Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Two optically active isoquinoline derivatives

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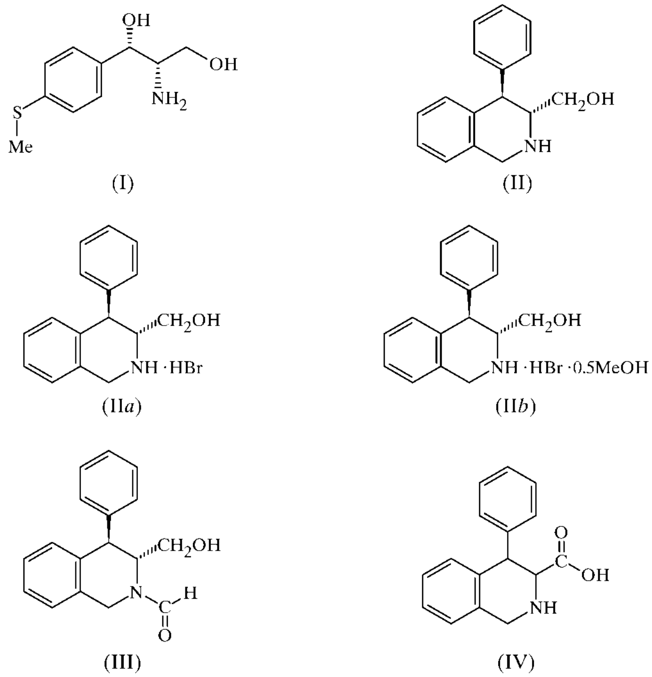
Received 10 May 2002
Accepted 4 July 2002
Online 20 July 2002

In the two title optically active tetrahydroisoquinoline derivatives, namely 3-hydroxymethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-2-ium bromide methanol hemisolvate, $C_{16}H_{18}NO^+ \cdot Br^- \cdot 0.5CH_3OH$, (II*b*), and 2-formyl-3-hydroxymethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, $C_{17}H_{17}NO_2$, (III), the absolute configurations have been confirmed as 3*R*,4*R* by structure refinement using Bijvoet-pair reflections. The hydroxymethyl and phenyl groups in (II*b*) are oriented in equatorial and pseudo-equatorial positions, respectively, whereas in (III), the corresponding groups are in axial and pseudo-axial positions, respectively; the hydroxymethyl and phenyl groups are *trans* with respect to one another in both structures. The heterocyclic rings in (II*b*) and (III) adopt envelope conformations inverted with respect to each other. In both structures, the molecules are linked through hydrogen bonds.

Comment

One of the steps in our synthesis of 4-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (4-phenyl-Tic), (IV), from (+)-thiomicamine, (I), involved *N*-formylation of the intermediate 3-hydroxymethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline hydrobromide, (II*a*), to give 2-formyl-3-hydroxymethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, (III) (Brózda *et al.*, 2000; see *Scheme*). The absolute configuration of both compounds, *i.e.* of (II*a*) and (III), as 3*R*,4*R* was implied by the 1*S*,2*S* configuration of the starting material (+)-thiomicamine, (I), and mechanistic considerations (Brózda *et al.*, 2000).

A half-chair or envelope conformation with a *trans* equatorial–pseudo-equatorial orientation of the C3 and C4 substituents in (II*a*), respectively, was confirmed by the value of the coupling constant (J = 10.2 Hz) between atoms H3 and H4 in the ^{1}H NMR spectrum. This value corresponds to that of axial–pseudo-axial H atoms in cyclohexene derivatives (Ehil & Wilen, 1994) and also to those in other *trans*-3,4-disubstituted tetrahydroisoquinoline derivatives (Bohe *et al.*, 1999; Pedrosa *et al.*, 2001).



