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Two pseudopolymorphic hydrates of brucine: brucine–water (1/4) and brucine–water (1/5.25) at 130 K

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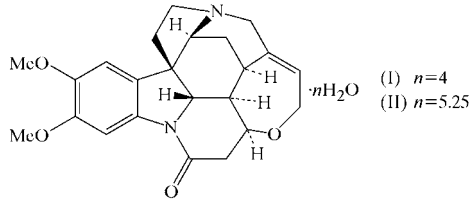
The structures of two pseudopolymorphic hydrates of brucine, $C_{23}H_{26}N_2O_4\cdot4H_2O$, (I), and $C_{23}H_{26}N_2O_4\cdot5.25H_2O$, (II), have been determined at 130 K. In both (I) and (II) (which has two independent brucine molecules together with 10.5 water molecules of solvation in the asymmetric unit), the brucine molecules form head-to-tail sheet substructures, which associate with the water molecules in the interstitial cavities through hydrogen-bonding associations and, together with water–water associations, give three-dimensional framework structures.

Comment

The commercially available form of the alkaloid brucine is a tetrahydrate, which was first reported by Groth (1919). The crystal structure of the anhydrous form (m.p. 451 K), readily obtained from the hydrate by heating at 373 K (O'Neil, 2001), has been reported recently (Bialońska & Ciunik, 2004*a*). Although the crystal cell data for the orthorhombic tetrahydrate have been reported (Eeles, 1953), its structure has not previously been determined. Reported along with the anhydrous brucine structure were the structures of two brucine solvate pseudopolymorphs (Bernstein, 1987; Kumar *et al.*, 1999), brucine acetone solvate and brucine 2-propanol solvate dihydrate (Bialońska & Ciunik, 2004*a*). This 2-propanol solvate structure is isomorphous with the previously reported brucine–ethanol–water (1/1/2) structure (Glover *et al.*, 1985). Molecular recognition has been demonstrated as being significant in dictating the selectivity shown by brucine for various molecules, including the classic Fischer-type resolved *N*-benzoyl-protected alanine enantiomers (Fischer, 1899; Gould & Walkinshaw, 1984) and the compound with an achiral molecule, brucinium 3-nitrobenzoate (Oshikawa *et al.*, 2002), where no crystalline products were obtained with the *ortho*- or *para*-substituted benzoic acid isomers. With brucine compounds generally, the brucine species commonly form regular undulating parallel or antiparallel host sheet substructures built from partially overlapping head-to-tail molecular associations (Gould & Walkinshaw, 1984; Dijksma, Gould, Parsons, Taylor & Walkinshaw, 1998; Białońska & Ciunik, 2004*b*). The compatible guest species then may occupy the interstitial cavities, associating with the host sheets through hydrogen-bonding interactions. Molecules of solvation (commonly water) act in either a proton-donor/acceptor or a space-filling capacity.



The tetrahydrate, (I), obtained as minor clusters of well formed prismatic needles from the attempted preparation of a brucine–adenosine adduct in 50% ethanol–water, was confirmed from the cell parameters and space group as being the orthorhombic tetrahydrate reported by Eeles (1953) (a = 7.6 Å, b = 11.6 Å, c = 26.6 Å, Z = 4 and space group $P2_12_12_1$). The second pseudopolymorphic hydrate, the 5.25-hydrate, (II), was similarly obtained, but in good yield, in an attempted preparation of a brucine–urea adduct in 50% ethanol–water. Initial diffraction data for (II), obtained at room temperature on a conventional four-circle diffractometer, provided a structure having an asymmetric unit comprising two ordered brucine molecules and 11 water molecules of solvation with varying occupancies in a centred monoclinic cell. The occupancies ranged from *ca* 0.3 to 0.9, indicating significant solvate lability, although negligible crystal decay was evident from the intensity-standards change (0.25%) during the data collection

