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# Structure of (+)-(7*S*,S*S*)-1,2,3,5,6,7-Hexahydro-7-methyl-8-(*p*-tolylsulfinyl)-5-indolizinone

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**Abstract.** $C_{16}H_{19}NO_2S$, $M_r = 289{\cdot}39$, orthorhombic, $P2_12_12_1$, $a = 11{\cdot}467\ (5)$, $b = 17{\cdot}207\ (8)$, $c = 7{\cdot}566\ (4)$ Å, $V = 1493\ (2)$ Å$^3$, $Z = 4$, $D_x = 1{\cdot}29$ g cm$^{-3}$, $\lambda$(Mo $K\alpha$) = 0·71069 Å, $\mu = 2{\cdot}07$ cm$^{-1}$, $F(000) = 616$, $T = 296$ K, $R = 0{\cdot}049$, 928 unique observed reflections. The structure determination combined with the known *S* configuration at the sulfur site discloses the stereochemistry of the title compound to be 7*S* and S*S*.

**Introduction.** In the studies involving the enantioselective synthesis of biologically active indolizidines, the asymmetric addition reactions of the anion derived from (+)-(S*R*)-3,4-dihydro-5-(*p*-tolylsulfinylmethyl)-2*H*-pyrrole (I) (Morrison & Boyd, 1987) and *trans*-methyl or -ethyl crotonates were investigated. The reaction afforded 80% yield (isolated) of the title compound (II) and its 7*R* isomer (III) (ratio of 1:2; same ratios were obtained in either methyl or ethyl crotonate reactions). The relative stereochemistry at the S atom and C(7) of (II) was proven by this X-ray study. This proof, in turn, provides firm evidence of the stereochemical course followed in asymmetric addition reactions of chiral $\alpha$-sulfinyl ketimine anions [such as (I)] with *trans*-alkyl crotonates.

**Experimental.** All new compounds displayed satisfactory $^1$H NMR (400 MHz), $^{13}$C NMR (100 MHz), UV, IR and low-resolution mass spectra (both EI and CI) and satisfactory elemental analysis. Title compound, (+)-(7*S*,S*S*)-1,2,3,5,6,7-hexahydro-7-methyl-8-(*p*-tolylsulfinyl)-5-indolizinone (II), and related compound, (−)-(7*R*,S*S*)-1,2,3,5,6,7-hexahydro-7-methyl-8-(*p*-tolylsulfinyl)-5-indolizinone (III) prepared as follows. To a cold (195 K) solution of 1 g (4·52 mmol) of (+)-S*R*-3,4-dihydro-5-(*p*-tolylsulfinylmethyl)-2*H*-pyrrole (I) [ketimine (I) prepared by treating 3 equivalents 3,4-dihydro-5-methyl-2*H*-pyrrole (Bielawski, Brandange & Lindblom, 1978) with 3 equivalents lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at 273 K for 30 min followed by 1 equivalent (−)-(S*S*)-1-menthyl *p*-toluenesulfinate in THF at 223 K for 1 h; 92% yield; $[\alpha]_D^{20°C}$ + 146° (*c* 0·645 in $CH_2Cl_2$)] in 30 ml THF under argon was added a solution (243 K) of 5·4 mmol of LDA in 20 ml of THF *via* cannula. Resulting yellow solution stirred at 195 K for 30 min, 0·62 g (5·4 mmol) *trans*-methyl crotonate added. After stirring at 298 K for 24 h, solution diluted with 50 ml of $H_2O$ and extracted with $CH_2Cl_2$ three times (100 ml each). Combined extracts washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel to give 0·354 g (27% yield) of (II); $[\alpha]_D^{22°C}$ + 69° (*c* 0·235, $CH_2Cl_2$), and 0·695 g (53% yield) of (III); $[\alpha]_D^{22°C}$ − 106° (*c* 0·51, $CH_2Cl_2$). Colorless prisms of (II) obtained by recrystallization from ether:hexane (1:2); m.p. 450–451 K. Recrystallization of solid (III) produced material unsuitable for single-crystal analysis; m.p. 415–416 K.

