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Leurosine methiodide–methanol–water (1/3/2)[1]

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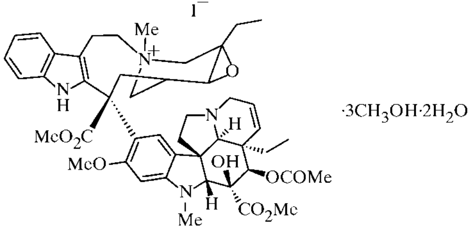
The crystal structure of a methanol–water solvate of leurosine methiodide, (leurosine-CH_3)$^+$$I^-$·$3CH_3OH$·$2H_2O$ ($C_{47}H_{59}IN_4O_9$·$3CH_3OH$·$2H_2O$), is described. The piperidine ring of the upper part of the molecule adopts a sofa conformation. An intramolecular hydrogen bond between the tertiary N and the hydroxyl group of the vindoline moiety of the molecule is present.

Comment

Leurosine is the most abundant dimeric antitumour alkaloid isolated from the Madagascan periwinkle *Catharanthus Roseus*. It belongs to the family of vinca alkaloids which includes, amongst others, vinblastine (Magnus *et al.*, 1990), vincristine (Mangeney *et al.*, 1979) and anhydrovinblastine (Scott *et al.*, 1978). These compounds and vinorelbine (Brossi & Suffness, 1990), a semisynthetic derivative, inhibit mitosis by binding to tubuline, thus allowing a broad spectrum of activity in the treatment of various carcinomas. The identification of leurosine was achieved by spectroscopic comparison with related alkaloids and by chemical synthesis. Indeed, the mild oxidation of anhydrovinblastine furnished, as the major product, the corresponding epoxidized leurosine (Langlois & Potier, 1979). However, no X-ray data have yet been reported for leurosine and the present study was initiated to resolve the solid state conformation of leurosine methiodide as the methanol–water solvate, (I).

The structure of (I) is ionic, (leurosine–CH_3)$^+$-I^-·$3CH_3OH$·$2H_2O$, and the cation structure is shown in Fig. 1. The central six-membered ring of the vindoline moiety, C2/C12/C19/C5/C4/C3, is in a boat conformation, the C3 and C19 atoms being 0.694 (9) and 0.439 (9) Å from the plane defined to within ±0.087 Å by the four remaining atoms. The other six-membered ring of the vindoline moiety, N9/C8/C7/C6/C5/C19, is in a sofa conformation: atoms C19, C5, C6 and C7 are coplanar to within ±0.016 Å and the N9 and C8 atoms are on the same side at 0.78 (1) and 0.23 (1) Å from this plane. The O3—N9 bond length of 2.614 (7) Å is indicative of a short intramolecular hydrogen bond between the tertiary N and the hydroxyl group: H3*A*···N9 1.84 Å and O3—H3*A*···N9 157.8°. The five-membered ring N9/C10/C11/C12/C19 adopts an envelope conformation, with atom C19 deviating by 0.657 (9) Å from the plane formed by the remaining four atoms to within ±0.018 Å. Comparison of the vindoline moiety of leurosine and of 18′-epivinblastine (Lynch *et al.*, 1991) shows that the conformation of these three rings is similar in both compounds.



(I)