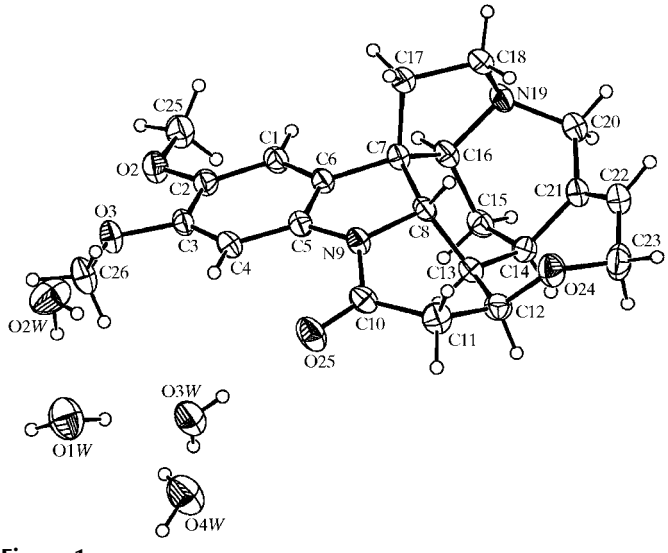


Figure 1
The molecular configuration and atom-numbering scheme for the brucine molecule and the four water molecules in the molecular repeat unit in (I). Non-H atoms are shown as 40% probability displacement ellipsoids.

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period. This lability has also been observed in a number of recently determined brucine structures (Gould *et al.*, 2002; Białońska *et al.*, 2005; Smith, Wermuth, Healy *et al.*, 2005; Smith, Wermuth & White, 2005). Low-temperature [130 (2) K] data were therefore re-collected for (II), and later for (I), using a CCD-detector-equipped diffractometer, effectively resolving the problem.

The atom-numbering scheme for (I) is shown in Fig. 1, while Fig. 2 shows the presence of two independent brucine molecules (*A* and *B*) and 11 water molecules of solvation (one

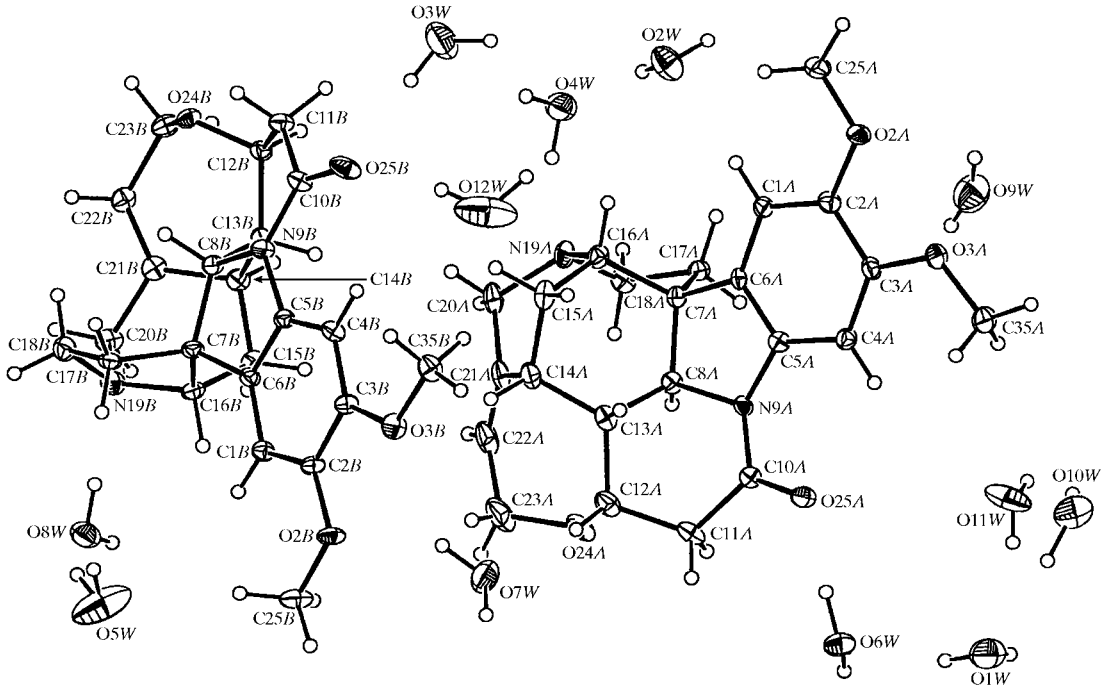

Figure 2
The molecular configuration and atom-numbering scheme for the two independent brucine molecules (*A* and *B*) and the 11 water molecules in the molecular repeat unit in (II). Water molecule O12*W* has 50% occupancy, while molecules O10*W* and O11*W* represent disordered portions of another water molecule (occupancy factors both *ca* 0.5). Non-H atoms are shown as 30% probability displacement ellipsoids.

