Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

2-(1-Benzyl-1*H*-indol-3-ylmethylene)-1-azabicyclo[2.2.2]octan-3-one

Vijayakumar N. Sonar,[a] Sean Parkin[b] and Peter A. Crooks[a]*

[a]Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington KY 40536, USA, and [b]Department of Chemistry, University of Kentucky, Lexington KY 40536, USA

Correspondence e-mail: pcrooks@uky.edu

Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.003 Å
R factor = 0.057
wR factor = 0.121
Data-to-parameter ratio = 13.2

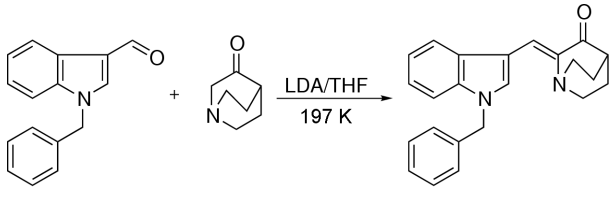
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 15 July 2003
Accepted 8 September 2003
Online 11 September 2003

The title compound, $C_{23}H_{22}N_2O$, was obtained in a condensation reaction of 1-benzyl-1*H*-indole-3-carboxaldehyde with 1-aza-bicyclo[2.2.2]octan-3-one. The crystal structure indicates the presence of a double bond, connecting an azabicyclic ring system to an indole-3-carboxaldehyde.

Comment

Indole derivatives have been found to exhibit a wide range of biological activity. Pyrido[1,2-*a*]indole derivatives have been identified as potent inhibitors of human immunodeficiency virus type 1 (Taylor *et al.*, 1999), and 5-chloro-3-(phenylsulfonyl)indole-2-carboxamide is reported to be a highly potent non-nucleoside inhibitor of HIV-1 reverse transcriptase (Williams *et al.*, 1993). Indole derivatives also exhibit antitumor activities (Andreani *et al.*, 2001; Bradlow *et al.*, 1999; Cirrincione *et al.*, 1999; Tiwari *et al.*, 1994; Dashwood *et al.*, 1994). Recently tryptamines have been found to be polyamine site antagonists at the *N*-methyl-D-asparatate receptor (Worthen *et al.*, 2001). As part of our synthetic strategy to obtain rigid analogs of tryptamine, we synthesized a series of 2-(1-substituted-1*H*-indol-3-ylmethylene)-1-aza-bicyclo[2.2.2]octan-3-ones. It was observed that, when 1-substituted indole-3-carboxaldehyes were condensed with 1-aza-bicyclo[2.2.2]-octan-3-one, different ratios of *E*/*Z* isomeric products were obtained, depending on the nature of the indolic *N*-substituent (Tønder *et al.*, 2000). In the case of an indolic *N*-methyl substituent, the *Z* isomer is the major product, although a small amount of the *E* isomer is obtained (Chapman *et al.*, 1986), whereas bulkier *N*-substituted indole carboxaldehydes favor formation of the *Z* isomer.



(I)

The X-ray structure analysis of the title compound (I) was carried out in order to obtain detailed information about the solid state stereochemistry and conformation of products resulting from condensation of indole carboxaldehydes with bulky *N*-substituents with 1-aza-bicyclo[2.2.2]-octan-3-one. The structure of (I) is illustrated in Fig. 1 and selected bond distances and angles are given in Table 1. It can be seen that the benzyl group is oriented away from the azabicyclo[2.2.2]octanone moiety by torsions of −101.0 (2)° (C2—

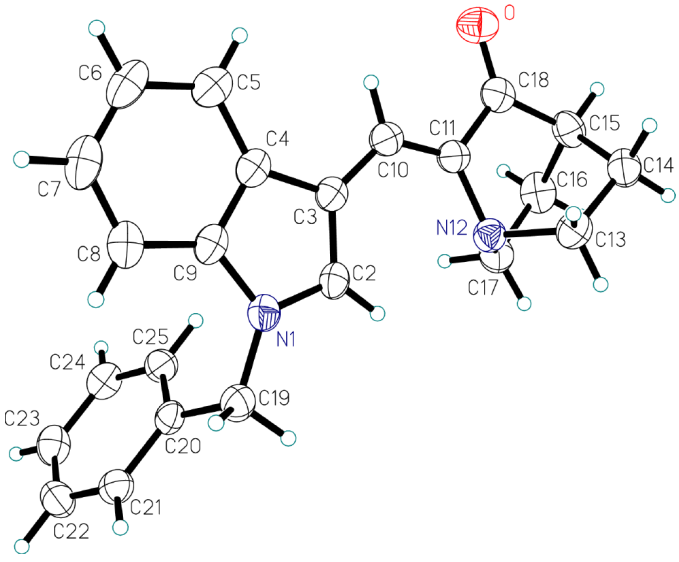


Figure 1
A view of the title compound, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms as spheres of arbitrary radius.

