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A (1*R*,2*R*,5*R*)-(+)-2*α*-hydroxypinan-3-one ketimine

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Key indicators

Single-crystal X-ray study
T = 173 K
Mean *σ*(C–C) = 0.004 Å
R factor = 0.047
wR factor = 0.109
Data-to-parameter ratio = 9.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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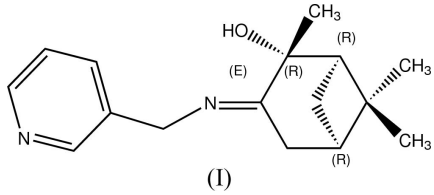
The title compound {systematic name: (1*R*,2*R*,5*R*)-(+)-2-hydroxy-2,6,6-trimethyl-3-[(3-pyridyl)methylimino]bicyclo-[3.1.1]heptane}, $C_{16}H_{22}N_2O$, was obtained by the condensation reaction of (1*R*,2*R*,5*R*)-(+)-2*α*-hydroxypinan-3-one with 3-(aminomethyl)pyridine in the presence of boron trifluoride. The compound was obtained as an enantiomerically pure isomer, and has the 1*R*,2*R*,5*R* configuration. In the crystal structure, molecules are linked together by intermolecular O—H···N hydrogen bonds between the hydroxy group of the pinanone group and the N atom of the pyridine ring, forming molecular chains.

Comment

Structure–activity studies have demonstrated that optical isomers of pharmacologically active tobacco alkaloids exhibit significant differences in their CNS activities (Dwoskin *et al.*, 1995). The tobacco alkaloid nornicotine is present in tobacco as a mixture of the two possible enantiomeric forms (Kisaki & Tamaki, 1966). The two optical isomers of nornicotine have similar binding affinities to the nicotinic acetylcholine receptor and there is evidence that the enantiomers differ in their behavioural and pharmacological activities (Bardo *et al.*, 1997). The preparation of nornicotine enantiomers has been reported (Seeman *et al.*, 1985). These preparations have generally involved resolutions of racemic intermediates, chiral chromatography of racemic nornicotine or HPLC separations of mixtures of diastereomeric analogues of nornicotine. Recently, we reported (Swango *et al.*, 1999) a new method for the synthesis of (*S*)-(−)- and (*R*)-(+)-enantiomers with moderately high enantioselectivity, utilizing the Schiff base (1*R*,2*R*,5*R*)-(+)-2*α*-hydroxypinan-3-one ketimine as a chiral template. The title compound, (I), is a synthetic intermediate, and was prepared by the condensation reaction of (1*R*,2*R*,5*R*)-(+)-2*α*-hydroxypinan-3-one with 3-(aminomethyl)pyridine in the presence of boron trifluoride. The structure of (I) was



(I)

initially identified by NMR spectroscopy. In order to confirm the azomethine double bond geometry and to obtain more detailed information on the structural conformation of the molecule that may be of value in studying its use in enantioselective alkylation reactions, its X-ray structure determination has also been carried out.

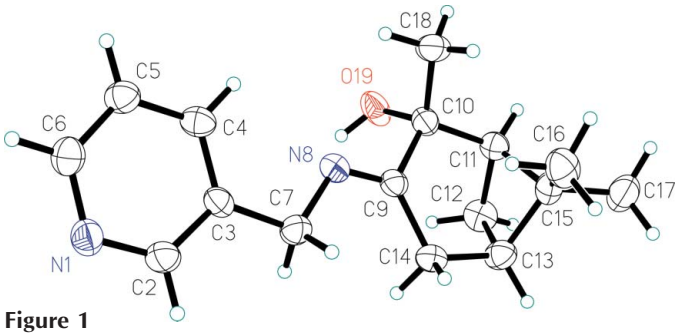


Figure 1
A view of (I). Displacement ellipsoids are drawn at the 50% probability level.

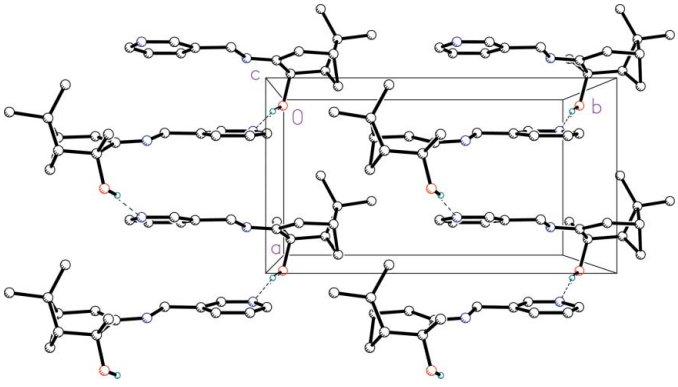


Figure 2
The crystal structure of (I), viewed along the *c* axis. Hydrogen bonds are shown as dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity.