Crystal of (II) used for data collection 0·27 × 0·22 × 0·19 mm, colorless, transparent fragment cut from larger crystal. Rigaku AFC5S diffractometer, graphite-monochromated Mo $K\alpha$ radiation, $\omega$ scans, scan speed 6° min$^{-1}$, maximum of 3 scan repetitions to obtain $\sigma F/F < 0{\cdot}10$. Lattice parameters from least-squares fit of 25 strong reflections in $2\theta$ range 24–33°. A total of 1534 reflections measured ($h$ 0 to 13, $k$ 0 to 20, $l$ 0 to 8), 606 reflections considered unobserved with $[I < 2\sigma(I)]$, data set comprised of 928 unique reflections, $[(\sin\theta)/\lambda]_{max} = 0{\cdot}60$ Å$^{-1}$. Three standard reflections (21$\bar{1}$, 230, 220) changed by 0·0, −0·6 and −0·5%, respectively; no decay correction applied. Data corrected for Lorentz, polarization, and absorption (empirical $\psi$-scan method, 3 reflections, transmission range 0·98–1·0). Direct methods provided the locations of all non-H atomic positions. Full-matrix least-squares refinement was performed to minimize $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2(|F_o|)$ and $p = 0{\cdot}05$ (details of $\sigma^2$ calculation

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Table 1. *Fractional atomic coordinates and equivalent isotropic temperature factors*

$B_{eq} = (8\pi^2/3)$ trace **U**.

| | $x$ | $y$ | $z$ | $B_{eq}$(Å$^2$) |
|---|---|---|---|---|
| S(1) | 0·0419 (2) | 0·2172 (1) | 0·4209 (3) | 4·41 (9) |
| O(1) | −0·1837 (5) | 0·3969 (3) | 0·9769 (7) | 5·6 (3) |
| O(2) | 0·1593 (4) | 0·1868 (3) | 0·4731 (8) | 6·5 (3) |
| C(1) | −0·0626 (7) | 0·3875 (4) | 0·402 (1) | 5·0 (4) |
| C(2) | −0·098 (1) | 0·4658 (5) | 0·459 (1) | 7·9 (6) |
| C(3) | −0·1374 (7) | 0·4639 (4) | 0·642 (1) | 5·1 (4) |
| N(4) | −0·1059 (5) | 0·3852 (3) | 0·7011 (7) | 3·6 (3) |
| C(5) | −0·1417 (6) | 0·3563 (4) | 0·861 (1) | 4·2 (4) |
| C(6) | −0·1296 (6) | 0·2693 (4) | 0·8763 (9) | 4·2 (3) |
| C(7) | −0·0237 (5) | 0·2345 (4) | 0·7831 (8) | 3·3 (3) |
| C(8) | −0·0172 (5) | 0·2683 (4) | 0·6005 (9) | 3·2 (3) |
| C(8a) | −0·0583 (5) | 0·3398 (4) | 0·5684 (9) | 3·4 (3) |
| C(9) | 0·0888 (6) | 0·2489 (5) | 0·885 (1) | 5·3 (4) |
| C(10) | −0·0558 (6) | 0·1345 (3) | 0·4224 (9) | 3·3 (3) |
| C(11) | −0·1724 (6) | 0·1453 (4) | 0·394 (1) | 3·9 (3) |
| C(12) | −0·2441 (6) | 0·0809 (4) | 0·382 (1) | 4·6 (4) |
| C(13) | −0·2018 (6) | 0·0070 (4) | 0·404 (1) | 3·9 (3) |
| C(14) | −0·0839 (7) | −0·0012 (4) | 0·437 (1) | 4·7 (4) |
| C(15) | −0·0102 (6) | 0·0618 (4) | 0·446 (1) | 4·2 (4) |
| C(16) | −0·2822 (8) | −0·0631 (5) | 0·393 (1) | 6·5 (5) |

