Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

(Z)-2-(1-Phenylsulfonyl-1H-indol-3-ylmethylene)-1-azabicyclo[2.2.2]-octan-3-one and (Z)-(S)-2-(1-phenyl-sulfonyl-1H-indol-3-ylmethylene)-1-azabicyclo[2.2.2]octan-3-ol

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

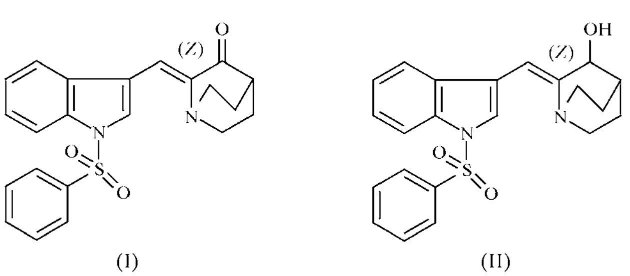
[a]Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY 40536, USA, and [b]Department of Chemistry, University of Kentucky, Lexington, KY 40506, USA
Correspondence e-mail: pcrooks@uky.edu

Received 22 June 2004
Accepted 29 June 2004
Online 11 August 2004

The title compounds, $C_{22}H_{20}N_2O_3S$, (I), and $C_{22}H_{22}N_2O_3S$, (II), crystallize in space groups $P\overline{1}$ and $P2_12_12_1$, respectively. The indole rings are planar and the benzene ring of the phenylsulfonyl group makes a dihedral angle with the mean plane of the indole ring of 90.2 (2)° in (I) and 94.0 (2)° in (II). In both molecules, the double bond connecting the aza-bicyclic and indole moieties has a *Z* geometry. Compound (II) was obtained as an enantiomerically pure crystal and has the 3*S* configuration.

Comment

Glutamate cysteine ligase, the rate-limiting enzyme in the synthesis of glutathione, is a novel target of chemoprevention paradigms. *GCLC* and *GCLM*, the genes encoding glutamate cysteine ligase subunits, are induced by indoles such as indomethacin (Sekhar *et al.*, 2002). In this regard, novel functionalized indole analogues and other structurally related compounds have been synthesized and utilized for comparative structure analysis of *GCLC* induction (Sekhar *et al.*, 2003). The second of the title compounds, (II), was found to be ten



(I) (II)

times more active than indomethacin in inducing GCLC, whereas the first of the title compounds, (I), is inactive. Aldol condensation of 1-phenylsulfonyl-1*H*-indole-3-carboxaldehyde with 1-azabicyclo[2.2.2]octan-3-one affords (I) as a single geometric isomer. Compound (I) was reduced to the corresponding alcohol with sodium borohydride in methanol. The compositions of (I) and (II) were initially identified by NMR spectroscopy. In order to confirm the double-bond geometry of these compounds, and to obtain more detailed information about the structural conformation of the molecules that may be of value in structure–activity analysis, their X-ray structure determination has also been carried out.

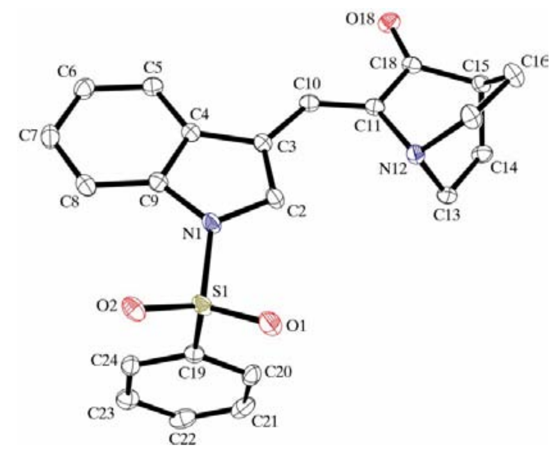


Figure 1
A view of the molecule of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

