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(*Z*)-2-(1*H*-Indol-3-ylmethylene)-1-azabicyclo[2.2.2]octan-3-one

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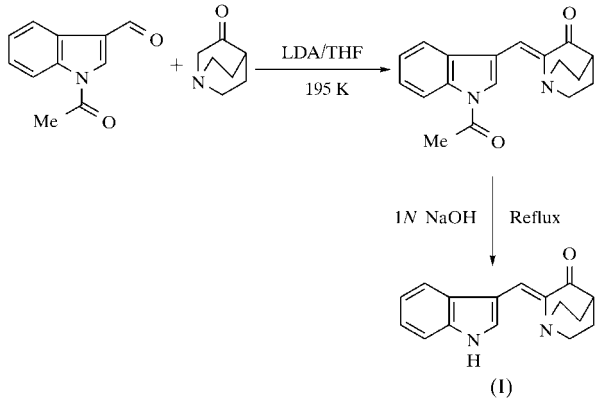
The title compound, $C_{16}H_{16}N_2O$, which contains a double bond connecting an azabicyclic ring system to an indol-3-ylmethylene group, crystallizes from a solution in ethyl acetate. The geometries of the two crystallographically independent molecules are nearly identical. The crystal packing of the title compound involves two types of intermolecular hydrogen bond.

Comment

Indole analogues, especially tryptamine derivatives, have been found to be polyamine site antagonists at the *N*-methyl-D-aspartate receptor (NMDAR; Worthen *et al.*, 2001). As part of our synthetic strategy to design rigid analogues of tryptamine (Sonar *et al.*, 2003), we focused on the synthesis of 2-(1*H*-indol-3-ylmethylene)-1-azabicyclo[2.2.2]octane, (II), from the reductive deoxygenation of the title compound. However, it was not possible to prepare *N*-unsubstituted analogues by base-catalyzed reaction of indole-3-carboxaldehyde, (III), with 1-azabicyclo[2.2.2]octan-3-one, (IV). The electron-withdrawing effect of the aldehyde group causes the N-bound H atom of (III) to become more acidic (pK_a 12) than indole itself (pK_a 17). Consequently, (III) forms an anion in the presence of a base, even under mild conditions, and delocalization of the negative charge on the N atom results in considerable reduction of the aldehyde character and hence in a loss of reactivity. The title compound was prepared by condensation of 1-acetylindole-3-carboxaldeyde with (IV) under base catalysis, affording a single geometric isomer of 2-(1-acetyl-1*H*-indol-3-ylmethylene)-1-aza-bicyclo[2.2.2]octan-3-one. Subsequent cleavage of the 1-acetyl group afforded an isomerically pure compound, (I), which was identified by NMR spectroscopy and tentatively assigned as the *Z* isomer. This azabicyclic analogue is a key intermediate in the synthesis of (II). Confirmation of the double-bond geometry in (I) is important, since this geometry will be maintained in the subsequent deoxygenated target molecule derived from this intermediate and thus will be of value in structure–activity analysis. In order to confirm the geometry of the double bond in (I), an X-ray structure determination has been carried out and the results are presented below.



(I)

In the asymmetric unit there are two crystallographically independent molecules, and their geometries are nearly identical. An ellipsoid plot of molecule (I*A*) is shown in Fig. 1, and selected geometric parameters are presented in Table 1. The molecule contains a double bond (C10═C11) that connects a 1-azabicyclo[2.2.2]octan-3-one ring system to an indol-3-ylmethylene group; geometric isomerism about this double bond affords the possibility of *E* and *Z* isomers. In the *Z* isomer, the C11—C18 bond is in a *trans* position with respect to the C3—C10 bond. The C10═C11 double bond has an essentially planar atomic arrangement, the r.m.s. deviation from the best plane passing through atoms N12*A*, C11*A*, C18*A*, C10*A* and C3*A* being 0.031 (15) Å. Deviations from ideal geometry are observed in the bond angles around atoms C3*A*, C10*A*, C11*A* and C18*A*. While the C10*A*═C11*A*—C18*A* angle [122.3 (2)°] is close to ideal (120°), the C2*A*═C3*A*—C10*A*, C3*A*—C10*A*═C11*A*, N12*A*—C11*A*—C18*A*, N12*A*—C13*A*—C14*A*, N12*A*—C17*A*—C16*A*, C10═C11—N12*A*, O18*A*═C18*A*—C11*A* and O18*A*═C18*A*—C15*A* angles are more distorted as a consequence of the strain induced by the C10*A*═C11*A* and C18*A*═O18*A* double-bond linkage. These deviations contribute to the relief of the intramolecular non-