X-ray crystallography confirmed the molecular structure and atom connectivity of (I) as illustrated in Fig. 1. Selected geometric parameters are presented in Table 1. The title compound adopts an *E* configuration about the azomethine C=N double bond and has the 1*R*,2*R*,5*R* configuration. The pyridine ring is planar and makes a dihedral angle of 11.31 (7)° with the plane of the azomethine bond. Deviations from ideal geometry are observed in the N8=C9—C10 and N8=C9—C14 bond angles [116.8 (2) and 125.0 (2)°, respectively], while the C10—C9—C14 [118.0 (2)°] angle is close to the ideal value of 120°. Within the pinane ring system the C11—C12—C13, C12—C11—C15, C12—C13—C15 and C11—C15—C13 bond angles deviate significantly from the tetrahedral angle, whereas the remainder of the angles around atoms C10, C14, C11 and C13 are close to tetrahedral geometry.

The packing of compound (I) along the *a* direction is illustrated in Fig. 2. In addition, intermolecular O19—H19···N1^{i} hydrogen bonding (see Table 2 for details and symmetry code) and van der Waals forces contribute to the stabilization of the crystal structure.

Experimental

Boron trifluoride–diethyl etherate (0.3 ml) was added to a solution of 3-(aminomethyl)pyridine (3.30 g, 30.6 mmol) and (1*R*,2*R*,5*R*)-(+)-2α-hydroxypinan-3-one (5.00 g, 29.8 mmol). The reaction mixture was refluxed for 2.5 h under nitrogen using a Dean–Stark apparatus. After cooling, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform–hexane–methanol, 12:2:1) and the product was crystallized from hexane to afford (I) (6.24 g, 81%) as white crystals, which were suitable for X-ray analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (*d*, *J* = 2.4 Hz, 1H), 8.48 (*dd*, *J* = 4.8 and 1.8 Hz, 1H), 7.70 (*d*, *J* = 7.8 Hz, 1H), 7.25 (*dd*, *J* = 7.8 and 4.8 Hz, 1H), 4.48 (*s*, 2H), 2.80 (*br s*, 1H), 2.58 (*m*, 2H), 2.34 (*m*, 1H), 2.06 (*m*, 2H), 1.56 (*d*, *J* = 10.8 Hz, 1H), 1.50 (*s*, 3H), 1.31 (*s*, 3H), 0.84 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.2, 149.3, 148.3, 135.8, 135.5, 123.6, 51.8, 50.5, 38.8, 38.5, 34.1, 28.6, 28.4, 27.5, 23.1.

Crystal data

$C_{16}H_{22}N_2O$
M_r = 258.36
Orthorhombic, $P2_12_12_1$
a = 7.2196 (5) Å
b = 12.9481 (9) Å
c = 15.1436 (9) Å
V = 1415.63 (16) Å^3
Z = 4
D_x = 1.212 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 7956 reflections
θ = 1.0–27.5°
μ = 0.08 mm^{-1}
T = 173 (2) K
Block, colorless
0.30 × 0.16 × 0.09 mm

Data collection

Nonius KappaCCD diffractometer
ω scans at fixed χ = 55°
7664 measured reflections
1613 independent reflections
1115 reflections with $I > 2\sigma(I)$
R_{int} = 0.069
θ_{max} = 26.0°
h = −8 → 8
k = −13 → 15
l = −18 → 18

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.109
S = 1.02
1613 reflections
177 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0541P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.006
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.009 (2)

Table 1
Selected geometric parameters (Å, °).

C3—C7	1.505 (4)	C9—C14	1.515 (3)
C7—N8	1.456 (3)	C9—C10	1.544 (4)
N8—C9	1.274 (3)	C10—O19	1.441 (3)
N8—C7—C3	111.4 (2)	O19—C10—C9	108.9 (2)
C9—N8—C7	119.1 (2)	C12—C11—C15	87.6 (2)
N8—C9—C14	125.0 (2)	C11—C12—C13	86.4 (2)
N8—C9—C10	116.8 (2)	C12—C13—C15	87.9 (2)
C14—C9—C10	118.1 (2)	C13—C15—C11	85.2 (2)
C2—C3—C7—N8	172.0 (3)	C4—C3—C7—N8	−9.6 (4)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O19—H19···N1^{i}	0.84	2.02	2.855 (3)	171

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

H atoms were located in difference Fourier maps and subsequently refined using riding models in which the H atoms were positioned geometrically. Bond distances for these H atoms were fixed as follows: aromatic C—H = 0.95 Å, CH_2 C—H = 0.99 Å, CH C—H = 1.00 Å, methyl C—H = 0.98 Å and O—H = 0.84 Å. Isotropic

displacement parameters for the H atoms were defined as $1.2U_{eq}$(C) for aromatic, CH_2 and CH H atoms, and $1.5U_{eq}$(C,O) for the methyl and hydroxy H atoms. In the absence of significant anomalous scattering, Friedel pairs were merged. The absolute configuration was assigned as the same as that of the starting material.

Data collection: *COLLECT* (Nonius, 1999); 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: *SHELXL97* (Sheldrick, 1997) and local procedures.

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