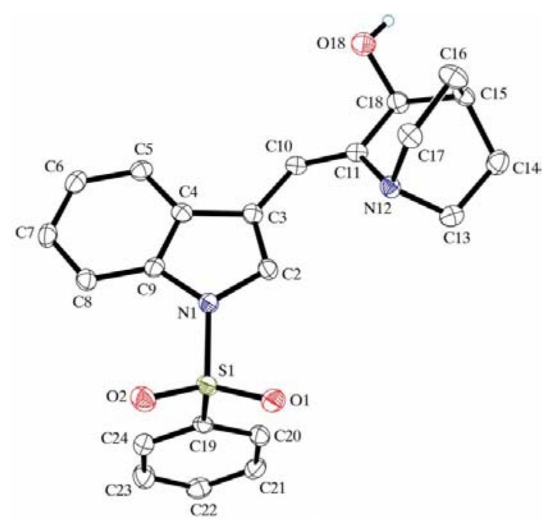


Figure 2
A view of the molecule of (II), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms, except that linked to atom O18, have been omitted for clarity.

X-Ray analysis confirms the molecular structure and atom connectivity for (I) and (II), as illustrated in Figs. 1 and 2; selected geometric parameters are presented in Tables 1 and 2, respectively. For each structure, the indole ring is planar, with bond distances and angles comparable to those reported previously for other indole derivatives (Mason *et al.*, 2003; Zarza *et al.*, 1988). The geometries around the S atoms are distorted from ideal tetrahedral, the largest deviations being in

 DOI: 10.1107/S0108270104015847

the O═S═O [O2═S1═O1 in (I) is 121.08 (6)° and in (II) is 120.64 (9)°] and O═S—N angles [O2═S1—N1 and O1═S1—N1 in (I) are 106.87 (6) and 105.68 (5)°, and in (II) are 106.61 (9) and 105.48 (8)°]. This type of deviation in the sulfonyl group has been reported previously and is due to the repulsive interaction between the short S═O bonds (Seshadri *et al.*, 2002). The S═O, S—C and S—N distances are comparable to those found in *N*-phenylsulfonamides (Gomes *et al.*, 1993). The conformation of the phenylsulfonyl group with respect to the indole ring is described by the O1═S1—N1—C2, O2═S1—N1—C9 and N1—S1—C19—C20 torsion angles. The benzene ring linked to the sulfonyl group is orthogonal to the indole ring system, forming a dihedral angle of 90.2 (2)° in (I) and 94.0 (2)° in (II).

Compounds (I) and (II) are both *Z* isomers; the C11—C18 bond is in a *trans* disposition with respect to the C3—C10 bond. The double bond has a nearly planar arrangement, with an r.m.s. deviation from the mean plane passing through atoms N12, C11, C18, C10 and C3 of 0.008 (11) Å in (I) and 0.0021 (11) Å in (II). Deviations from ideal geometry are observed in the bond angles around atoms C3, C10 and C11. While the C10═C11—C18 angle is close to the ideal value of 120°, the C2═C3—C10, C3—C10═C11 and N12—C11—C18 angles are more distorted in both molecules as a consequence of the strain induced by the C10═C11 double-bond linkage. In both molecules, the aza-bicyclic system exhibits very small distortions around atoms N12, C13, C14, C15, C16 and C17. The values of the C2═C3—C10═C11 torsion angles [−2.2 (2)° in (I) and −21.0 (3)° in (II)] indicate that the deviation of the indole ring from the plane of the double bond connected to the aza-bicyclic ring is greater in (II) than it is in (I). The C3—C10 bond length, when compared with the standard value for a $C_{ar}—Csp^2$ single bond [1.470 (15) Å; Wilson, 1992], suggests extensive conjugation, beginning at atom O18 and extending through to the aromatic ring in (I), which is also evident from the C11—C18 and C18—O18 bond lengths. However, in the case of (II), where the carbonyl group has been reduced to the corresponding alcohol, the C11—C18 and C18—O18 bond lengths have a purely single-bond character, and conjugation begins at C11 and extends to the aromatic ring. This extended conjugation in (I) and (II) explains the difference in the C2═C3—C10═C11 torsion angle.

