Verticine ethanol hydrate (2/1/1)

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The two symmetry-independent molecules of the title compound, cevane-3β,6α,20-triol ethanol hydrate (2/1/1), $2C_{27}H_{45}NO_3 \cdot C_2H_6O \cdot H_2O$, have the same stereochemical assignments. The six-membered rings A, B, E and F are in the chair conformation, while ring D is in a boat conformation. The ring fusions are A/B trans, B/C trans, C/D cis, D/E trans and E/F trans. The verticine molecules are bridged by water

and ethanol molecules via hydrogen bonds to form two-dimensional layers, and the crystal structure is built up by stacking of these layers.

Comment

'Beimu' (*Bulbs fritillaria*), derived from the dried bulbs of numerous species of the genus *Fritillaria* (Liliaceae), is most commonly used in mainland China, Hong Kong and other Chinese communities throughout the world, and has been for centuries (Xu & Xu, 1991). The main biologically active members of the various *Fritillaria* species are steroidal alkaloids, and include verticine, verticinone and imperialine, among which verticine is one of the major active alkaloids (Li *et al.*, 1988, 1990, 1992, 1993; Ji *et al.*, 1993). The structure of

(I)
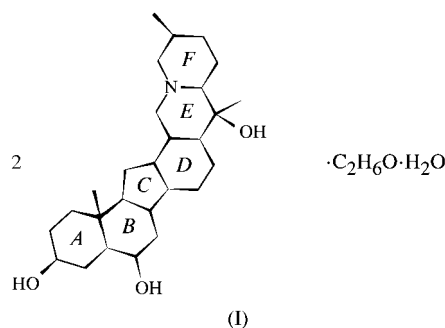
verticine has been characterized previously by NMR and MS spectrometric analyses (Ito *et al.*, 1961, 1963; Shô *et al.*, 1968). In the present study, the single-crystal X-ray crystallographic analysis of verticine ethanol hydrate (2/1/1), (I), is reported.

All bond distances in the molecule of (I) are within the normal range (Allen *et al.*, 1987). As illustrated in Fig. 1, the two independent verticine molecules in the asymmetric unit have the same stereochemical assignments. The six-membered rings A, B, E and F are in the chair conformation, whereas ring D is in a boat conformation, and the ring fusions are A/B trans, B/C trans, C/D cis, D/E trans and E/F trans. While our analysis establishes the relative stereochemistry, it does not allow us to establish the absolute configuration. The configuration shown in Fig. 1 and the scheme is chosen to be in accord with that established previously for other verti-
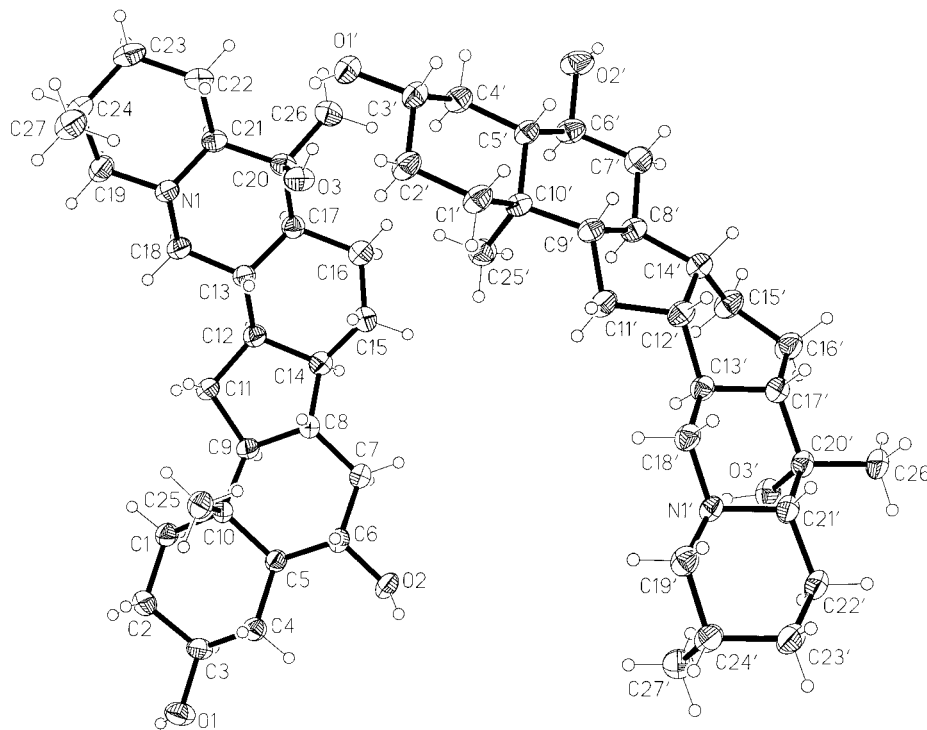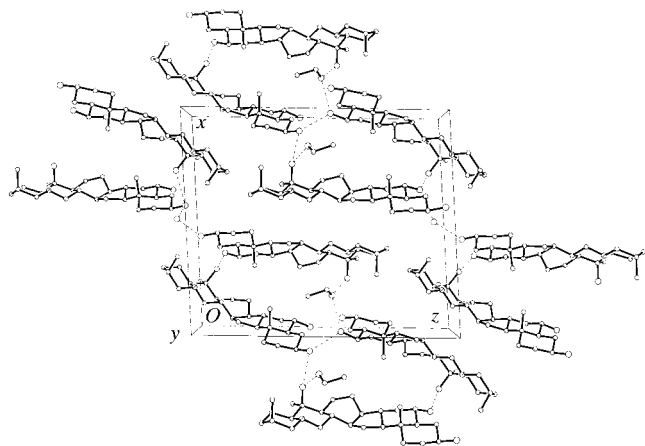