In the ^{1}H NMR spectrum of formamide (III), however, atoms H3 and H4 appear as singlets, suggesting a conformational inversion within the hydrogenated heterocyclic ring. We suspected that intramolecular hydrogen bonding involving the hydroxyl H and amide O atoms was responsible for this change (Brózda *et al.*, 2000). Such a ring inversion would then place these H atoms in equatorial–pseudo-equatorial positions, respectively, with a torsion angle θ of *ca* 90°, for which, according to the Karplus equation, $^3J \simeq 0$ (Haasnoot *et al.*, 1980). There was also a possibility of steric hindrance between

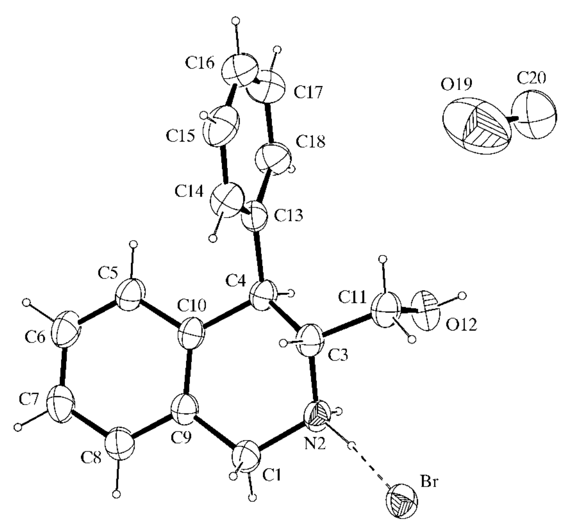


Figure 1
The molecular structure of (II*b*), showing the atomic labelling scheme. Only one position of the disordered C20 atom is shown. Non-H atoms are drawn as 30% probability displacement ellipsoids and H atoms are drawn as spheres of an arbitrary size.

 DOI: 10.1107/S0108270102011915

the C3 substituent and the introduced *N*-formyl group, resulting in a change of conformation. In order to solve this problem, X-ray single-crystal analyses were performed on compounds (II*b*) and (III).

The asymmetric unit of (II*b*) contains one 3-hydroxymethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline molecule in the form of its ammonium cation (*i.e.* with an NH_2^+ group), a Br^- anion and half a methanol molecule (Fig. 1). In compound (III), the asymmetric unit contains two independent 2-formyl-3-hydroxymethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline molecules (Fig. 2).

The results obtained for the title compounds confirm the absolute 3*R*,4*R* configuration of both compounds proposed earlier on the basis of ^{1}H NMR studies (Brózda *et al.*, 2000). Moreover, upon formylation of (II), the distorted envelope conformation of the heterocyclic ring in the tetrahydroisoquinoline system [Cremer & Pople (1975) puckering parameters for (II*b*): Q = 0.512 (3) Å, Θ = 132.4 (3)° and Φ = 131.9 (5)°; for (III): Q = 0.446 (2) Å, Θ = 52.1 (3)° and Φ = 310.6 (3)° (molecule *A*), and Q = 0.469 (2) Å, Θ = 53.5 (2)° and Φ = 302.1 (3)° (molecule *B*)] has undergone inversion, leading to a change in the mutual orientation of the substituents at C3 and C4. The deviation of atom C3 from the almost planar system of the other five atoms of the heterocyclic ring is 0.691 (4) Å for (II*b*), 0.611 (2) Å for molecule *A* of (III) and 0.646 (2) Å for molecule *B* of (III) (Sheldrick, 1997). In (II*b*), the substituents at C3 and C4 have a mutually *trans* equatorial–pseudo-equatorial orientation, but in (III), they have a *trans* axial–pseudo-axial orientation. A similar stereochemistry of the partially reduced isoquinoline core of (II*b*) and (III) seems to be preserved in solution, as may be judged from the values of the coupling constants in their ^{1}H NMR spectra (see above). In (II*b*), the torsion angle C11—C3—C4—C13 [−58.5 (3)°] indicates a synclinal conformation of the C11 atom in the hydroxymethyl group with respect to the C13 atom of the phenyl group, while in (III), the analogous angle C13—C3—C4—C15 [−157.89 (16)° (molecule *A*) and −161.42 (14)° (molecule *B*)] reveals a mutual orientation between anticlinal and antiperiplanar for atoms C13 and C15. It can be concluded that the above-mentioned inversion of the conformation of the hetrocyclic ring in the partially reduced isoquinoline core occurred as a result of a steric hindrance between the C3-hydroxymethyl substituent and the *N*-formyl group or/and a change in the hybridization state of atom N2, which suggests a considerable contribution of the ionic form in the resonance hybrid of the amide group. The N2—C11 bond distance [1.324 (3) Å (molecule *A*) and 1.318 (2) Å (molecule *B*)] is somewhat shorter than a tertiary amide distance [1.346 (5) Å; Allen *et al.*, 1987]. The sum of the valency angles around N2 is 359.8 (3)° for molecule *A* and 359.6 (3)° for molecule *B*.