The crystal of compound (II) appeared to be enantiomerically pure, presumably as a result of spontaneous resolution during crystallization. A standard test (Bernardinelli & Flack, 1985) suggested that it has the 3*S* configuration. Nonetheless, the chemistry should show no preference for any particular enantiomer, so, in all likelihood, half of the crystals obtained would have been in the 3*R* configuration. The H atom attached to atom O18 is involved in an intermolecular hydrogen bond (2.30 Å) with atom O18 of another molecule (Table 3), thus forming an infinite chain running in the *a* direction. In addition to C—H···O and C—H···π weak interactions, van der Waals forces contribute to the stabilization of the crystal structures of (I) and (II).

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 hydrochloride completely dissolved (20 min). The temperature was lowered to 195 K and a solution of 1-phenylsulfonyl-1*H*-indole-3-carboxaldehyde (2.63 g, 9.2 mmol) in THF (30 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 an aqueous saturated $NaHCO_3$ solution 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, filtered and evaporated to afford a yellow solid. Crystallization from methanol gave (I) as a yellow crystalline product suitable for X-ray analysis. ^{1}H NMR ($CDCl_3$): δ 1.85–1.91 (*m*, 4H), 2.49 (*p*, 1H), 2.78–2.87 (*m*, 2H), 3.02–3.11 (*m*, 2H), 7.07 (*s*, 1H), 7.10–7.21 (*m*, 2H), 7.27–7.32 (*m*, 2H), 7.36–7.42 (*m*, 1H), 7.56–7.59 (*dd*, 1H), 7.73–7.76 (*m*, 2H), 7.79–7.82 (*dd*, *J* = 1.5 and 7.7 Hz, 1H), 8.52 (*s*, 1H); ^{13}C NMR ($CDCl_3$): δ 26.4, 40.7, 47.5, 113.7, 115.0, 116.1, 119.4, 124.0, 125.3, 127.0, 129.5, 130.5, 134.2, 134.5, 138.0, 144.9, 205.3. To a stirred solution of (I) (0.392 g, 1 mmol) in methanol (15 ml) at 273 K was added $NaBH_4$ (0.379 g, 10 mmol) over a period of 15 min and stirring was continued for 2 h at room temperature. Water (50 ml) was added and the mixture was extracted with $CHCl_3$ (3 × 10 ml). The combined organic layers were dried over Na_2SO_4 and evaporated to give (II) as a colorless solid. Crystallization from methanol afforded colorless needles suitable for X-ray analysis. ^{1}H NMR ($CDCl_3$): δ 1.46–1.61 (*m*, 2H), 1.72–1.90 (*m*, 4H), 2.05–2.08 (*p*, 1H), 4.38 (*s*, 1H), 6.42 (*d*, 1H), 7.21–7.32 (*m*, 2H), 7.37–7.43 (*m*, 2H), 7.47–7.52 (*m*, 1H), 7.6 (*d*, 1H), 7.86 (*d*, 2H), 7.98 (*d*, 1H), 8.42 (*s*, 1H); ^{13}C NMR ($CDCl_3$): δ 19.4, 25.7, 31.5, 46.9, 48.0, 71.4, 110.9, 111.0, 113.8, 117.5, 119.1, 123.4, 124.7, 126.4, 126.8, 129.3, 130.7, 133.8, 134.6, 138.3, 153.2.