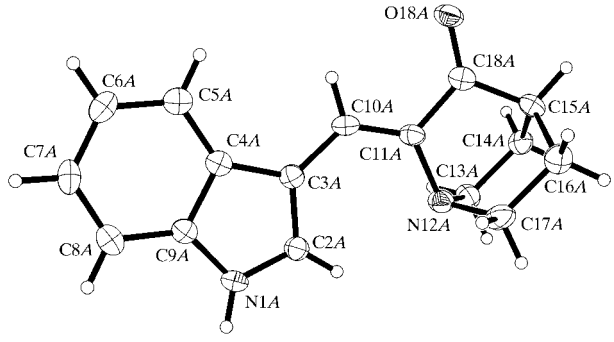


Figure 1
A view of the molecule of (I*A*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

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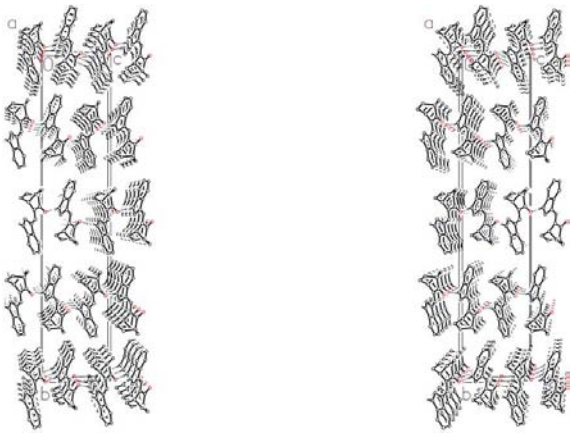

Figure 2
A stereoview of the crystal packing of (I*A*) (left) and (I*B*) (right), viewed along the *a* axis. H atoms have been omitted for clarity.

bonded interactions of the 1-azabicyclo[2.2.2]octan-3-one moiety, which is caused by the effect of the C10*A*═C11*A* and C18*A*═O18*A* double bonds on the bicyclic system. In both cases, Csp^2 atoms replace Csp^3 atoms, and as a result, atoms N12*A*, C11*A*, C18*A* and C15*A* assume an almost planar configuration [N12*A*—C11*A*—C18*A*—C15*A* = −2.2 (3)°], with partial conjugation between the double bond and the carbonyl bond, as indicated by the significant shortening of the C11*A*—C18*A* single bond [1.466 (4) Å]. The bond angles for atoms C14*A*, C15*A*, C16*A* and N12*A* are, on average, slightly smaller than the ideal tetrahedral value, while those for atoms C13*A* and C17*A* are, on average, larger than the tetrahedral value, and the bond angles on the sp^2 atoms C3*A*, C10*A*, C11*A* and C18*A* show values larger than the ideal value. As expected, the indole ring itself is essentially planar.

The mode of packing of (I*A*) and (I*B*) in stereoprojection along the *a* direction is illustrated in Fig. 2. In addition to van der Waals forces, intermolecular hydrogen bonding contributes to the stabilization of the crystal structure. There are two types of intermolecular N1—H···O18 hydrogen bond, *viz*. one involving only *A* molecules and the other only *B* molecules (Table 2). No π–π interaction was observed.

