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Methyl (3*R**,4*R**)-4-Hydroxy-3-phenyl-2-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydro-4-isoquinolinylacetate

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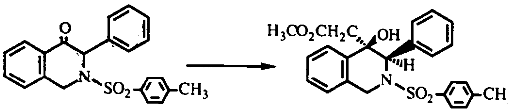
Abstract

The X-ray structure analysis of the title compound, $C_{25}H_{25}NO_5S$, establishes unambiguously the absolute configuration of the asymmetric C atoms as *R* (C9) and *R* C(10), with the hydroxyl and phenyl substituents in *cis* positions. The heterocyclic ring exhibits a flattened sofa conformation. The crystal structure shows an intramolecular hydrogen bond between the hydroxyl group and the carbonyl O atom.

Comment

The benzo[*c*]phenanthridines (Simâneck, 1985) are a family of isoquinoline alkaloids which possess, in many cases, strong pharmacological activity. For example, nitidine and fagaronine are employed for the treatment of some types of leukemia (Sethi, 1985). One of the procedures utilized in organic chemistry for the synthesis of this class of tetracycles involves the use of 3-arylisoquinoline derivatives appropriately substituted at the C4 atom. Thus, the title compound (I) has been prepared by applying a typical Reformatsky reaction to a convenient precursor, 4-oxo-3-phenyl-2-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline (II) (Badía, Domínguez & González-Cameno, 1992). Knowledge of the stereochemistry of derivative (I) appeared interesting with respect to the future preparation of the final benzo[*c*]phenanthridine.



(II) (I)

Although NMR spectra and measurements of the difference Nuclear Overhauser Effect (NOE experiments), carried out at ambient temperature in the difference mode by irradiation of all the lines of a multiplet (Hall & Sanders, 1980; Kinns & Sanders, 1984), gave some indication of the stereochemistry of (I), it was not possible to ascertain its exact structure as diagnostic data were not obtained. However, the X-ray analysis was successful in establishing unambiguously the absolute configuration of the target compound as methyl (3*R*,4*R*)-4-hydroxy-3-phenyl-2-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydro-4-isoquinolinylacetate.

A *SCHAKAL* diagram (Keller, 1988) of the title molecule together with the atom-numbering scheme is shown in Fig. 1 and a view of the unit-cell packing is shown in Fig. 2. The molecule consists of an aromatic ring condensed with a hydrogenated heterocyclic ring containing substituents bonded to the asymmetric C9 and C10 atoms and linked to the *p*-toluenesulfonyl group through the N8 atom. The planes of the two rings of the 1,2,3,4-tetrahydroisoquinoline fragment form an angle of 12.07 (8)° with one another and the bond distances and angles are in good agreement with the values reported for other related compounds (Arrieta, Badía, Domínguez, Lete, Igartua, Germain, Vlassi & Debaerdemaeker, 1988; Arrieta, Badía, Domíguez, Lete, Martínez de Marigorta, Germain, Vlassi & Debaerdemaeker, 1988).

The structure of (I) displays a *cis* configuration of the hydroxyl group bonded to the C10 atom and the

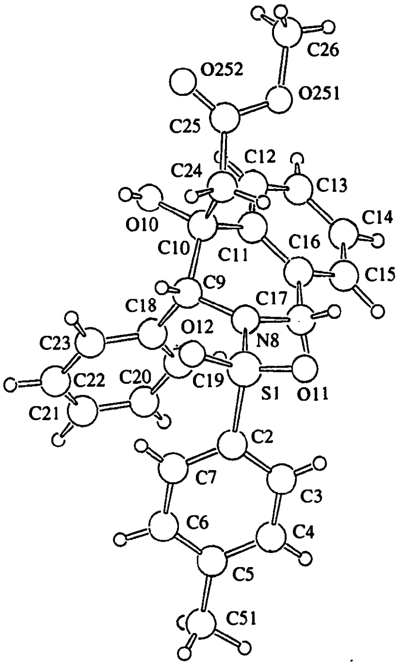


Fig. 1. View of the title compound showing the labelling of the non-H atoms.

