N-[(R)-1-(2-Hydroxy-3,5-dimethylphenyl)ethyl]-N-[(R)-2-methyl-1-phenylpropyl]ammonium chloride

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2,4-Dimethyl-6-[(1R)-1-{[(1R)-2-methyl-1-phenylpropyl]-amino}ethyl]phenol, (I), has been synthesized and its absolute configuration has been determined by reference to the crystal structure of the title compound, $C_{20}H_{28}NO^+ \cdot Cl^-$, (II), the hydrochloride of (I). The new stereogenic centre (the C atom adjacent to the N atom on the phenol side) was unambiguously determined to have an R configuration.

Comment

The synthesis of enantiopure amino alcohols which have different functionalities is an important subject of research because these compounds are widespread in natural products, show pharmacological activity, and have recently found application in asymmetric synthesis as chiral bases, auxiliaries and ligands (Cimarelli *et al.*, 2002). Chiral amino phenols, which are similar to amino alcohols, are important building blocks in organic synthesis and have attracted increasing attention in recent years, owing to their effect in asymmetric synthesis and asymmetric induction (Palmieri, 1999, 2000; Cimarelli & Palmieri, 1998, 2000; Cimarelli *et al.*, 2001; Berrisford *et al.*, 1995; Soai & Niwa, 1992; Kitamura *et al.*, 1989; Juaristi *et al.*, 1998; Rijnberg *et al.*, 1997; Nakano *et al.*, 1997; Watanabe *et al.*, 1991; Kitamura *et al.*, 1986; Hayase *et al.*, 1997; Sola *et al.*, 1998; Xu *et al.*, 2002).

In this paper, we report the crystal structure of the hydrochloride derivative, (II), of one example of this class of amino alkylphenols, namely 2,4-dimethyl-6-[(1R)-1-{[(1R)-2-methyl-1-phenylpropyl]amino}ethyl]phenol. The occurrence of a Cl atom in compound (II) helps in establishing the absolute configuration of the compound and thus in deducing the absolute configuration of (I).
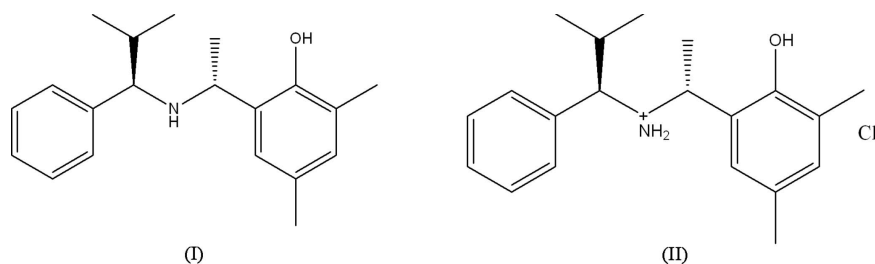
A view of the asymmetric unit of (II) is given in Fig. 1. The absolute configuration of (II) is (R,R), as clearly indicated by the refinement of the Flack parameter (Flack, 1983). Thus, we can infer that the absolute configuration of (I) is also (R,R).

The two benzene rings (C15–C20 and C1–C8) are roughly parallel to each other, making a dihedral angle of only 13.003 (9)°. An interesting feature of the structure is the
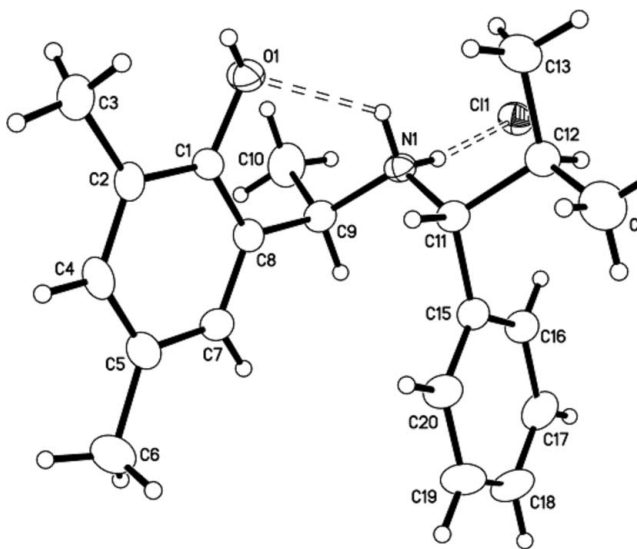
Figure 1