Experimental

To a stirred solution of diisopropylamine (1.923 g, 19 mmol) in tetrahydrofuran (THF, 20 ml) at 273 K under nitrogen was added a solution of 2.0 *M* *n*-butyllithium (9 ml, 18.8 mmol) and the mixture was stirred at 273 K for 30 min. To this solution at 273 K was added 1-azabicyclo[2.2.2]octan-3-one hydrochloride (1.5 g, 9.28 mmol) in one portion, and stirring was continued until the solid dissolved completely (20 min). The temperature was lowered to 195 K and a solution of 1-acetyl-1*H*-indole-3-carboxaldehyde (1.722 g, 9.2 mmol) in THF (25 ml) was added dropwise. Stirring was continued for 30 min at this temperature and then for 90 min at 273 K. The reaction mixture was poured into saturated $NaHCO_3$ at 273 K and the resulting solution was extracted with $CHCl_3$ (3 × 15 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to afford (*Z*)-2-(1-acetyl-1*H*-indol-3-ylmethylene)-1-azabicyclo[2.2.2]octan-3-one, which was subsequently refluxed with sodium hydroxide solution (25 ml, 1 *N*) for 30 min. The reaction mixture was cooled to room temperature, and the yellow solid that separated was collected by filtration, washed with cold water and dried. Crystallization from methanol gave a yellow crystalline product suitable for X-ray analysis. ^{1}H NMR (DMSO-d_6): δ 1.76–2.04 (*m*, 4H), 2.46 (*p*, 1H), 2.82–2.91 (*m*, 2H), 3.11–3.20 (*m*, 2H), 7.10–7.20 (*m*, 2H), 7.25 (*s*, 1H), 7.46 (*d*, *J* = 7.2 Hz, 1H), 7.89 (*d*, *J* = 7.5 Hz, 1H), 8.31 (*s*, 1H), 11.78 (*s*, 1H); ^{13}C NMR (DMSO-d_6): δ 25.7, 39.9, 47.2, 109.4, 111.8, 117.3, 118.5, 120.2, 121.9, 127.1, 131.4, 135.7, 139.9, 203.3.

Crystal data

$C_{16}H_{16}N_2O$
M_r = 252.31
Monoclinic, *Cc*
a = 6.1800 (12) Å
b = 44.160 (9) Å
c = 9.774 (2) Å
β = 108.26 (3)°
V = 2533.1 (10) Å^3
Z = 8
D_x = 1.323 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 22 075 reflections
θ = 1.0–27.5°
μ = 0.08 mm^{-1}
T = 173 (1) K
Broken lath, yellow
0.25 × 0.14 × 0.05 mm

Data collection

Nonius KappaCCD diffractometer
ω scans
Absorption correction: multi-scan (*SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.979, T_{max} = 0.996
28 160 measured reflections
2906 independent reflections
2589 reflections with $I > 2\sigma(I)$
R_{int} = 0.038
θ_{max} = 27.5°
h = −8 → 8
k = −56 → 56
l = −12 → 12

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.080
S = 1.12
2906 reflections
344 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0249P)^2 + 0.9406P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0035 (4)

Table 1
Selected geometric parameters (Å, °).

C2*A*—C3*A*	1.388 (4)	C2*B*—C3*B*	1.384 (4)
C3*A*—C10*A*	1.431 (4)	C3*B*—C10*B*	1.436 (4)
C10*A*—C11*A*	1.351 (3)	C10*B*—C11*B*	1.343 (4)
C11*A*—C18*A*	1.466 (4)	C11*B*—C18*B*	1.477 (4)
C18*A*—O18*A*	1.236 (3)	C18*B*—O18*B*	1.224 (3)
C2*A*—C3*A*—C10*A*	128.2 (2)	C2*B*—C3*B*—C10*B*	129.5 (3)
C11*A*—C10*A*—C3*A*	128.8 (2)	C11*B*—C10*B*—C3*B*	129.3 (3)
C10*A*—C11*A*—N12*A*	123.9 (2)	C10*B*—C11*B*—N12*B*	124.0 (2)
C10*A*—C11*A*—C18*A*	122.3 (2)	C10*B*—C11*B*—C18*B*	121.7 (3)
N12*A*—C11*A*—C18*A*	113.6 (2)	N12*B*—C11*B*—C18*B*	114.1 (2)
N12*A*—C17*A*—C16*A*	112.6 (2)	N12*B*—C17*B*—C16*B*	111.8 (2)
C2*A*—C3*A*—C10*A*—C11*A*	−1.8 (5)	C2*B*—C3*B*—C10*B*—C11*B*	2.4 (5)
C10*A*—C11*A*—C18*A*—O18*A*	−6.3 (4)	C10*B*—C11*B*—C18*B*—O18*B*	−6.2 (4)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1*A*—H1*A*···O18*A*^{i}	0.88	1.94	2.812 (3)	174
N1*B*—H1*B*···O18*B*^{ii}	0.88	2.01	2.872 (3)	166

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

H atoms were placed at calculated positions and treated using a riding model (aromatic C—H = 0.95 Å, methylene C—H = 0.99 Å and N—H = 0.88 Å). U_{iso}(H) values were set to $1.2U_{eq}$ of the attached C or N atom. The absolute structure was not determined and Friedel pairs were averaged.

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL*/*PC* (Sheldrick, 1995); software used to prepare material for publication: *SHELXL*97 and local procedures.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1450). Services for accessing these data are described at the back of the journal.

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