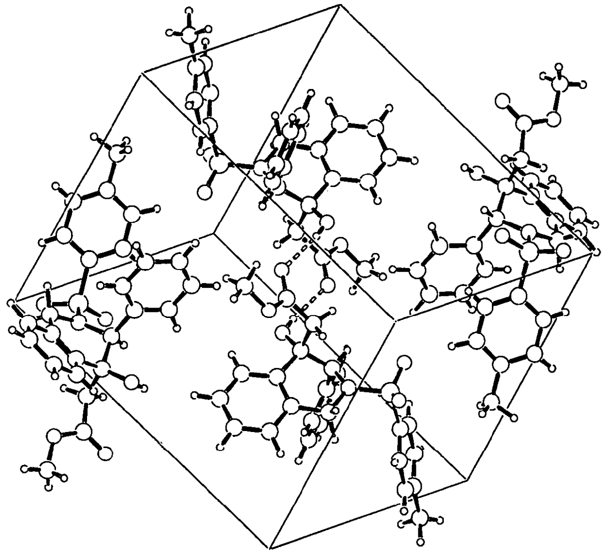


Fig. 2. Crystal packing of the title molecule.

phenyl group bonded to the C9 atom [torsion angle C18—C9—C10—O10 46.2 (3)°]. The methoxycarbonylmethyl group at C10 and the phenyl group have an *anti* conformation [torsion angle C18—C9—C10—C24 165.4 (2)°], although this conformation is not strictly periplanar. Thus, X-ray crystallographic analysis establishes an *R* (C9) and *R* (C10) configuration for compound (I).

The heterocyclic ring exhibits a sofa conformation. The C10—C11—C16—C17 torsion angle is equal to 1.2 (4)° and the remaining endocyclic torsion angles are consistent with the proposed conformation (Plywaczyk, Tykarska, Jaskólski & Kosturkiewicz, 1984). The sum of the valence angles around the N atom is 356.9° indicating sp^2 character similar to other molecules in which the heteroatom is bonded to a *p*-toluenesulfonyl group (Arriortua, Urtiaga, Badía, Domínguez, González-Cameno & Solans, 1995). The C10 and C17 atoms are coplanar with the C11–C16 aromatic ring [C10 deviates by 0.022 (3) and C17 deviates by 0.039 (3) Å]. However, the C9 atom deviates significantly [0.872 (3) Å] from this plane, whereas the N8 atom deviates slightly [0.268 (2) Å], flattening the sofa conformation.

Inspection of the intramolecular non-bonding contacts shows that the hydroxyl group of molecule (I) with an (*R*,*R*) configuration is engaged in an intermolecular interaction with the O atom of the carbonyl group of its translated (*S*,*S*) enantiomer with symmetry $1-x$, $-y$, $2-z$ [O10···O252 2.779 (3) Å].

Experimental

Crystal data

$C_{25}H_{25}NO_5S$
$M_r = 451.536$
Monoclinic
$P2_1/c$
$a = 15.606\ (2)$ Å
$b = 10.624\ (2)$ Å
$c = 13.499\ (2)$ Å
$\beta = 98.89\ (1)°$
$V = 2211.2\ (6)$ Å^3
$Z = 4$
$D_x = 1.356$ Mg m^{-3}

Mo $K\alpha$ radiation
$\lambda = 0.71069$ Å
Cell parameters from 25 reflections
$\theta = 1\text{–}25°$
$\mu = 0.175$ mm^{-1}
$T = 295$ K
Prismatic
0.09 × 0.07 × 0.06 mm
Colourless

Data collection

Philips PW1100 diffractometer
$\omega\text{–}2\theta$ scans
Absorption correction: none
3428 measured reflections
3072 independent reflections
2595 observed reflections $[I > 2\sigma(I)]$

$R_{\rm int} = 0.023$
$\theta_{\rm max} = 25°$
$h = -16 \rightarrow 16$
$k = 0 \rightarrow 11$
$l = 0 \rightarrow 14$
3 standard reflections
frequency: 60 min
intensity variation: 1.0%