In (II*b*), the methanol solvate molecule lies near the twofold rotation axis, showing orientational disorder (see *Experimental*).

The hydroxyl group in molecule *A* of (III) also exhibits orientational disorder. Both positions of the hydroxyl group favour the formation of an intermolecular hydrogen bond with atom O12 of the carbonyl group of molecule *B* (Table 2).

In the crystal lattice of (II*b*), the Br^- anion is involved in three hydrogen bonds as an H-atom acceptor. In these bonds, the H-atom donors are the N2 atoms from two different molecules and atom O12 of the hydroxyl group belonging to a third molecule (Table 1). Additionally, there is a possible intermolecular C—H···O hydrogen bond (Table 1). In this way, chains are formed parallel to the *y* axis.

In the crystal lattice of (III), the *A* and *B* molecules are connected by hydrogen bonds (O141···O12B^{i}, O142···O12B^{i} and O14*B*···O12A^{ii}; see Table 2 for symmetry codes), forming chains parallel to the *y* axis. A comparison of IR absorption in spectra of (III), recorded in the solid state (KBr) and in solution (CH_2Cl_2), suggests the existence of similar intermolecular interactions in both phases.

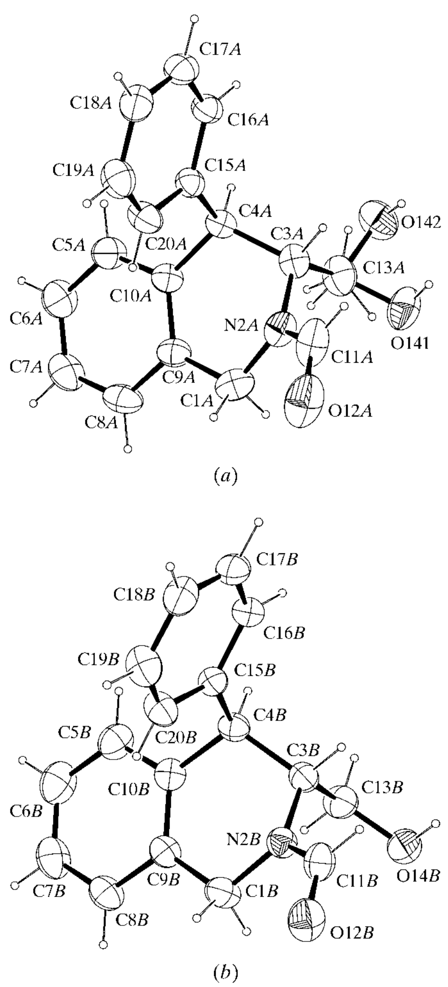


Figure 2
The molecular structure of (*a*) molecule *A* and (*b*) molecule *B* of (III). Non-H atoms are drawn as 30% probability displacement ellipsoids and H atoms are drawn as spheres of an arbitrary size.

Experimental

Compounds (II*b*) and (III) were prepared according to the method of Brózda *et al.* (2000). Crystals of both compounds suitable for single-crystal X-ray diffraction analysis were selected directly from the analytical samples.

Compound (II*b*)

Crystal data

$C_{16}H_{18}NO^{+}\cdot Br^{-}\cdot 0.5CH_4O$
$M_r = 336.25$
Monoclinic, $C2$
$a = 20.5882$ (14) Å
$b = 6.4413$ (6) Å
$c = 11.7354$ (6) Å
$\beta = 91.004$ (5)°
$V = 1556.0$ (2) Å^3
$Z = 4$
$D_x = 1.435$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 58 reflections
$\theta = 10.2$–29.4°
$\mu = 3.58$ mm^{-1}
$T = 293$ (2) K
Block, colourless
0.43 × 0.14 × 0.10 mm

Data collection

Kuma KM-4 diffractometer
ω–2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.395$, $T_{max} = 0.699$
2953 measured reflections
2827 independent reflections
2713 reflections with $I > 2\sigma(I)$
$R_{int} = 0.020$
$\theta_{max} = 70.1°$
$h = -24 \rightarrow 24$
$k = -7 \rightarrow 7$
$l = 0 \rightarrow 14$
2 standard reflections every 100 reflections intensity decay: 3.4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.028$
$wR(F^2) = 0.081$
$S = 1.06$
2827 reflections
198 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0498P)^2 + 0.8792P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.019$
$\Delta\rho_{max} = 0.36$ e Å^{-3}
$\Delta\rho_{min} = -0.43$ e Å^{-3}
Absolute structure: Flack (1983), 1205 Friedel reflections
Flack parameter = −0.01 (2)