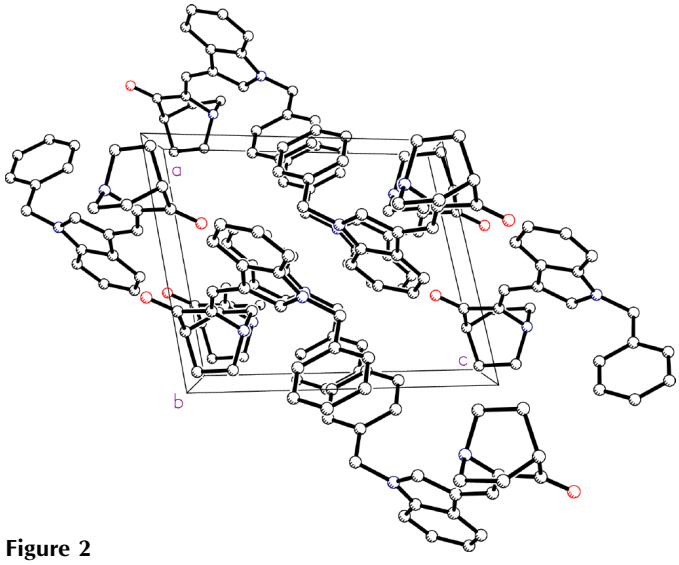


Figure 2
Crystal packing of (I), viewed down the *b* axis. H atoms have been omitted for clarity.

N1—C19—C20) and −155.3 (2)° (N1—C19—C20—C21). This conformation is stabilized by pairing of the benzyl groups of inversion-related molecules (Fig. 2) and a C—H···O interaction (Table 2). As expected, the linkage between the indolyl and azabicyclo[2.2.2]octanone moieties is close to planar, forming exclusively the *Z* isomer [torsion angle C2—C3—C10—C11 is −4.4 (3)°]. This isomer is favored because the alternative *E* isomer would result in a steric clash between the carbonyl O atom and the hydrogen attached to C2 of the benzyl group.

Experimental

To a stirred solution of diisopropylamine (1.923 g, 19 mmol) in 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-aza-bicyclo[2.2.2]-octan-3-one hydrochloride (1.5 g, 9.28 mmol) in one portion and stirring was continued until the mixture completely dissolved (20 min). The temperature was lowered to 195 K and a solution of 1-benzyl-1*H*-indole-3-carboxaldehyde (2.16 g, 9.2 mmol) in THF (25 ml) was added dropwise. Stirring was continued for 30 min at this temperature and then at 273 K for 90 min. The reaction mixture was poured into aqueous saturated $NaHCO_3$ solution at 273 K and the resulting solution extracted with $CHCl_3$ (3 × 15 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated to afford a yellow solid. Crystallization from methanol gave yellow crystals suitable for X-ray analysis. ^{1}H NMR ($CDCl_3$, p.p.m.): 2.02 (*m*, 4H), 2.63 (*p*, *J* = 3.3 Hz, 1H), 2.98 (*m*, 2H), 3.13 (*m*, 2H), 5.38 (*s*, 2H), 7.11–7.31 (*m*, 8H), 7.48 (*s*, 1H), 7.90 (*m*, 1H), 8.39 (*s*, 1H). ^{13}C NMR ($CDCl_3$, p.p.m.): 26.8, 40.8, 47.8, 50.9, 110.4, 110.5, 118.2, 119.3, 121.2, 122.8, 126.7, 127.9, 129.0, 134.6, 136.2, 136.7, 140.8, 205.4.

Crystal data

$C_{23}H_{22}N_2O$
M_r = 342.43
Triclinic, $P\overline{1}$
a = 9.245 (2) Å
b = 10.015 (3) Å
c = 11.245 (3) Å
α = 112.38 (2)°
β = 92.78 (2)°
γ = 109.51 (2)°
V = 888.8 (4) Å^3
Z = 2
D_x = 1.280 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 26987 reflections
θ = 1.0–27.5°
μ = 0.08 mm^{-1}
T = 173 (1) K
Irregular plate, pale yellow
0.44 × 0.38 × 0.04 mm

Data collection

Nonius KappaCCD diffractometer
ω scans at fixed χ = 55°
Absorption correction: none
6198 measured reflections
3118 independent reflections
2342 reflections with $I > 2\sigma(I)$
R_{int} = 0.041
θ_{max} = 25.0°
h = −10 → 10
k = −11 → 11
l = −13 → 13

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.057
$wR(F^2)$ = 0.121
S = 1.08
3118 reflections
236 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0457P)^2 + 0.2487P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}
Extinction correction: *SHELXL*
Extinction coefficient: 0.017 (3)

Table 1
Selected geometric parameters (Å, °).

