

Two isomers of 2,4-dibenzyl-8-aza-bicyclo[3.2.1]octan-3-ol

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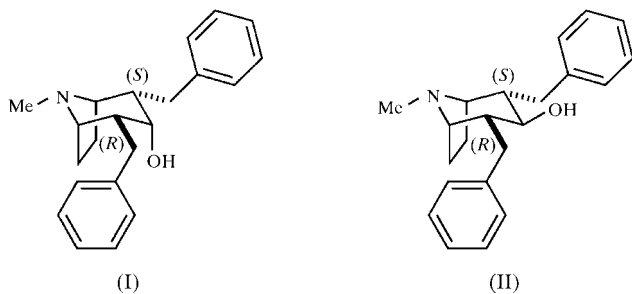
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The crystal structures of the title compounds, 2 α ,4 α -dibenzyl-3 α -tropanol (2 α ,4 α -dibenzyl-8-methyl-8-azabicyclo[3.2.1]octan-3 α -ol), C₂₂H₂₇NO, (I), and 2 α ,4 α -dibenzyl-3 β -tropanol (2 α ,4 α -dibenzyl-8-methyl-8-azabicyclo[3.2.1]octan-3 β -ol), C₂₂H₂₇NO, (II), show that both compounds have a piperidine ring in a chair conformation and a pyrrolidine ring in an envelope conformation. Isomer (I) is asymmetric, the benzyl groups having different orientations, whereas isomer (II) is mirror symmetric, and the N and O atoms, the C atom attached to the hydroxy group, and the methyl C atom attached to the N atom lie on the mirror plane. In the crystal structures of both (I) and (II), the molecules are linked together by intermolecular O—H...N hydrogen bonds to form chains that run parallel to the *a* direction in (I) and parallel to *b* in (II).

Comment

The tropane ring system is present in the natural product cocaine and in a number of other compounds that display interesting pharmacological properties. Numerous novel tropane analogs have been synthesized and evaluated as inhibitors of dopamine, serotonin and norepinephrine transporters in an effort to probe the topology of the cocaine



binding site on these biogenic amine transporters (Carrol *et al.*, 1999; Newman, 2000; Cappelli *et al.*, 2002; Newman & Kulkarni, 2002). In efforts to develop novel therapeutic agents

for treating central nervous system disorders, we have designed and synthesized a number of tropane derivatives. Compounds (I) and (II) are two isomeric tropane derivatives that we prepared recently. Both (I) and (II) were synthesized stereospecifically and identified initially by MS and NMR spectroscopy. In order to confirm unequivocally the stereochemistry of these compounds, and to gather more information on the structural conformation of the molecules for our molecular recognition studies, the crystal structures of (I) and (II) have been determined.

The molecular structures of (I) and (II) are shown in Fig. 1, while selected geometric parameters are presented in Tables 1 and 2. As expected, the structures of (I) and (II) are similar, with the piperidine ring in a chair conformation, the pyrrolidine ring in an envelope conformation with atom N as the flap, and the benzyl groups and the bridgehead *N*-methyl group bonded equatorially to the piperidine ring. However, in (I), the hydroxy group is attached axially to the piperidine ring on atom C3, whereas in (II), the hydroxy group is attached equatorially to the piperidine ring on atom C3. In (I), because of the steric interactions between the hydroxy group and the benzyl groups, the C2 and C4 benzyl groups are not mirror symmetric, as indicated by the unequal torsion angles around the C2—C9 and C9—C10 bonds and around the C4—C16 and

