

***N*-[(*R*)-1-(2-Hydroxy-5-methylphenyl)-ethyl]-*N*-[(*R*)-1-(2-methoxy-5-methylphenyl)-2-phenylethyl]aminium chloride**Xiao-Feng Yang,<sup>a\*</sup> Guang-You Zhang,<sup>a</sup> Yan Zhang,<sup>b</sup>  
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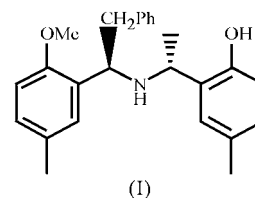
The title compound,  $C_{25}H_{30}NO_2^+ \cdot Cl^-$ , has been synthesized, and the crystal structure shows that it is mainly stabilized through intermolecular  $N-H \cdots Cl$  and  $O-H \cdots Cl$  and intramolecular  $N-H \cdots O$  hydrogen bonds. The absolute configuration of the new stereogenic center (the C atom adjacent to the N atom on the phenol side) was determined to have an *R* configuration.

**Comment**

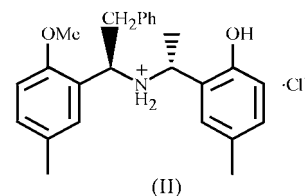
The synthesis of enantiopure amines is an important research subject, because this class of compounds has found widespread application in biological systems showing pharmacological activity. These compounds are used as resolving agents, chiral bases and auxiliaries in asymmetric synthesis (Juraristi, 1997; Clifton *et al.*, 1982; Palmieri, 1999, 2000; Cimarelli & Palmieri, 1998, 2000), and most have been derived from a few readily available natural products (Soai & Niwa, 1992; Ager *et al.*, 1996). To increase the understanding of asymmetric reactions, the design and synthesis of chiral ligands from non-natural resources is an essential research area in the field of synthetic organic chemistry (Vidal-Ferran *et al.*, 1997; Bolm *et al.*, 1998; Reddy *et al.*, 1999; Paleo *et al.*, 2000; Nugent, 2002) and chiral aminoalkylphenols are gaining increasing importance (Palmieri, 2000; Vyskocil *et al.*, 1998; Cardellicchio *et al.*, 1998, 1999; Bernardinelli *et al.*, 2000; Liu *et al.*, 2001; Cimarelli *et al.*, 2001; Zhang *et al.*, 2003).

We report here the molecular structure of one example of this class of aminoalkylphenols, namely 2-[(*R*)-1-[(*R*)-1-(2-methoxy-5-methylphenyl)-2-phenylethylamino]ethyl]-4-methylphenol, (I). The aminoalkylphenol was prepared by conventional condensation of (*R*)-(-)-1-[(2-methoxy-5-methyl)phenyl]-2-phenylethylamine with 2-hydroxy-5-methyl-

acetophenone (both purchased from J&K Chemical Ltd), followed by reduction using sodium borohydride in a tetrahydrofuran (THF)/ethanol (1:1 *v/v*) mixture. The *R,R* diastereoisomer is obtained as the main product; the chemical yield of purified and isolated (*R,R*)-(I) and the diastereoisomeric excess, d.e. (determined by <sup>1</sup>H NMR of the crude reaction mixture), are 89.2 and 99.0%, respectively. Generally, the reduction should take place after the B atom coordinates to the imine N atom, activating the C=N double bond, which assumes predominantly an *E* configuration, to nucleophilic attack. Subsequently, an intramolecular hydride transfer from NaBH<sub>4</sub> to the C atom on the *si* or *re* face of the C=N double bond takes place. Calculations were performed to find the energies of the transition states (*R,R*)-(I)-Ts and (*S,R*)-(I)-Ts, minimized at the PM3 semiempirical level, corresponding to the two different situations. Transition state (*R,R*)-(I)-Ts was more stable, with a difference of 1.35 kcal mol<sup>-1</sup>, and this value is in agreement with the experimental d.e., which shows (*R,R*)-(I) as the major product. This result is in agreement with the fact that for *si* attack the hydride enters on the less hindered side, *i.e.* on the same side as the H atom of the chiral auxiliary (*R*)-1-(2-methoxy-5-methyl)-2-phenylethyl group. At the same time, the N-atom lone pair is *gauche* between the (2-hydroxy-5-methyl)phenyl and the methyl groups of the same chiral group, in a very favorable position. On the other hand, the attack on the *re* face is on the more hindered side (Me) and with the N-atom lone pair in a less convenient position between the (2-hydroxy-5-methyl)phenyl group and the H atom.