Figure 1
A perspective view of (I) with 35% displacement ellipsoids, showing the molecular conformation and the atomic labelling. H atoms are drawn as spheres of arbitrary radii.

organic compounds

Figure 2
A perspective view of the crystal structure of (I), showing the packing of the two-dimensional layers corresponding to the (101) plane. Hydrogen bonds are indicated by broken lines.

cine salt derivatives, such as the chloride (Kettmann *et al.*, 1982, 1990) and perchlorate (Codding, 1983).

In the crystal structure of (I), pairs of verticine molecules are parallel and arranged in a head-to-tail manner, interlinked by intermolecular hydrogen bonds (Fig. 2). Hydrogen bonding (see Table 1 for full details of all hydrogen-bond parameters) involving the independent water molecule and three hydroxy
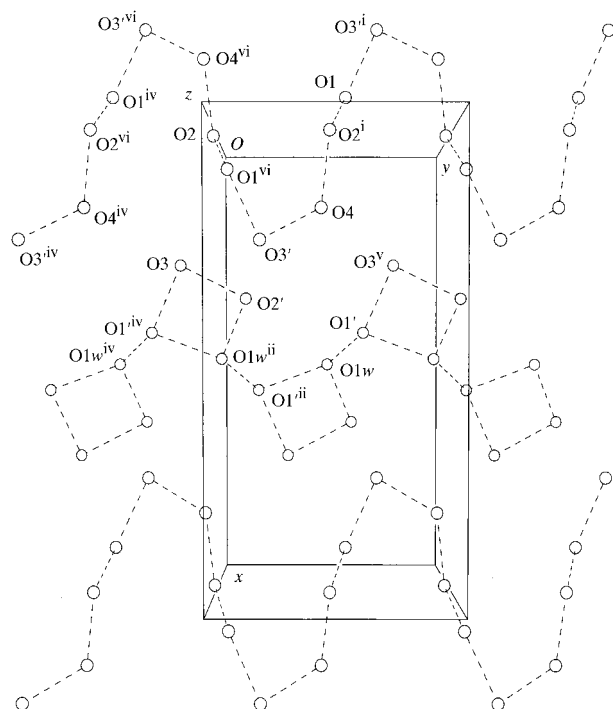