The asymmetric unit of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitray radii. Hydrogen bonds are represented by dashed lines.
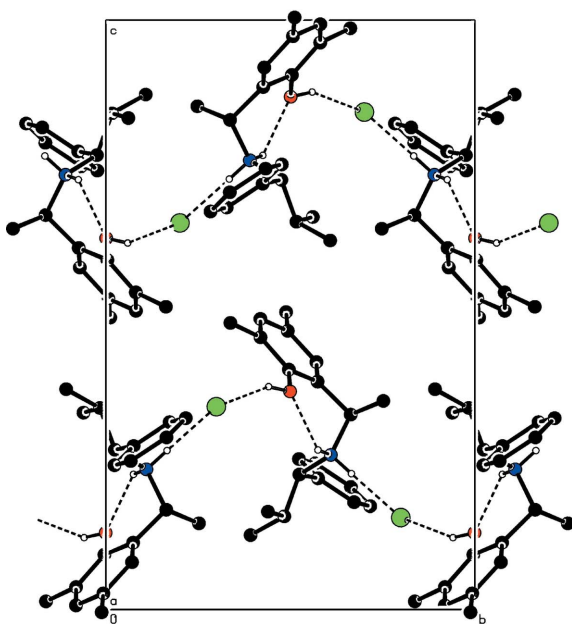

Figure 2

A packing view, showing the formation of helical chains through N—H···Cl and O—H···Cl hydrogen bonds (dashed lines). H atoms not involved in hydrogen bonding have been omitted.

occurrence of intra- and intermolecular hydrogen bonds. Intermolecular N—H···Cl and O—H···Cl hydrogen-bonding interactions result in the formation of helical chains running parallel to the b axis (Fig. 2 and Table 1).

Experimental

The title compound was prepared according to the procedure of Yang *et al.* (2005). (*R*)-2-Methyl-1-phenylpropan-1-amine (0.9 mmol) and

1-(2-hydroxy-3,5-dimethylphenyl)ethanone (0.9 mmol) were dissolved in methanol (10 ml) and reacted at room temperature for 48 h. After removal of the solvent, NaBH$_4$ (4.5 mmol) was added to the solution in tetrahydrofuran–ethanol (20 ml; 1:1 *v/v*) and stirred at 273 K until the solution became colourless. The solvent was then removed under reduced pressure. Water was added to the residue and 1 N HCl was added until the pH was 10. The mixture was extracted with CHCl$_3$, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. Further purification was carried out by thin-layer silica-gel chromatography (chloroform) to give chiral (I) {colourless solid; 86.3%; $[\alpha]^{22}_D = 84.1$ ($c_{0.5}$, CHCl$_3$)}. Since only the major diastereoisomer was obtained pure by thin-layer silica-gel chromatography, the ^{1}H NMR signals for the minor diastereoisomer were deduced from the spectrum of the crude reaction mixture. Compound (I) and concentrated HCl were reacted in methanol at room temperature. The solvent was removed and the solid residue was recrystallized from a solution in a mixture of ethyl acetate and ethanol (95.1 *v/v*) to yield compound (II) (m.p. 467.1–467.4 K).

Crystal data

C$_{20}$H$_{28}$NO$^+$·Cl$^-$	Mo $K\alpha$ radiation
$M_r = 333.88$	Cell parameters from 5813
Orthorhombic, $P2_12_12_1$	reflections
$a = 9.0404$ (12) Å	$\theta = 2.5$–27.8°
$b = 11.7373$ (15) Å	$\mu = 0.20$ mm^{-1}
$c = 18.768$ (2) Å	$T = 298$ (2) K
$V = 1991.5$ (4) Å^3	Block, colourless
$Z = 4$	$0.50 \times 0.34 \times 0.25$ mm
$D_x = 1.114$ Mg m^{-3}	

Data collection

Bruker SMART CCD area-detector diffractometer	3558 reflections with $I > 2\sigma(I)$
φ and ω scans	$R_{int} = 0.027$
Absorption correction: none	$\theta_{max} = 25.5°$
10401 measured reflections	$h = -10 \rightarrow 6$
3687 independent reflections	$k = -14 \rightarrow 14$
	$l = -22 \rightarrow 21$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0466P)^2$
$R[F^2 > 2\sigma(F^2)] = 0.044$	$+ 0.2784P]$
$wR(F^2) = 0.103$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.19$	$(\Delta/\sigma)_{max} = 0.001$
3687 reflections	$\Delta\rho_{max} = 0.20$ e Å^{-3}
214 parameters	$\Delta\rho_{min} = -0.21$ e Å^{-3}
H-atom parameters constrained	Absolute structure: Flack (1983), 1763 Friedel pairs
	Flack parameter: 0.01 (6)

Table 1

Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···O1	0.90	2.16	2.792 (2)	127
N1—H1B···Cl1	0.90	2.22	3.1122 (18)	171
O1—H1···Cl1^i	0.82	2.39	3.1371 (17)	152

Symmetry code: (i) $-x + 2, y + \frac{1}{2}, -z + \frac{3}{2}$.

All H atoms were included in calculated positions and treated as riding on their parent atoms, with N—H = 0.90, O—H = 0.82, C—H(methyl) = 0.96 and C—H(methine) = 0.98 Å, and with U_{iso}(H) = 1.2U_{eq}(C,N,O) or 1.5U_{eq}(CH$_3$).

Data collection: *SMART* (Bruker, 1997); cell refinement: *SAINT* (Bruker, 1997); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXTL* (Bruker, 2001).

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