O—C18	1.232 (2)	C11—N12	1.446 (2)
N1—C9	1.383 (3)	C11—C18	1.471 (3)
N1—C19	1.456 (3)	N12—C17	1.481 (3)
C3—C10	1.442 (3)	N12—C13	1.483 (3)
C10—C11	1.340 (3)	C15—C18	1.506 (3)
C2—N1—C9	108.68 (17)	N12—C17—C16	112.40 (17)
C2—C3—C10	128.90 (19)	O—C18—C11	125.0 (2)
C11—C10—C3	129.6 (2)	O—C18—C15	124.0 (2)
N12—C11—C18	113.64 (18)	C11—C18—C15	111.01 (18)
C11—N12—C17	109.50 (16)	N1—C19—C20	112.62 (16)
N12—C13—C14	111.59 (17)		
C2—C3—C10—C11	−4.4 (3)	N1—C19—C20—C21	−155.31 (17)
C2—N1—C19—C20	−101.0 (2)		

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

D—H···A	D—H	H···A	D···A	D—H···A
C2—H2···N12	0.95	2.54	3.077 (3)	116
C10—H10···O	0.95	2.55	2.894 (3)	101
C21—H21···O^{i}	0.95	2.37	3.301 (3)	167

Symmetry code: (i) $x, 1+y, 1+z$.

H atoms were located in Fourier difference maps, but were subsequently included at calculated positions using an appropriate riding model. C—H distances were fixed at C—H 0.95 Å, CH_2 and CH_3 0.99 Å and U_{iso}(H) = 1.2 U_{eq}(parent C atom).

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* (Sheldrick, 1995); software used to prepare material for publication: *SHELXL*97 and local procedures.

This investigation was supported by the National Institute of Alcohol Abuse and Alcoholism, Grant AA12600.

References

Andreani, A., Granaiola, M., Locatelli, A., Morigi, R., Rambaldi, M., Giorgi, G., Salvini, L. & Garaliene, V. (2001). *Anticancer Drug Des*. **16**, 167–174.
Bradlow, H. L., Sepkovic, D. W., Telang, N. T. & Osborne, M. P. (1999). *Ann. N. Y. Acad. Sci.* **889**, 204–213.
Chapman, R. F., Phillips, N. I. J. & Ward, R. S. (1986). *Heterocycles*, **24**, 3115–3128.
Cirrincione, G., Almerico, A. M., Barraja, P., Diana, P., Lauria, A., Passannanti, A., Musiu, C., Pani, A., Murtas, P., Minnei, C., Marongiu, M. E. & La Colla, P. (1999). *J. Med. Chem.* **42**, 2561–2568.
Dashwood, R. H., Fong, A. T., Arbogast, D. N., Bjeldanes, L. F., Hendricks, J. D. & Bailey, G. S. (1994). *Cancer Res.* **54**, 3617–3619.
Nonius (1999). *COLLECT*. Nonius, BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr and R. M. Sweet, pp. 307–326. New York: Academic Press.
Sheldrick (1995). *XP* in *SHELXTL/PC*. Siemens Analytical Instruments Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.
Taylor, D. L., Ahmed, P. S., Chambers, P., Tyms, A. S., Bedard, J., Duchaine, J., Falardeau, G., Lavallee, J. F., Brown, W., Rando, R. F. & Bowlin, T. (1999). *Antivir. Chem. Chemother.* **10**, 79–86.
Tiwari, R. K., Guo, L., Bradlow, H. L., Telang, N. T. & Osborne, M. P. (1994). *J. Natl Cancer Inst.* **86**, 126–131.
Tønder, J. E., Begtrup, M., Hansen, J. B. & Olesen, P. H. (2000). *Tetrahedron*, **56**, 1139–1146.
Williams, T. M., Ciccarone, T. M., MacTough, S. C., Rooney, C. S., Balani, S. K., Condra, J. H., Emini, E. A., Goldman, M. E., Greenlee, W. J. & Kauffman, L. R. (1993). *J. Med. Chem.* **36**, 1291–1294.
Worthen, D. R., Gibson, D. A., Rogers, D. T., Bence, A. K., May Fu, Littleton, J. M. & Crooks, P. A. (2001). *Brain Res.* **890**, 343–346.