Table 2. *Selected bond distances* (Å), *bond angles* (°), *and their e.s.d.'s*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| S(1) | O(2) | 1·498 (5) | | C(6) | C(7) | 1·526 (9) | |
| S(1) | C(8) | 1·755 (6) | | C(7) | C(8) | 1·500 (8) | |
| S(1) | C(10) | 1·812 (6) | | C(7) | C(9) | 1·525 (9) | |
| O(1) | C(5) | 1·218 (8) | | C(8) | C(8a) | 1·339 (8) | |
| C(1) | C(2) | 1·47 (1) | | C(10) | C(11) | 1·368 (9) | |
| C(1) | C(8a) | 1·51 (1) | | C(10) | C(15) | 1·368 (9) | |
| C(2) | C(3) | 1·46 (1) | | C(11) | C(12) | 1·383 (9) | |
| C(3) | N(4) | 1·470 (9) | | C(12) | C(13) | 1·371 (9) | |
| N(4) | C(5) | 1·374 (9) | | C(13) | C(14) | 1·383 (9) | |
| N(4) | C(8a) | 1·385 (8) | | C(13) | C(16) | 1·52 (1) | |
| C(5) | C(6) | 1·51 (1) | | C(14) | C(15) | 1·38 (1) | |
| O(2) | S(1) | C(8) | 108·6 (3) | S(1) | C(8) | C(7) | 122·5 (5) |
| O(2) | S(1) | C(10) | 106·2 (3) | S(1) | C(8) | C(8a) | 117·1 (5) |
| C(8) | S(1) | C(10) | 98·6 (3) | C(7) | C(8) | C(8a) | 120·3 (6) |
| C(2) | C(1) | C(8a) | 105·2 (6) | C(1) | C(8a) | N(4) | 106·6 (6) |
| C(1) | C(2) | C(3) | 110·1 (7) | C(1) | C(8a) | C(8) | 131·6 (7) |
| C(2) | C(3) | N(4) | 103·5 (7) | N(4) | C(8a) | C(8) | 121·7 (6) |
| C(3) | N(4) | C(5) | 121·8 (6) | S(1) | C(10) | C(11) | 119·8 (5) |
| C(3) | N(4) | C(8a) | 113·4 (6) | S(1) | C(10) | C(15) | 118·9 (5) |
| C(5) | N(4) | C(8a) | 123·6 (6) | C(11) | C(10) | C(15) | 121·3 (6) |
| O(1) | C(5) | N(4) | 122·9 (7) | C(10) | C(11) | C(12) | 118·8 (6) |
| O(1) | C(5) | C(6) | 123·6 (7) | C(11) | C(12) | C(13) | 121·7 (6) |
| N(4) | C(5) | C(6) | 113·4 (7) | C(12) | C(13) | C(14) | 117·5 (6) |
| C(5) | C(6) | C(7) | 115·3 (6) | C(12) | C(13) | C(16) | 121·0 (7) |
| C(6) | C(7) | C(8) | 108·3 (5) | C(14) | C(13) | C(16) | 121·5 (7) |
| C(6) | C(7) | C(9) | 112·0 (5) | C(13) | C(14) | C(15) | 122·0 (6) |
| C(8) | C(7) | C(9) | 111·3 (5) | C(10) | C(15) | C(14) | 118·6 (6) |

given in Robinson, Hinckley & Kibala, 1988). After anisotropic convergence the methyl, methylene and phenyl H atoms were placed in assumed positions (C—H = 0·95 Å), methyl group orientations fixed on the basis of H-atom positions obtained from difference Fourier synthesis. The H(9) atomic site obtained directly from a difference Fourier synthesis. H-atom positions were not refined due to the poor adjustable parameter-to-observation ratio (apparently a result of the high overall thermal motion of the compound). Final stages of refinement performed with 182 variables including all non-H positional and anisotropic thermal parameters, one scale factor, and a secondary-extinction coefficient ($0{\cdot}11789 \times 10^{-5}$). Convergence yielded $R = 0{\cdot}049$, $wR = 0{\cdot}054$, $S = 1{\cdot}23$ and $(\Delta/\sigma)_{max} = 0{\cdot}00$. Final difference synthesis produced $(\Delta\rho)_{max} = 0{\cdot}22$ and $(\Delta\rho)_{min} = -0{\cdot}18$ e Å$^{-3}$. Atomic scattering factors and anomalous-dispersion corrections from Cromer & Waber (1974). All computer programs from the *TEXSAN* crystal-structure-analysis package (Molecular Structure Corporation, 1985).

**Discussion.** Final atomic coordinates with equivalent isotropic temperature factors are given in Table 1; Table 2 contains selected interatomic distances and angles.* Fig. 1 shows the molecular configuration, atom-numbering scheme, and thermal motion, while Fig. 2 depicts the molecular packing.

The double bond [C(8)=C(8a)] of the molecule is conjugated with the amide functional group through

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52723 (15 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

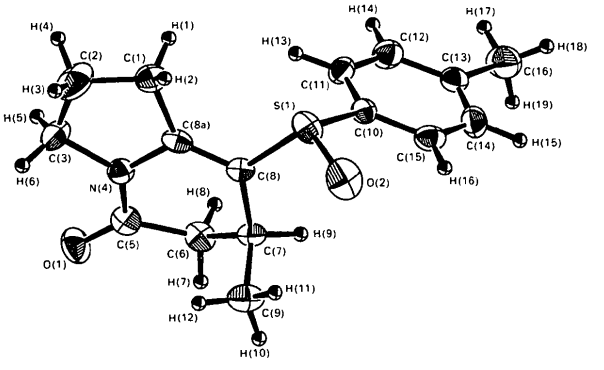


Fig. 1. Molecular configuration and IUPAC atom-numbering scheme for the non-H atoms, thermal ellipsoids at the 30% probability level. H atoms show as isotropic spheres with $B$'s of 1·0 Å$^2$.