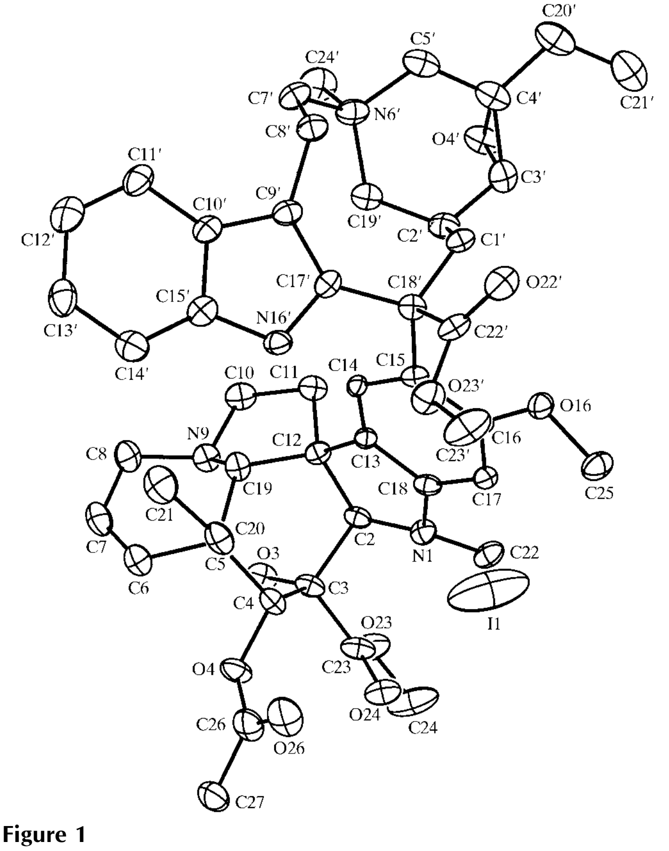


Figure 1
The structure of (I) showing 50% probability displacement ellipsoids and the atom-numbering scheme. H atoms and the solvent molecules are omitted for clarity.

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[1] Chemical Abstracts name: 4′-deoxy-3′,4′-epoxy-6′-methylvincaleukoblastin-6′-ium iodide–methanol–water (1/3/2).

The piperidine ring of the upper part of the molecule adopts a sofa conformation. Atoms C2′, C3′, C4′ and C5′ are coplanar to within 0.010 Å, with atoms C19′ and N6′ being 0.97 (1) and 0.81 (1) Å out of this plane, respectively; the oxiran atom O4′ is on the same side at 1.206 (8) Å, leading to a boat conformation for the seven-membered ring. In 18′-epivinblastine the corresponding piperidine ring has a chair conformation. On the other hand, a similar boat–chair conformation is observed in both compounds for the azacyclononene ring.

The structure of (I) is stabilized by hydrogen bonds between methanol and water molecules [O···O 2.63 (1)–2.87 (2) Å], between a water molecule and the I atom [I1···O31($x-\frac{1}{2}$, $\frac{7}{2}-y$, $-z$) 3.52 (1) and I2···O31 2.99 (2) Å] and between the indolino-H(—N16′) atom and a methanol molecule [N16′···O29($x-1$, y, z) 2.959 (8) Å and N16′–H16*A*···O29($x-1$, y, z) 149.3°].

Experimental

Leurosine (0.5 g) was added portionwise to iodomethane (5 ml). The solution was stirred at room temperature for 1 h and the solvent was then removed under reduced pressure. Suitable crystals of (I) were obtained by slow evaporation of a methanol–water–tetrahydrofuran solution.

Crystal data

$C_{47}H_{59}IN_4O_9\cdot 3CH_4O\cdot 2H_2O$
$M_r = 1083.04$
Orthorhombic, $P2_12_12_1$
$a = 9.5567\ (19)$ Å
$b = 20.491\ (4)$ Å
$c = 27.169\ (5)$ Å
$V = 5320.5\ (18)$ Å^3
$Z = 4$
$D_x = 1.352$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from about 10 000 reflections
$\theta = 3$–30°
$\mu = 0.668$ mm^{-1}
$T = 123\ (2)$ K
Irregular, colourless
0.30 × 0.20 × 0.15 mm

Data collection

Nonius KappaCCD diffractometer
φ rotation scans with 2° steps
Absorption correction: empirical (*MULABS* in *PLATON*; Spek, 1998)
$T_{min} = 0.867$, $T_{max} = 0.905$
17 090 measured reflections
5258 independent reflections plus 2851 Friedel-related reflections
5893 reflections with $I > 2\sigma(I)$
$R_{int} = 0.055$
$\theta_{max} = 25.05°$
$h = -11 \rightarrow 11$
$k = -24 \rightarrow 24$
$l = -32 \rightarrow 32$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.073$
$wR(F^2) = 0.211$
$S = 0.965$
8109 reflections
633 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.1266P)^2 + 8.9316P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.022$
$\Delta\rho_{max} = 1.11$ e Å^{-3}
$\Delta\rho_{min} = -0.78$ e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter = −0.06 (3)

H atoms (except those of the solvent molecules) were introduced at calculated positions as riding atoms, with an isotropic displacement parameter equal to 1.2 (CH, CH_2) or 1.5 (CH_3) times that of the parent atom. The I atom was found disordered on two positions, with occupancy factors of 0.755 (4) and 0.241 (4). The maximum peak in the difference map was found 1.83 Å from C30 and the minimum 1.12 Å from I1.

Data collection: *DENZO-SMN* (Otwinowski & Minor, 1997); cell refinement: *DENZO-SMN*; data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *SHELXTL* (Sheldrick, 1997); software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GS1056). Services for accessing these data are described at the back of the journal.

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