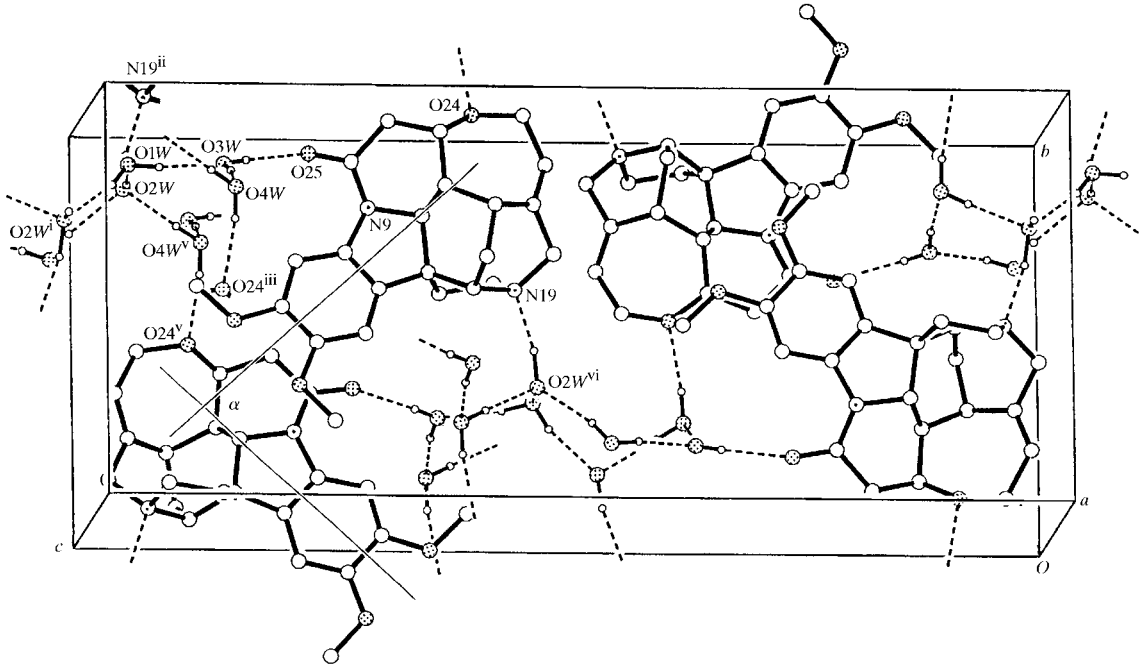

Figure 3
A perspective view of the packing of (I), viewed approximately along the *a* axial direction. The angle (α) between the lines through the centres of the indole rings in the brucine repeat unit is also shown. Hydrogen-bonding associations are shown as broken lines. [Symmetry codes: (v) $x-1, y, z$; (vi) $-x+1, y-\frac{1}{2}, -z+\frac{3}{2}$; for other codes, see Table 1.]