Compound (I)

Crystal data

$C_{22}H_{20}N_2O_3S$	$Z = 2$
$M_r = 392.46$	$D_x = 1.433$ Mg m^{-3}
Triclinic, $P\bar{1}$	Mo $K\alpha$ radiation
$a = 7.7070$ (1) Å	Cell parameters from 4073 reflections
$b = 10.7080$ (2) Å	$\theta = 1.0$–27.5°
$c = 12.3080$ (2) Å	$\mu = 0.21$ mm^{-1}
$\alpha = 94.5900$ (7)°	$T = 90.0$ (2) K
$\beta = 104.1170$ (7)°	Irregular wedge, yellow
$\gamma = 110.1160$ (7)°	0.35 × 0.25 × 0.15 mm
$V = 909.86$ (3) Å^3	

Data collection

Nonius KappaCCD diffractometer	$R_{int} = 0.018$
ω scans	$\theta_{max} = 27.5°$
8085 measured reflections	$h = -9 \rightarrow 9$
4145 independent reflections	$k = -13 \rightarrow 13$
3720 reflections with $I > 2\sigma(I)$	$l = -15 \rightarrow 15$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0439P)^2 + 0.4878P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.034$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.090$	$\Delta\rho_{max} = 0.36$ e Å^{-3}
$S = 1.02$	$\Delta\rho_{min} = -0.49$ e Å^{-3}
4145 reflections	Extinction correction: *SHELXL*97
254 parameters	Extinction coefficient: 0.008 (3)
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °) for (I).

S1—O2	1.4280 (9)	C3—C10	1.4493 (16)
S1—O1	1.4282 (10)	C10—C11	1.3404 (17)
S1—N1	1.6643 (11)	C11—N12	1.4455 (15)
S1—C19	1.7609 (13)	C11—C18	1.4888 (16)
N1—C2	1.4000 (15)	N12—C17	1.4844 (16)
N1—C9	1.4145 (16)	O18—C18	1.2228 (15)
O2—S1—O1	121.08 (6)	C11—C10—C3	128.56 (12)
O1—S1—N1	105.68 (5)	C10—C11—C18	121.74 (11)
O1—S1—C19	108.92 (6)	N12—C11—C18	113.76 (10)
N1—S1—C19	104.68 (6)	O18—C18—C11	124.79 (11)
C2—C3—C10	128.56 (12)	C11—C18—C15	110.44 (10)
O1—S1—N1—C2	32.66 (12)	C3—C10—C11—C18	178.18 (11)
O2—S1—N1—C9	−38.89 (12)	C10—C11—C18—O18	6.4 (2)
C2—C3—C10—C11	−2.2 (2)	N12—C11—C18—O18	−175.02 (11)
C3—C10—C11—N12	−0.2 (2)	N1—S1—C19—C20	87.02 (11)

Table 2
Selected geometric parameters (Å, °) for (II).

S1—O2	1.4247 (15)	C3—C10	1.463 (3)
S1—O1	1.4276 (14)	C10—C11	1.332 (3)
S1—N1	1.6591 (16)	C11—N12	1.441 (2)
S1—C19	1.7620 (19)	C11—C18	1.524 (3)
N1—C2	1.408 (2)	N12—C17	1.486 (2)
N1—C9	1.416 (2)	O18—C18	1.426 (2)
O2—S1—O1	120.64 (9)	C11—C10—C3	126.31 (18)
O1—S1—N1	105.48 (8)	C10—C11—C18	123.55 (17)
O1—S1—C19	108.59 (9)	N12—C11—C18	114.56 (16)
N1—S1—C19	106.19 (9)	O18—C18—C11	108.35 (16)
C2—C3—C10	128.12 (17)	C11—C18—C15	107.22 (15)
O1—S1—N1—C2	30.04 (17)	C3—C10—C11—C18	179.54 (18)
O2—S1—N1—C9	−46.13 (18)	C10—C11—C18—O18	52.0 (2)
C2—C3—C10—C11	−21.0 (3)	N12—C11—C18—O18	−128.56 (17)
C3—C10—C11—N12	0.1 (3)	N1—S1—C19—C20	85.76 (16)

Compound (II)