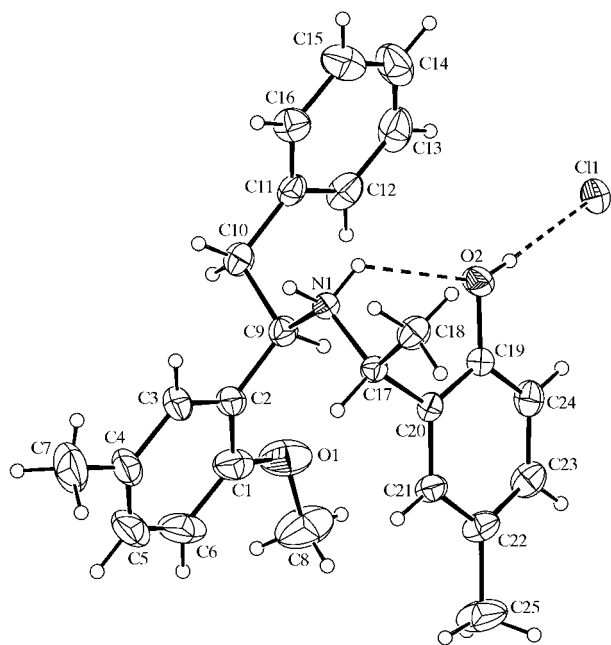


It is noteworthy that a novel chiral aminoalkylphenol, *viz.* (I), was synthesized. To confirm the structure of (I), an X-ray study of the title compound, (II), was carried out (Fig. 1).

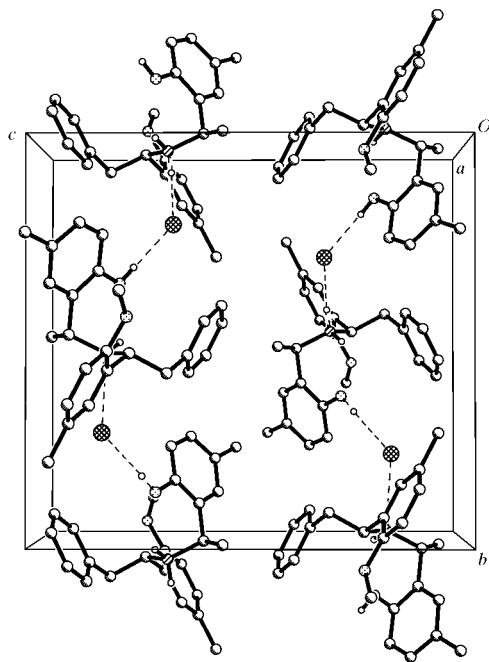


The molecular structure of (II) is shown in Fig. 1. The C1–C6 and C11–C16 aromatic rings are approximately parallel (Fig. 2), the dihedral angle between their planes being 4.5°. The dihedral angle between the planes of the C1–C6 and C19–C24 aromatic rings is 20.0°, while that between the C11–C16 and C19–C24 planes is 14.0°.

Selected bond lengths and angles, including those of the new stereogenic carbon center (C17), are reported in Table 1. The absolute configuration of (I) and (II) is *R,R*, as shown in Fig. 1.



**Figure 1**  
A view of (II), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. The methyl H atoms at C7, C8 and C25 were disordered and only one orientation is shown at each site.



**Figure 2**  
A view of the packing in (II). Hydrogen bonds are shown as dashed lines. All H atoms not involved in hydrogen bonding have been omitted.

Within the asymmetric unit, atom N1 acts as a hydrogen-bond donor to phenol atom O2 (Fig. 2 and Table 2). The molecular structure depends on two further pairs of N—H...Cl and O—H...Cl hydrogen bonds, from atoms N1 and O2 in the cation to atom Cl1 (Fig. 2 and Table 2).