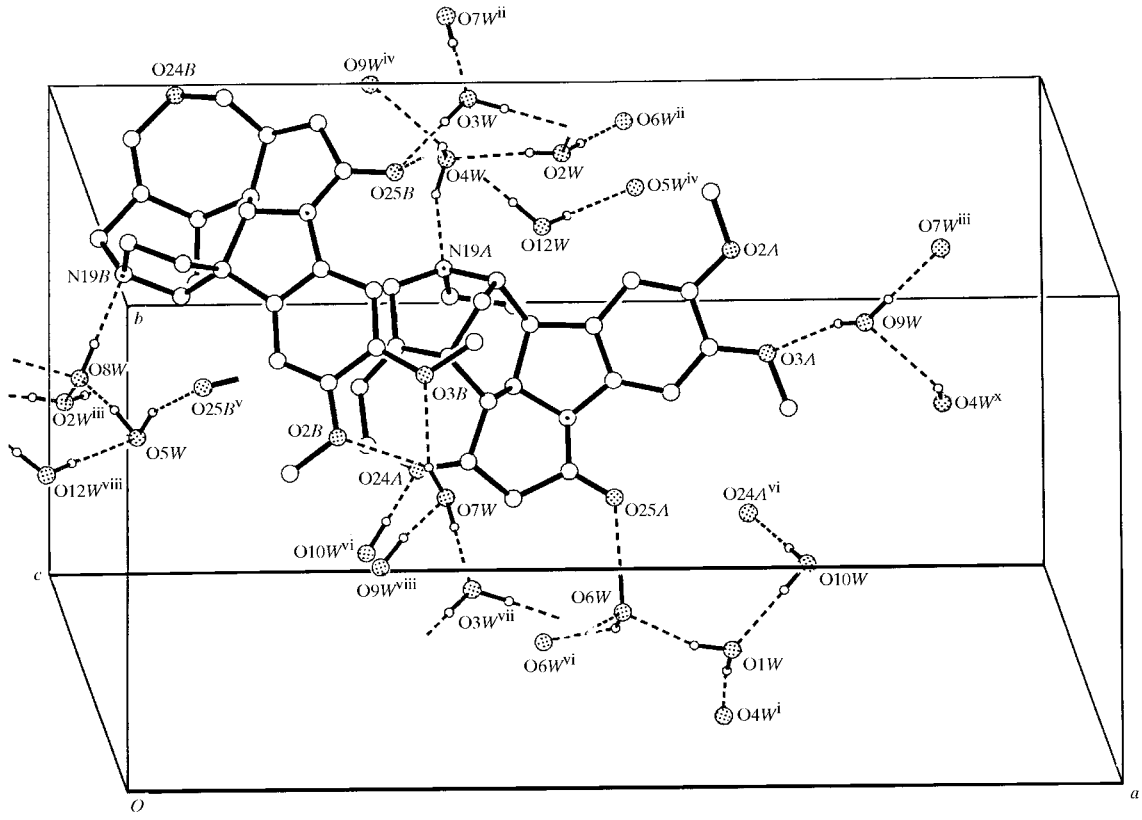

Figure 4
A perspective view of the partial packing of (II), viewed approximately along the *c* axial direction, showing brucine–water and water–water hydrogen-bonding interactions. [Symmetry code: (x) $x + \frac{1}{2}, y - \frac{1}{2}, z$; for other codes, see Table 2.]

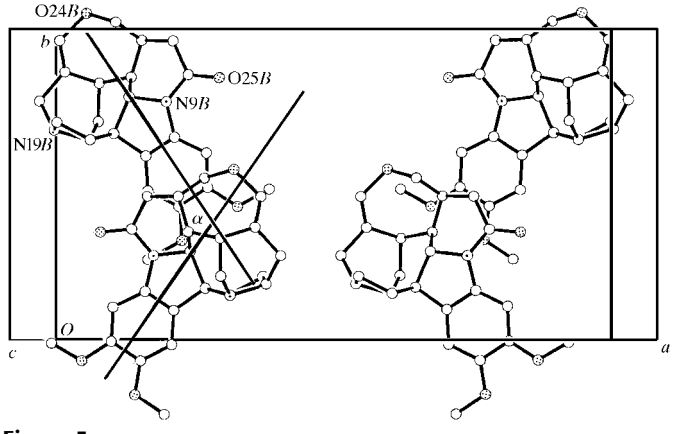

Figure 5
A view of the unit cell in (II), showing the brucine *B* molecules only and their propagation down the *b* axial direction.

with an occupancy of 0.5) in the molecular repeat unit of (II). In addition, one of the water molecules in (II) is disordered over two approximately equal close sites [O10*W* with occupancy factor = 0.543 (17), and O11*W* with occupancy factor = 0.457 (17)]. The atom numbering for the brucine species in both (I) and (II) follows the original Robinson convention (Holmes, 1952), and both have the overall Cahn–Ingold–Prelog absolute configuration for the neutral brucine molecule [C7(*R*), C8(*S*), C12(*S*), C13(*R*), C14(*R*), C16(*S*); Eliel, 1962]. As expected, the rigid brucine molecules show negligible conformational variation, including the methoxy substituent groups, which are invariably *anti*-related and lie essentially in the plane of the benzene ring.