Figure 3
The mode of hydrogen bonding and molecular packing indicated by the water and hydroxy O atoms involved in the hydrogen-bonding network in the crystal structure of (I). Hydrogen bonds are indicated by broken lines [symmetry codes: (i) $-x, y + \frac{1}{2}, 1 - z$; (ii) $1 - x, y - \frac{1}{2}, -z$; (iv) $x, y - 1, z$; (v) $x, 1 + y, z$; (vi) $-x, y - \frac{1}{2}, 1 - z$].

groups from three neighbouring verticine molecules gives rise to a nearly coplanar square ring; such rings are further connected with two other adjacent rings by hydrogen bonds to generate an infinite chain extending in the y direction, as shown in Fig. 3. In addition, verticine molecules are bridged by the ethanol hydroxy group to form a one-dimensional ribbon running parallel to the y direction. The packing of the molecules in the crystal structure is characterized by a two-dimensional network approximately parallel to the (101) plane (Fig. 2). The crystal structure is built up by a stacking of these layers such that the interlayer interactions are mainly of the van der Waals type.

Experimental

The dried and ground bulbs of *Fritillaria cirrhosa* were extracted with 50% aqueous acetone. After removal of the acetone under reduced pressure, the aqueous extracts were passed through a Diaion HP-20 column, eluting first with water, followed by 50% aqueous methanol and finally methanol. The combined methanol fractions were alkalinized with 13% ammonia and extracted with chloroform. A crude alkaloid extract was obtained after removal of the chloroform solvent and it was separated by silica-gel column chromatography with a gradient elution of petroleum ether–EtOAc–Et$_2$NH (120:1:1→6:1:1). The fractions containing verticine were combined and further purified by silica-gel column chromatography, eluting with chloroform–EtOH (60:1). The solvents of the collected fractions containing verticine were removed under reduced pressure. Compound (I) was obtained by crystallization from an ethanol–water (50:1) solution.

Crystal data

$2C_{27}H_{45}NO_3 \cdot C_2H_6O \cdot H_2O$	$D_x = 1.156$ Mg m^{-3}
$M_r = 927.36$	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 25
$a = 16.146$ (3) Å	reflections
$b = 8.660$ (2) Å	$\theta = 5.0$–$12.5°$
$c = 19.096$ (4) Å	$\mu = 0.075$ mm^{-1}
$\beta = 93.74$ (3)°	$T = 293$ (2) K
$V = 2664.4$ (10) Å^3	Plate, colourless
$Z = 2$	$0.32 \times 0.22 \times 0.10$ mm

Data collection

Siemens $P4$ diffractometer	$R_{int} = 0.037$
ω scans (Sparks, 1976)	$\theta_{max} = 26.75°$
Absorption correction: empirical	$h = 0 \rightarrow 19$
(Kopfmann & Huber, 1968)	$k = -10 \rightarrow 10$
$T_{min} = 0.967$, $T_{max} = 1.000$	$l = -24 \rightarrow 24$
9866 measured reflections	3 standard reflections
5611 independent reflections	every 97 reflections
5425 reflections with $I > 2\sigma(I)$	intensity decay: 98%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0550P)^2$
$R(F) = 0.050$	$+ 0.5886P]$
$wR(F^2) = 0.120$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.124$	$(\Delta/\sigma)_{max} = 0.002$
5611 reflections	$\Delta\rho_{max} = 0.28$ e Å^{-3}
616 parameters	$\Delta\rho_{min} = -0.18$ e Å^{-3}
H atoms treated by a mixture of	Extinction correction: *SHELXL*97
independent and constrained	Extinction coefficient: 0.023 (2)
refinement	

Table 1
Hydrogen-bonding geometry (Å, °).