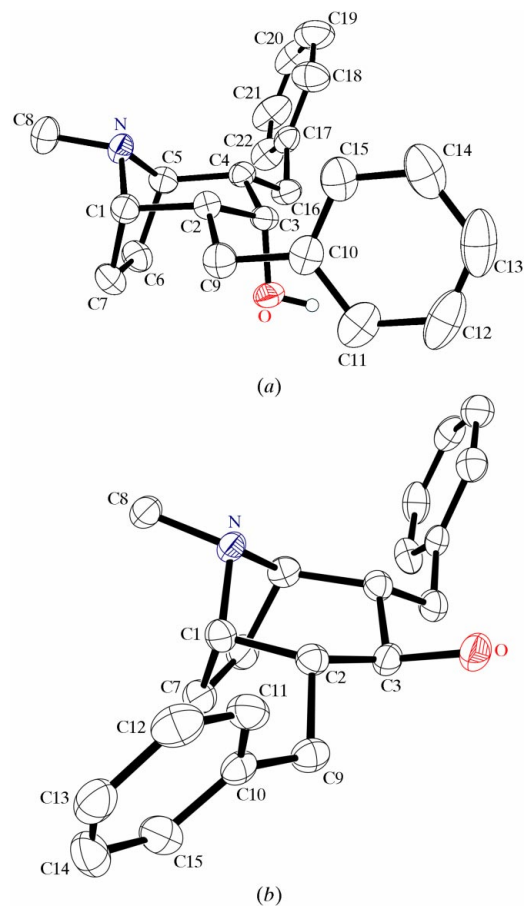


Figure 1

A view of the molecules of (a) isomer (I) and (b) isomer (II). Displacement ellipsoids are drawn at the 50% probability level.

C16–C17 bonds (Table 1). This conformation probably results from a repulsive interaction between the H atoms on atom C16 and the hydroxy group on atom C3, which causes the exocyclic O–C3–C4 angle [112.36 (16)°] to be slightly larger than the O–C3–C2 angle [109.51 (15)°]. In addition to the asymmetric phenyl rings in (I), the tropane ring system itself is also slightly contorted, as evidenced by the endocyclic bond lengths and angles (Table 1). The C1–C2 and C9–C10 bonds in (I) are approximately coplanar [C1–C2–C9–C10 = –176.53 (18)°]. In (II), where there is less intramolecular crowding, the whole molecule is mirror symmetric, with atoms N, O, C3 and C8 lying on the mirror plane (Table 2). In contrast to (I), the C2–C3 and C9–C10 bonds in (II) are approximately coplanar, as evidenced by the C3–C2–C9–C10 torsion angle [173.7 (2)°].

The molecules of (I) form infinite chains along the *a* axis (Fig. 2), and the molecules in these chains are connected by a zigzag pattern of intermolecular O–H···N hydrogen bonds [symmetry code: $x - \frac{1}{2}, -y + \frac{1}{2}, -z$; H···N = 1.96 Å, O···N = 2.793 (2) Å and O–H···N = 170°]. In the crystal

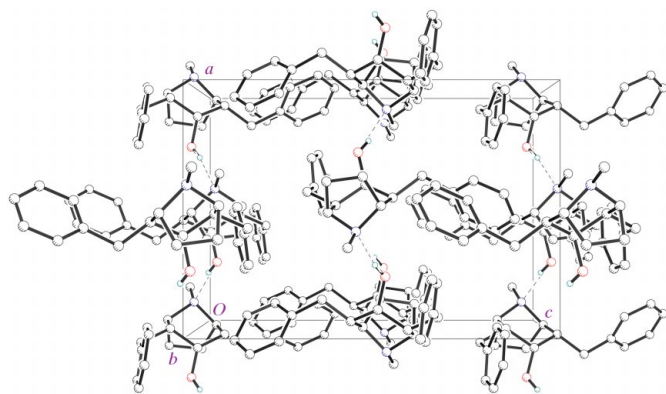


Figure 2
The crystal packing of (I), viewed along the *b* axis. Intermolecular hydrogen bonds are shown as dashed lines.