The brucine molecules in (I) form the previously described undulating sheet substructures, which extend through the crystal along the *b*-cell direction (Fig. 3). These are generated by the 2_1 screw operation along the *c* axis, giving antiparallel sheet propagation along *b*, with a dimeric repeat in that direction of 11.53 Å (the *a*-cell dimension). This value is significantly shorter than the common repeat of *ca* 12.5 Å found in a number of brucine structures, *e.g.* brucinium *N*-benzoyl-D-alaninate–water (1/4.5) (antiparallel, 12.42 Å; Gould & Walkinshaw, 1984); brucinium D-glucuronate trihydrate (parallel, 12.66 Å) and brucinium D-galacturonate monohydrate (antiparallel, 12.37 Å) (Dijksma, Gould, Parsons & Walkinshaw, 1998); two brucinium cyanohydrin complexes (both antiparallel, 12.39 and 12.52 Å; Pinkerton *et al.*, 1993), brucine 2-propanol solvate dihydrate (antiparallel, 12.37 Å; Białońska & Ciunik, 2004*a*); and brucine–ethanol–water (1/1/2) (antiparallel, 12.34 Å; Glover *et al.*, 1985). This shortening of the repeat interval parallels a contraction of the angle, α [*ca* 87° in (I) but typically greater than 100°], between the lines drawn down the centres of the indole ring systems of adjacent brucine molecules in the head-to-tail interactive sequence (see Fig. 3).

In (II), the brucine substructure generated by the two independent molecules in the asymmetric unit differs signifi-

cantly from that seen in (I) (Fig. 4). However, if the *B* molecules alone are considered, these do form into similar undulating sheet structures, which extend along the *b*-cell direction with an approximate 12.2 Å dimer repeat (Fig. 5). In both (I) and (II), the intersheet cavities generated accommodate the water molecules of solvation, the overall structures being characterized by extensive hydrogen-bonding interactions (Tables 1 and 2). These involve all available proton donors and acceptors in water–brucine [both N19 and O25 (carbonyl) acceptors] and water–water interactions. In addition, there are unusual (for brucine) water–O(cage ether) interactions in both structures, *viz.* O4*W*—H···O24^{iii} [symmetry code: (iii) $-x+2, y-\frac{1}{2}, -z+\frac{3}{2}$] in (I) and O10*W*—H···O24*A*^{vi} [symmetry code: (vi) $-x+1, y, -z+1$] in (II). Furthermore, in (II), there are water–O(methoxy) interactions, *viz.* O7*W*—H···O2*B*,O3*B* (symmetrical three-centred) and O9*W*—H···O3*A* (linear), also unusual for brucine and its compounds. In both pseudopolymorphs, three-dimensional framework structures are generated.

In the structure of (II), the molecular asymmetric unit comprises two brucine molecules and 11 water molecules [one of which (O12*W*) has half-occupancy], together with the previously mentioned, approximately equal, partial-occupancy disordered molecules O10*W* [0.543 (17)] and O11*W* [0.457 (17)]. The observation in (II) that there was no apparent physical crystal deterioration during the room-temperature conventional diffractometer data collection period indicates the stability of the basic brucine substructure, which is retained with some variation in the structure of the anhydrous form (Białońska & Ciunik, 2004*a*) (where there are no interstitial species, hence only intersheet interactions), resulting in a larger angle (*ca* 123°) between adjacent brucine molecules in the parallel-mode substructure. This gives a longer dimer repeat (12.7 Å), and compares with *ca* 115° in the *N*-benzoyl-D-alaninate salt, *ca* 115° in the 2-propanol hydrate structure and *ca* 113° for the *B*-molecule chains in (II).

Experimental

Brucine tetrahydrate, (I), was obtained as isolated clusters of well formed colourless prismatic needles [m.p. 378 K (literature) (Moffat, 1986; Buckingham, 1982)] from the attempted preparation of a brucine–adenosine adduct in 50% ethanol–water, after partial room-temperature evaporation. Hydrate (II) was obtained as large colourless prismatic crystals (m.p. 386.9–388.2 K) from the attempted preparation of a brucine–urea adduct in 50% ethanol–water.

Pseudopolymorph (I)

Crystal data

$C_{23}H_{26}N_2O_4\cdot 4H_2O$
$M_r = 466.52$
Orthorhombic, $P2_12_12_1$
$a = 7.555$ (2) Å
$b = 11.531$ (3) Å
$c = 26.492$ (8) Å
$V = 2307.9$ (11) Å^3
$Z = 4$
$D_x = 1.343$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2584 reflections
$\theta = 2.7$–$20.5°$
$\mu = 0.10$ mm^{-1}
$T = 130$ (2) K
Cut plate, colourless
0.50 × 0.25 × 0.05 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
11874 measured reflections
2346 independent reflections
1727 reflections with $F^2 > 2\sigma(F^2)$
$R_{int} = 0.066$
$\theta_{max} = 25.0°$
$h = -8 \rightarrow 8$
$k = -12 \rightarrow 13$
$l = -31 \rightarrow 30$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.043$
$wR(F^2) = 0.084$
$S = 0.89$
2346 reflections
301 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0319P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.002$
$\Delta\rho_{max} = 0.17$ e Å^{-3}
$\Delta\rho_{min} = -0.21$ e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0025 (4)