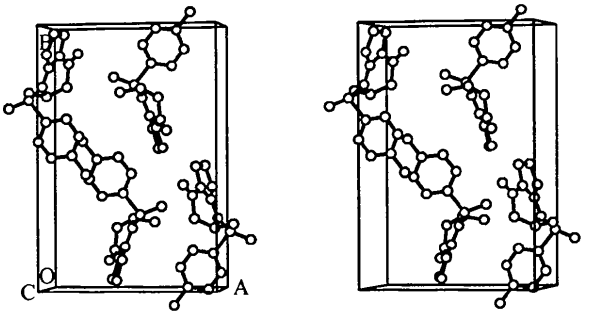


Fig. 2. Stereoscopic illustration of the molecular packing.

the lone pair of the N atom. The bond angle C(3)—N(4)—C(5) of 121·8 (6)° confirms the $sp^2$ hybridization at N. The bond angle C(1)—C(8a)=C(8) of 131·6 (7)° is larger than the 120° value for alkene. The bond angle C(8)—S(1)—C(10), and bond lengths C(8)—S(1) and S(1)=O(2) are normal (Bandoli, Panattoni, Clemente, Tondello, Dondoni & Mangini, 1971). The stereochemistry determined at C(7) and S is in line with the prediction that the anion derived from (+)-(I) approaches alkyl *trans*-crotonate predominantly from the *re* face (Izumi & Tai, 1977).

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# Structures of Colchicine Analogues. III. 2-Methoxy-5-(2′,3′-dimethoxyphenyl)- and 2-Methoxy-5-(3′,4′-dimethoxyphenyl)cycloheptа-2,4,6-trien-1-one

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**Abstract.** (4) and (5): $C_{16}H_{16}O_4$, $M_r = 272·3$, Cu $K\alpha$, $\lambda = 1·5418$ Å, $T = 295$ (1) K. 5-(2,3-Dimethoxyphenyl)-2-methoxycyclohepta-2,4,6-trien-1-one (4): orthorhombic, $P2_12_12_1$, $a = 7·330$ (1), $b = 8·992$ (1), $c = 21·416$ (1) Å, $V = 1411·6$ (4) Å$^3$, $Z = 4$, $D_m$ (flotation) = 1·28 (1), $D_x = 1·281$ Mg m$^{-3}$, $\mu = 0·67$ mm$^{-1}$, $F(000) = 576$. Final $R = 0·032$ for 1248 observed data. 5-(3,4-Dimethoxyphenyl)-2-methoxycyclohepta-2,4,6-trien-1-one (5): monoclinic, $C2/c$, $a = 26·131$ (5), $b = 7·634$ (1), $c = 14·158$ (2) Å, $\beta = 104·78$ (2)°, $V = 2731$ (1) Å$^3$, $Z = 8$, $D_m$ (flotation) = 1·33 (1), $D_x = 1·324$ Mg m$^{-3}$, $\mu = 0·69$ mm$^{-1}$, $F(000) = 1152$. Final $R = 0·047$ for 1584 observed data. Molecules of (4) and (5) assume a solid-state conformation that resembles that of isocolchicine rather than colchicine. The dihedral angle between the rings is 52·6° in (4) and 43·4° in (5) compared with 53° in colchicine.

**Introduction.** The potent antimitotic properties of colchicine (1) (Brossi, Yeh, Chrzanowska, Wolff, Hamel, Lin, Quin, Suffness & Silverton, 1988) and the bicyclic analogues (2) (Fitzgerald, 1976) and (3) (Banwell, Herbert, Buckleton, Clark, Rickard, Lin & Hamel, 1988) stem from the ability of these molecules to bind to the protein tubulin and thereby interfere with cellular processes that depend upon polymerization of that protein. On the basis of extensive physicochemical and structural studies (Banwell, Herbert, Buckleton, Clark, Rickard, Lin & Hamel, 1988), it has been argued that (1) and (2) undergo reversible binding to tubulin, giving an initial complex which is then converted into a more stable one. There is evidence suggesting that preliminary binding of (1) and (2) occurs with a skewed conformation of these molecules, while binding in the more stable complex involves a near-planar relationship between the tropone (*C*) and aryl (*A*) rings. The existence of two partial binding sites on the protein has been established, one for the trimethoxyphenyl *A* ring and one for the troponoid *C* ring. On the basis of the foregoing, it seems that conformational preferences

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