Crystal data

$C_{22}H_{22}N_2O_3S$	Mo $K\alpha$ radiation
M_r = 394.48	Cell parameters from 2500 reflections
Orthorhombic, $P2_12_12_1$	θ = 1.0–27.5°
a = 6.1300 (1) Å	μ = 0.20 mm^{-1}
b = 12.9500 (2) Å	T = 90.0 K
c = 23.6800 (4) Å	Block, colorless
V = 1879.80 (5) Å^3	0.25 × 0.22 × 0.15 mm
Z = 4	
D_x = 1.394 Mg m^{-3}	

Data collection

Nonius KappaCCD diffractometer	R_{int} = 0.049
ω scans	θ_{max} = 27.5°
23 509 measured reflections	$h = -7 \rightarrow 7$
4283 independent reflections	$k = -16 \rightarrow 16$
3780 reflections with $I > 2\sigma(I)$	$l = -30 \rightarrow 30$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0532P)^2 + 0.3905P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.038	$(\Delta/\sigma)_{max}$ = 0.004
$wR(F^2)$ = 0.094	$\Delta\rho_{max}$ = 0.31 e Å^{-3}
S = 1.05	$\Delta\rho_{min}$ = −0.33 e Å^{-3}
4283 reflections	Absolute structure: Flack (1983), 1807 Friedel pairs
253 parameters	Flack parameter = 0.00 (7)
H-atom parameters constrained	

All H atoms were located in difference Fourier syntheses, and were subsequently positioned geometrically and treated as riding, with bond distances to parent atoms of 0.95 (C_{ar}—H), 0.99 (C_{sec}—H), 1.00 (C_{tert}—H) and 0.89 Å (O—H). The absolute structure of (II) was determined by refinement of the Flack parameter (Flack, 1983; Bernardinelli & Flack, 1985), the value of which indicates the probable correctness of the assignment.

For both compounds, 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.

Table 3
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O18—H18O···O18^{i}	0.89	2.30	3.142 (3)	157

Symmetry code: (i) $x - \frac{1}{2}, \frac{5}{2} - y, 2 - z$.

This investigation was supported by the National Institute of Alcohol Abuse and Alcoholism (grant No. AA12600).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1739). Services for accessing these data are described at the back of the journal.

References

Bernardinelli, G. & Flack, H. D. (1985). *Acta Cryst.* A**41**, 500–511.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Gomes, A. C., Biswas, G., Biswas, S., Biswas, G. K., Iitaka, Y. & Banerjee, A. (1993). *J. Crystallogr. Spectrosc. Res.* **23**, 513–517.
Mason, M. R., Barnard, T. S., Segla, M. F., Xie, B. & Kirschbaum, K. (2003). *J. Chem. Crystallogr.* **33**, 531–540.
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 & R. M. Sweet, pp. 307–326. New York: Academic Press.
Sekhar, K. R., Crooks, P. A., Sonar, V. N., Friedman, D. B., Chan, J. Y., Meredith, M. J., Starnes, J. H., Kelton, K. R., Summar, S. R., Sasi, S. & Freeman, M. L. (2003). *Cancer Res.* **63**, 5636–5645.
Sekhar, K. R., Spitz, D. R., Harris, S., Nguyen, T. T., Meredith, M. J., Holt, J. T., Guis, D., Marnett, L. J., Summar, M. L. & Freeman, M. L. (2002). *Free Radical Biol. Med.* **32**, 650–662.
Seshadri, P. R., Velmurugan, D., Govindaraj, J., Kannadasan, S., Srinivasan, P. C., Shanmuga Sundara Raj, S., Fun, H.-K. & Kim, M. J. (2002). *Acta Cryst.* C**58**, o700–o703.
Sheldrick, G. M. (1995). *XP* in *SHELXTL*/*PC*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.
Wilson, A. J. C. (1992). *International Tables for Crystallography*, Vol. C, Table 9.5.1.1. Dordrecht/Boston/London: Kluwer Academic Publishers.
Zarza, P. M., Gill, P., Gonzales, M. C. D., Reyes, M. G. M., Arrieta, J. M., Nastopoulos, V., Germain, G. & Debaerdemaeker, T. (1988). *Acta Cryst.* C**44**, 678–681.