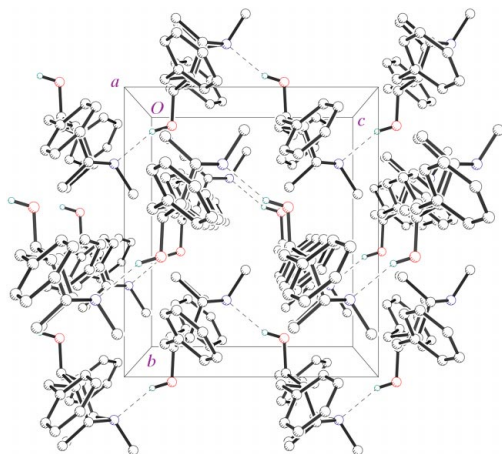


Figure 3
The crystal packing of (II), viewed along the *a* axis. Intermolecular hydrogen bonds are shown as dashed lines.

structure of (II), parallel intermolecular O–H···N hydrogen bonds [symmetry code: $-x, -y + 1, z - \frac{1}{2}$; H···N = 2.07 Å, O···N = 2.846 (3) Å and O–H···N = 154°] link the molecules into an infinite one-dimensional linear array, which is parallel to the *b* axis (Fig. 3).

Experimental

2(*E*),4(*E*)-Dibenzylidenetropanone (Jung *et al.*, 2001) was reduced stereoselectively to 2 α ,4 α -dibenzyltropanone by catalytic hydrogenation (45 psi H₂) over Pd/C (10%) in absolute methanol. Using diisobutylaluminium hydride at 195 K in tetrahydrofuran, 2 α ,4 α -dibenzyltropanone was then reduced stereoselectively to (I), which was purified by flash column chromatography on silica gel and then recrystallized from acetonitrile (m.p. 489 K). ¹H NMR (300 MHz, CDCl₃): δ 7.13–7.32 (*m*, 10H), 3.56 (*m*, 1H), 2.79 (*m*, 2H), 2.61–2.78 (*m*, 4H), 2.19 (*s*, 3H), 2.10–2.23 (*m*, 4H), 1.83 (*m*, 2H), 1.29 (*d*, *J* = 5.4 Hz, 1H, OH); ¹³C NMR (75 MHz, CDCl₃): δ 140.48, 129.17, 128.52, 126.03, 69.08, 64.03, 47.39, 40.89, 35.72, 22.00. Compound (II) was prepared stereoselectively by reduction of 2 α ,4 α -dibenzyltropanone with Zn/Hg in 20% HCl/1,4-dioxane (1:1) under reflux. Crude (II) was purified by the same method as used for (I) (m.p. 508 K). ¹H NMR (300 MHz, CDCl₃): δ 7.12–7.22 (*m*, 10 H), 3.10–3.22 (*m*, 3H), 2.80 (*m*, 2H), 2.33 (*dd*, *J* = 13.5, 10.2 Hz, 2H), 2.12 (*s*, 3H), 2.01 (*m*, 2H), 1.86 (*m*, 2H), 1.68 (*m*, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 140.45, 129.18, 128.59, 126.10, 74.39, 63.65, 50.97, 40.25, 36.56, 22.02. Crystals of (I) and (II) suitable for X-ray diffraction studies were obtained by slow evaporation of acetonitrile solutions at room temperature. X-ray data were collected from flash-cooled crystals. Crystals of (I) were observed to shatter upon cooling below ~200 K, so for this crystal, data were collected at 206 K.

Isomer (I)

Crystal data

C₂₂H₂₇NO
M_r = 321.45
 Orthorhombic, *P*2₁2₁2₁
a = 10.4244 (4) Å
b = 11.4988 (5) Å
c = 15.1602 (5) Å
V = 1817.22 (12) Å³
Z = 4
D_x = 1.175 Mg m^{–3}

Mo *K* α radiation
 Cell parameters from 11 302 reflections
 θ = 1.0–27.5°
 μ = 0.07 mm^{–1}
T = 206 (1) K
 Block, colorless
 0.24 × 0.24 × 0.20 mm

Data collection

Nonius KappaCCD diffractometer
 ω scans at fixed χ = 55°
 14 506 measured reflections
 2371 independent reflections
 1902 reflections with *I* > 2 σ (*I*)

*R*_{int} = 0.066
 θ _{max} = 27.5°
h = –13 → 13
k = –14 → 14
l = –19 → 19

Table 1

Selected geometric parameters (Å, °) for (I).