$D-\text{H}\cdots A$	$D-\text{H}$	$\text{H}\cdots A$	$D\cdots A$	$D-\text{H}\cdots A$
O1—H1···O3′i	0.82	1.99	2.777 (3)	160
O2—H2···O1ii	0.82	1.94	2.746 (3)	168
O3—H3···O1′iii	0.82	2.16	2.950 (3)	163
O1′—H1′···O1W	0.82	1.94	2.743 (4)	165
O2′—H2′···O3	0.82	2.36	3.097 (3)	151
O3′—H3′···O4	0.82	2.06	2.785 (4)	147
O4—H4···O2i	0.82	1.94	2.758 (3)	174
O1W—H51···O1′iv	0.86 (2)	2.18 (2)	3.025 (4)	167 (4)
O1W—H52···O2′v	0.86 (2)	1.96 (2)	2.802 (4)	166 (5)

Symmetry codes: (i) $-x, \frac{1}{2}+y, 1-z$; (ii) $-x, y-\frac{1}{2}, 1-z$; (iii) $x, y-1, z$; (iv) $1-x, y-\frac{1}{2}, -z$; (v) $1-x, \frac{1}{2}+y, -z$.

All H atoms except those of the water molecule were treated as riding atoms (C—H 0.96–0.98 Å and O—H 0.82 Å). The H atoms of the water molecule were visible in difference maps and were allowed to refine with a fixed isotropic vibration parameter subject to a *DFIX* restraint that the O—H distance be 0.86 (2) Å. A complete Friedel data set was collected, but initial refinement led to an indeterminate Flack value of 0.7 (10) for this all-light-atom structure. For the final refinement, the Friedel reflection data were merged.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *SHELXTL/PC* (Siemens, 1990); software used to prepare material for publication: *SHELXTL*93.

References

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, pp. S1–19.
Codding, P. W. (1983). *J. Am. Chem. Soc.* **105**, 3172–3176.
Ito, S., Kato, M., Shilbata, K. & Nozoe, T. (1961). *Chem. Pharm. Bull.* **9**, 253–355.
Ito, S., Kato, M., Shilbata, K. & Nozoe, T. (1963). *Chem. Pharm. Bull.* **11**, 1337–1340.
Ji, H., Li, P., Yao, L., Zhou, S. & Xu, G. J. (1993). *J. China Pharm. Univ.* **24**, 95–97.
Kettmann, V., Mašterová, I. & Tomko, J. (1982). *Acta Cryst.* B**38**, 978–980.
Kettmann, V., Mašterová, I. & Tomko, J. (1990). *Acta Cryst.* C**46**, 1334–1336.
Kopfmann, G. & Huber, R. (1968). *Acta Cryst.* A**24**, 348–351.
Li, P., Ji, H., Yao, L., Zhou, S. & Xu, G. J. (1993). *Zhong Cao Yao*, **9**, 475–477. (In Chinese.)
Li, P., Kitamura, Y., Kaneko, K., Shiro, M., Xu, G. J., Chen, Y. P. & Hsu, H. Y. (1988). *Chem. Pharm. Bull.* **36**, 4316–4329.
Li, P., Kitamura, Y., Kaneko, K., Shiro, M., Xu, G. J., Chen, Y. P. & Hsu, H. Y. (1992). *Phytochemistry*, **31**, 2190–2191.
Li, P., Li, X. G. & Kaneko, K. (1990). *J. China Pharm. Univ.* **21**, 198–200.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1993). *SHELXL*93. University of Göttingen, Germany.
Shô, I., Yoshimasa, F. & Tomako, O. (1968). *Tetrahedron Lett.* **51**, 5373–5375.
Siemens (1990). *SHELXTL/PC*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Siemens (1996). *XSCANS*. Version 2.2. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Sparks, R. A. (1976). *Crystallographic Computing Techniques*, edited by F. R. Ahmed, p. 452. Copenhagen: Munksgaard.
Xu, D. M. & Xu, Y. J. (1991). *Zhong Cao Yao*, **8**, 132–139. (In Chinese.)