Refinement

Refinement on F
$R = 0.037$
$wR = 0.037$
$S = 0.873$
2591 reflections
390 parameters
Unit weights applied

$(\Delta/\sigma)_{\rm max} = 0.20$
$\Delta\rho_{\rm max} = 0.29$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.24$ e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$$B_{\rm eq} = (8\pi^2/3)\Sigma_i\Sigma_jU_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$B_{\rm eq}$
S1	0.14190 (8)	0.05830 (10)	0.86850 (10)	3.649 (1)
O11	0.0813 (1)	−0.0075 (2)	0.9186 (1)	4.969 (4)
O12	0.1901 (1)	0.1618 (2)	0.9159 (1)	4.772 (5)
C2	0.0852 (2)	0.1107 (2)	0.7532 (2)	3.358 (7)
C3	0.0146 (2)	0.0446 (3)	0.7069 (2)	4.002 (13)
C4	−0.0263 (2)	0.0830 (3)	0.6134 (2)	4.504 (13)
C5	0.0017 (2)	0.1877 (3)	0.5666 (2)	4.425 (3)
C51	−0.0434 (2)	0.2291 (4)	0.4647 (2)	6.247 (22)
C6	0.0717 (2)	0.2540 (3)	0.6153 (2)	4.664 (9)
C7	0.1135 (2)	0.2161 (3)	0.7075 (2)	4.238 (11)
N8	0.2123 (1)	−0.0460 (2)	0.8439 (1)	3.066 (4)
C9	0.2983 (2)	−0.0054 (2)	0.8237 (2)	2.953 (2)
C10	0.3626 (1)	−0.1103 (2)	0.8645 (2)	2.900 (6)
O10	0.4461 (1)	−0.0818 (2)	0.8420 (1)	3.502 (7)
C11	0.3347 (2)	−0.2343 (2)	0.8149 (2)	2.871 (6)
C12	0.3944 (2)	−0.3223 (3)	0.7915 (2)	3.507 (5)
C13	0.3672 (2)	−0.4342 (3)	0.7450 (2)	4.152 (9)
C14	0.2800 (2)	−0.4597 (3)	0.7212 (2)	4.483 (14)
C15	0.2195 (2)	−0.3733 (3)	0.7433 (2)	3.946 (8)
C16	0.2470 (2)	−0.2605 (2)	0.7910 (2)	3.247 (12)
C17	0.1779 (2)	−0.1697 (3)	0.8104 (2)	4.209 (18)
C18	0.3018 (2)	0.0375 (2)	0.7173 (2)	3.52 (6)
C19	0.2661 (2)	−0.0284 (3)	0.6328 (2)	4.104 (9)
C20	0.2691 (2)	0.0192 (4)	0.5378 (2)	5.148 (23)
C21	0.3087 (2)	0.1327 (4)	0.5263 (2)	5.758 (12)
C22	0.3454 (2)	0.1982 (3)	0.6092 (3)	5.687 (12)
C23	0.3423 (2)	0.1515 (3)	0.7046 (2)	4.393 (7)
C24	0.3656 (2)	−0.1151 (3)	0.9798 (2)	3.473 (8)
C25	0.4392 (2)	−0.1914 (3)	1.0331 (2)	3.329 (10)
O251	0.4187 (1)	−0.3111 (2)	1.0392 (1)	4.046 (5)
O252	0.5091 (1)	−0.1493 (2)	1.0682 (1)	4.236 (7)
C26	0.4833 (2)	−0.3895 (3)	1.0978 (2)	4.483 (8)

Table 2. *Selected geometric parameters* (Å, °)