N–C5	1.486 (2)	C2–C9	1.531 (3)
N–C1	1.488 (2)	C3–C4	1.539 (3)
C2–C3	1.530 (3)	C4–C16	1.527 (3)
N–C1–C2	106.88 (15)	O–C3–C4	112.36 (16)
C3–C2–C9	112.98 (15)	C16–C4–C3	112.27 (15)
O–C3–C2	109.51 (15)	N–C5–C4	107.22 (15)
C3–C2–C9–C10	55.7 (2)	C3–C4–C16–C17	–157.74 (18)
C1–C2–C9–C10	–176.53 (18)	C4–C16–C17–C18	61.0 (3)
C2–C9–C10–C15	58.9 (3)		

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.043$
 $wR(F^2) = 0.096$
 $S = 1.44$
 2371 reflections
 219 parameters
 H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0496P)^2 + 0.0877P]$
 where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} = 0.005$
 $\Delta\rho_{\max} = 0.18 \text{ e } \text{\AA}^{-3}$
 $\Delta\rho_{\min} = -0.17 \text{ e } \text{\AA}^{-3}$
 Extinction correction: *SHELXL97*
 Extinction coefficient: 0.0126 (17)

Isomer (II)

Crystal data

$\text{C}_{22}\text{H}_{27}\text{NO}$
 $M_r = 321.45$
 Orthorhombic, *Cmc2₁*
 $a = 17.8580$ (8) \AA
 $b = 10.5480$ (9) \AA
 $c = 9.2364$ (8) \AA
 $V = 1739.8$ (2) \AA^3
 $Z = 4$
 $D_x = 1.227 \text{ Mg m}^{-3}$

Mo $K\alpha$ radiation
 Cell parameters from 4871 reflections
 $\theta = 1.0\text{--}27.5^\circ$
 $\mu = 0.07 \text{ mm}^{-1}$
 $T = 173$ (1) K
 Needle, colorless
 $0.50 \times 0.10 \times 0.08 \text{ mm}$

Data collection

Nonius KappaCCD diffractometer
 ω scans at fixed $\chi = 55^\circ$
 5089 measured reflections
 1085 independent reflections
 861 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.075$
 $\theta_{\max} = 27.4^\circ$
 $h = -23 \rightarrow 22$
 $k = -13 \rightarrow 13$
 $l = -11 \rightarrow 8$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.050$
 $wR(F^2) = 0.085$
 $S = 1.49$
 1085 reflections
 117 parameters
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0372P)^2P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$
 $\Delta\rho_{\max} = 0.20 \text{ e } \text{\AA}^{-3}$
 $\Delta\rho_{\min} = -0.21 \text{ e } \text{\AA}^{-3}$
 Extinction correction: *SHELXL97*
 Extinction coefficient: 0.0042 (10)

For both structures, Friedel pairs were merged prior to the final refinement cycles because values of the Flack (1983) parameters (obtained in each case as a variable in the full-matrix least-squares scheme against unmerged data) refined to values with no physical interpretation.

Table 2

Selected geometric parameters (\AA , $^\circ$) for (II).

N—C1	1.485 (3)	C2—C3	1.531 (3)
N—C1 ⁱ	1.486 (3)	C3—C2 ⁱ	1.531 (3)
O—C3—C2	108.83 (16)	O—C3—C2 ⁱ	108.83 (16)
C9—C2—C3—O	−73.4 (3)	C1—C2—C9—C10	−61.6 (3)
C3—C2—C9—C10	173.7 (2)		

Symmetry code: (i) $-x, y, z$.

For both compounds, data collection: *COLLECT* (Nonius, 1998); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL/PC* (Sheldrick, 1995); software used to prepare material for publication: *SHELX97-2* (Sheldrick, 1997) and local procedures.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ1138). Services for accessing these data are described at the back of the journal.

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