	123.7(36)	C12–C13–C14	117.4(36)
C13–C14–C15	121.5(38)	C14–C15–C16	120.0(37)
C11–C16–C15	117.7(36)	N–C17–C18	108.0(31)
C17–C18–C19	111.5(30)	C18–C19–C20	110.1(32)
C19–C20–C21	109.3(33)	N–C21–C20	109.9(30)
O1–C22–O2	121.6(37)	O1–C22–C23	113.4(35)
O2–C22–C23	124.3(34)	O3–C23–C22	112.8(32)
O3–C23–C24	111.1(32)	C22–C23–C24	105.9(31)
O4–C24–C23	109.2(33)	O4–C24–C25	111.9(32)
C23–C24–C25	108.2(32)	O5–C25–O6	127.4(38)
O5–C25–C24	117.9(34)	O6–C25–C24	114.5(35)

refined with isotropic temperature factors. The final *R*-value was 7.6 % (R_w = 5.6 %) for 889 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 may be found in Table 2. Fig. 1 is a perspective drawing of the molecule showing the numbering of atoms. 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 alcohol **2** at muscarinic receptor sub-types will be reported elsewhere.[19]

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