S1—O11	1.428 (2)	C11—C12	1.390 (4)
S1—O12	1.427 (2)	C11—C16	1.385 (4)
S1—C2	1.758 (3)	C12—C13	1.380 (4)
S1—N8	1.630 (2)	C13—C14	1.376 (4)
C2—C3	1.373 (4)	C14—C15	1.382 (4)
C2—C7	1.383 (4)	C15—C16	1.396 (4)
C3—C4	1.385 (4)	C16—C17	1.500 (4)
C4—C5	1.383 (4)	C18—C19	1.380 (4)
C5—C51	1.510 (4)	C18—C23	1.389 (4)
C5—C6	1.378 (4)	C19—C20	1.386 (4)
C6—C7	1.373 (4)	C20—C21	1.375 (6)
N8—C9	1.475 (4)	C21—C22	1.366 (5)
N8—C17	1.464 (4)	C22—C23	1.388 (5)
C9—C10	1.543 (3)	C24—C25	1.496 (4)
C9—C18	1.516 (4)	C25—O251	1.317 (4)
C10—O10	1.416 (2)	C25—O252	1.206 (3)
C10—C11	1.511 (3)	O251—C26	1.446 (3)
C10—C24	1.551 (4)		
C2—S1—N8	107.3 (1)	O10—C10—C24	109.6 (2)
O12—S1—N8	106.9 (1)	O10—C10—C11	107.6 (2)
O12—S1—C2	108.1 (1)	C10—C11—C16	119.0 (2)
O11—S1—N8	106.3 (1)	C10—C11—C12	122.0 (2)
O11—S1—C2	107.2 (1)	C11—C12—C13	120.8 (3)
O11—S1—O12	120.5 (1)	C12—C11—C16	119.0 (2)
S1—C2—C7	120.0 (2)	C12—C13—C14	120.0 (3)
S1—C2—C3	120.0 (2)	C13—C14—C15	120.2 (3)
C3—C2—C7	120.0 (3)	C14—C15—C16	119.9 (3)
C2—C3—C4	119.2 (3)	C11—C16—C15	120.1 (3)
C3—C4—C5	121.3 (3)	C15—C16—C17	117.0 (2)
C4—C5—C6	118.4 (3)	C11—C16—C17	122.8 (2)
C4—C5—C51	121.0 (3)	N8—C17—C16	113.1 (2)
C51—C5—C6	120.6 (3)	C9—C18—C23	117.6 (2)
C5—C6—C7	120.9 (3)	C9—C18—C19	124.2 (2)
S1—N8—C17	116.5 (2)	C19—C18—C23	118.3 (2)
S1—N8—C9	120.0 (2)	C18—C19—C20	120.8 (3)
C9—N8—C17	120.4 (2)	C19—C20—C21	120.3 (3)
C2—C7—C6	120.1 (3)	C20—C21—C22	119.6 (3)
N8—C9—C18	115.5 (2)	C21—C22—C23	120.5 (3)
N8—C9—C10	106.4 (2)	C18—C23—C22	120.5 (3)
C10—C9—C18	116.0 (2)	C10—C24—C25	113.7 (2)
C9—C10—C24	107.4 (2)	C24—C25—O252	124.6 (3)
C9—C10—C11	110.2 (2)	C24—C25—O251	112.2 (2)
C9—C10—O10	109.8 (2)	O251—C25—O252	123.2 (3)
C11—C10—C24	112.2 (2)	C25—O251—C26	115.8 (2)
C9—N8—C17—C16	20.8 (3)	C10—C11—C16—C17	1.2 (4)
C17—N8—C9—C10	−53.3 (3)	C11—C16—C17—N8	7.8 (4)
N8—C9—C10—C11	57.9 (2)	C18—C9—C10—O10	46.2 (3)
C9—C10—C11—C16	−35.3 (3)	C18—C9—C10—C24	165.4 (2)

Program used to solve structure: *MULTAN*87 (Debaerdemaeker *et al.*, 1987). Program used to refine structure: *SHELX*76 (Sheldrick, 1976). Program used to draw figure: *SCHAKAL* (Keller, 1988). Most of the calculations were performed using *PARST* (Nardelli, 1983). H atoms were refined with an overall isotropic temperature factor $U_{\rm iso}$ = 0.048 (6) Å^2.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and bond distances and angles involving H atoms have been deposited with the IUCr (Reference: LI1101). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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