Table 1
Hydrogen-bonding geometry (Å, °) for (IIb).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2A···Br^{i}	0.91 (4)	2.40 (4)	3.259 (3)	157 (3)
N2—H2B···Br	0.99 (5)	2.37 (5)	3.298 (2)	158 (3)
O12—H12···Br^{ii}	0.80 (5)	2.74 (5)	3.339 (3)	132 (4)
C1—H1A···O12^{iii}	0.97	2.44	3.406 (4)	171

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

Compound (III)

Crystal data

$C_{17}H_{17}NO_2$
$M_r = 267.32$
Orthorhombic, $P2_12_12_1$
$a = 11.097$ (2) Å
$b = 11.742$ (2) Å
$c = 21.829$ (4) Å
$V = 2844.3$ (9) Å^3
$Z = 8$
$D_x = 1.248$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 45 reflections
$\theta = 14.9$–26.1°
$\mu = 0.65$ mm^{-1}
$T = 293$ (2) K
Prism, colourless
0.52 × 0.16 × 0.11 mm

Data collection

Kuma KM-4 diffractometer
ω–2θ scans
5771 measured reflections
5213 independent reflections
4350 reflections with $I > 2\sigma(I)$
$R_{int} = 0.028$
$\theta_{max} = 70.1°$
$h = 0 \rightarrow 13$
$k = 0 \rightarrow 14$
$l = -26 \rightarrow 26$
2 standard reflections every 100 reflections intensity decay: 6.8%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.033$
$wR(F^2) = 0.099$
$S = 1.05$
5213 reflections
375 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0599P)^2 + 0.1727P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.28$ e Å^{-3}
$\Delta\rho_{min} = -0.14$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0054 (3)
Absolute structure: Flack (1983), 2181 Friedel reflections
Flack parameter = −0.1 (2)

Table 2
Hydrogen-bonding geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
O141—H141···O12B^{i}	0.82	2.12	2.912 (3)	161
O142—H142···O12B^{i}	0.82	2.18	2.958 (6)	158
O14B—H14B···O12A^{ii}	0.82	2.04	2.797 (3)	154
C3A—H3A···O12B^{i}	0.98	2.53	3.287 (3)	134
C3B—H3B···O12A^{ii}	0.98	2.50	3.235 (3)	132
C8B—H8B···O14B^{iii}	0.93	2.59	3.426 (3)	151

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

The positions of the H atoms bonded to N and O atoms in the partially reduced isoquinoline core of (II*b*) were obtained from difference Fourier maps and were refined freely. For molecule *A* of (III), the hydroxyl group, which was disordered over two positions (O141 and O142, with occupation factors of 67 and 33%), was allowed to rotate freely around the C—O bond. Atoms H141/H142 was placed geometrically and converged to positions that could be interpreted as favourable for the formation of hydrogen bonds. The remaining H atoms of (II*b*) and (III) were positioned geometrically, and were refined with a riding model (O—H = 0.82 Å and C—H = 0.93–0.98 Å) and with U_{iso} values constrained to be 1.5 (for hydroxyl H atoms) or 1.2 (for all other H atoms) times the U_{eq} value of the parent atom.

In (II*b*), the methanol solvate molecule lies near the twofold axis and shows orientational disorder; the equivalent isotropic displacement parameter of atom O19 is high [0.211 (5) Å^2], and is associated with an interatomic O19—C20 distance [1.247 (14) Å] shortened by about 11σ relative to the normal value for a Csp^3—O single bond [1.413 (4) Å; Allen *et al.*, 1987]. The position of atom O19 was fixed on the twofold axis, and atom C20 was introduced with a site-occupation factor of 50%. A significant degree of disorder of the methanol solvate molecule prevents identification of the positions of the H atoms, so making it difficult to perform a correct determination of the positions of the O and C atoms in the molecule. Nevertheless, the assumption of the inverse positions of the atoms leads to worse results.

For both compounds, data collection: *KM*-4 *Software* (Kuma, 1991); cell refinement: *KM*-4 *Software*; data reduction: *KM*-4 *Software*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

This work was financially supported by KBN grant No. 3-T09A 027 17.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ1510). Services for accessing these data are described at the back of the journal.

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