## Experimental

For the preparation of the title compound, (*R*)-(-)-1-[(2-methoxy-5-methylphenyl)-2-phenylethylamine (3 mmol) and 2-hydroxy-5-methylacetophenone (3 mmol) (both purchased from J&K Chemical Ltd) were dissolved in methanol (20 ml) and reacted at room temperature for 12 h. The solvent was removed and NaBH<sub>4</sub> (15 mmol) was added to the solution in THF/ethanol (20 ml; 1:1 v/v). The reaction was allowed to stand and was monitored by thin-layer silica-gel chromatography. The reaction was stopped at constant conversion of starting material. 6 M HCl was added dropwise to the reaction mixture until hydrogen production ceased and the mixture was then neutralized with Na<sub>2</sub>CO<sub>3</sub>. The aqueous solution was extracted with CHCl<sub>3</sub>, and the organic layer was dried with anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure. Further purification was carried out by thin-layer silica-gel chromatography [first run: chloroform/methanol (40:1 v/v); second run: chloroform/methanol (60:1 v/v)] to give chiral (I) [canary oil; 89.2%;  $[\alpha]_D^{18} = -19.5$  (*c* 1/2, CHCl<sub>3</sub>)]. Since only the major diastereoisomer was obtained pure by thin-layer silica-gel chromatography, the <sup>1</sup>H NMR signals for the minor diastereoisomer were deduced from the spectra of the crude reaction mixture. Compound (I) and concentrated HCl were reacted at room temperature and a white solid was precipitated. The solvent was removed and the solid residue was recrystallized from ethanol to yield compound (II) (m.p. 473.0–473.2 K).

## Crystal data

C<sub>25</sub>H<sub>30</sub>NO<sub>2</sub><sup>+</sup>·Cl<sup>-</sup>  
*M<sub>r</sub>* = 411.95  
 Orthorhombic, *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>  
*a* = 9.227 (3) Å  
*b* = 15.323 (6) Å  
*c* = 16.504 (6) Å  
*V* = 2333.4 (15) Å<sup>3</sup>  
*Z* = 4  
*D<sub>x</sub>* = 1.173 Mg m<sup>-3</sup>

Mo *K*α radiation  
 Cell parameters from 3690 reflections  
 $\theta = 2.5$ – $22.3^\circ$   
 $\mu = 0.18$  mm<sup>-1</sup>  
*T* = 298 (2) K  
 Block, colorless  
 0.43 × 0.35 × 0.31 mm

## Data collection

Siemens SMART CCD area-detector diffractometer  
 $\varphi$  and  $\omega$  scans  
 Absorption correction: multi-scan (SADABS; Sheldrick, 1996)  
 $T_{\min} = 0.926$ ,  $T_{\max} = 0.946$   
 12 327 measured reflections

4115 independent reflections  
 3080 reflections with  $I > 2\sigma(I)$   
 $R_{\text{int}} = 0.031$   
 $\theta_{\max} = 25.0^\circ$   
 $h = -10 \rightarrow 10$   
 $k = -18 \rightarrow 18$   
 $l = -19 \rightarrow 14$

## Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.045$   
 $wR(F^2) = 0.130$   
 $S = 1.04$   
 4115 reflections  
 262 parameters  
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0695P)^2 + 0.2951P]$   
 where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\max} < 0.001$   
 $\Delta\rho_{\max} = 0.37$  e Å<sup>-3</sup>  
 $\Delta\rho_{\min} = -0.15$  e Å<sup>-3</sup>  
 Absolute structure: Flack (1983),  
 1763 Friedel pairs  
 Flack parameter:  $-0.03$  (7)

**Table 1**

Selected geometric parameters (Å, °).

N1—C9	1.507 (4)	C10—C11	1.494 (4)
N1—C17	1.512 (3)	C17—C20	1.502 (4)
C2—C9	1.508 (4)	C17—C18	1.530 (4)
C9—C10	1.530 (4)		
N1—C9—C2	111.8 (2)	C20—C17—N1	110.5 (2)
N1—C9—C10	108.1 (2)	C20—C17—C18	114.3 (2)
C2—C9—C10	113.1 (2)	N1—C17—C18	108.3 (2)

**Table 2**  
Hydrogen-bond geometry (Å, °).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N1—H1A...Cl1 <sup>i</sup>	0.90	2.21	3.103 (3)	170
N1—H1B...O2	0.90	2.18	2.774 (3)	123
O2—H2...Cl1 <sup>ii</sup>	0.82	2.30	3.115 (2)	177

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

Difference maps showed that the methyl H atoms at C7, C8 and C25 were not well resolved and these were allowed for in subsequent refinement cycles as being disordered over six sites of 0.5 occupancy. Other H atoms were visible in difference maps. All H atoms were treated as riding atoms, with C—H distances of 0.93 (aromatic), 0.96 (CH<sub>3</sub>), 0.97 (CH<sub>2</sub>) and 0.98 Å (CH). In all cases, H-atom isotropic displacement parameters were set at 1.2 times the equivalent anisotropic displacement parameter of the attached C or N atom.

Data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SAINTE* (Bruker, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Siemens, 1995); software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: HJ1041). Services for accessing these data are described at the back of the journal.

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