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
O1*W*—H11*W*···O2*W*^{i}	0.89	1.92	2.791 (4)	166
O1*W*—H12*W*···O3*W*	0.92	1.84	2.749 (4)	172
O2*W*—H21*W*···O1*W*	0.83	1.91	2.736 (4)	170
O2*W*—H22*W*···N19^{ii}	0.88	1.92	2.793 (3)	173
O3*W*—H31*W*···O25	0.90	1.91	2.819 (4)	179
O3*W*—H32*W*···O4*W*	0.89	1.90	2.790 (4)	180
O4*W*—H41*W*···O24^{iii}	0.90	2.03	2.922 (3)	172
O4*W*—H42*W*···O2*W*^{iv}	0.86	1.94	2.794 (3)	175

Symmetry codes: (i) $x+\frac{1}{2}, -y+\frac{3}{2}, -z+2$; (ii) $-x+1, y+\frac{1}{2}, -z+\frac{3}{2}$; (iii) $-x+2, y-\frac{1}{2}, -z+\frac{3}{2}$; (iv) $x+1, y, z$.

Pseudopolymorph (II)

Crystal data

$C_{23}H_{26}N_2O_4\cdot 5.25H_2O$
$M_r = 489.0$
Monoclinic, $C2$
$a = 23.351$ (5) Å
$b = 12.200$ (3) Å
$c = 16.972$ (4) Å
$\beta = 96.202$ (4)°
$V = 4806.7$ (19) Å^3
$Z = 8$
$D_x = 1.352$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4189 reflections
$\theta = 2.2$–$24.9°$
$\mu = 0.10$ mm^{-1}
$T = 130$ (2) K
Block, colourless
0.35 × 0.30 × 0.15 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
12710 measured reflections
4461 independent reflections
3673 reflections with $I > 2\sigma(I)$
$R_{int} = 0.098$
$\theta_{max} = 25.0°$
$h = -19 \rightarrow 27$
$k = -14 \rightarrow 10$
$l = -18 \rightarrow 20$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.066$
$wR(F^2) = 0.173$
$S = 1.01$
4461 reflections
621 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0961P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.49$ e Å^{-3}
$\Delta\rho_{min} = -0.28$ e Å^{-3}

H atoms potentially involved in hydrogen-bonding interactions were generally located by difference methods. However, a number of the H atoms of the water molecules of (II) could not be located and were included in the refinement at calculated sites dictated by the assumed hydrogen-bonding geometry. Because of the low reflection/refined parameter ratio, all water H atoms were constrained in the refinement. Brucine H atoms were included at calculated positions

(aromatic C—H = 0.95 Å and aliphatic C—H = 0.96–0.99 Å) and treated as riding, with U_{iso}(H) values of $1.2U_{eq}$(C), or $1.5U_{eq}$(C) for methyl atoms. The atom-numbering scheme for brucine (Figs. 1 and 2) follows the original Robinson convention used for strychnine (Holmes, 1952). The absolute configuration determined for the parent strychnine (Peerdeman, 1956) was invoked.

Table 2
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O1*W*—H11*W*···O4*W*^{i}	0.91	1.90	2.813 (8)	179
O1*W*—H12*W*···O6*W*	0.71	2.12	2.776 (6)	154
O2*W*—H21*W*···O6*W*^{ii}	0.89	1.85	2.739 (6)	179
O2*W*—H22*W*···O4*W*	0.82	1.98	2.769 (6)	162
O3*W*—H31*W*···O8*W*^{iii}	0.92	1.77	2.688 (6)	179
O3*W*—H32*W*···O25*B*	0.90	1.92	2.811 (7)	179
O4*W*—H41*W*···O9*W*^{iv}	0.90	1.83	2.731 (7)	179
O4*W*—H42*W*···N19*A*	0.92	1.86	2.742 (7)	158
O5*W*—H51*W*···O25*B*^{v}	0.86	2.16	2.942 (8)	150
O5*W*—H52*W*···O8*W*	0.91	1.89	2.798 (8)	179
O6*W*—H61*W*···O25*A*	0.97	1.78	2.746 (5)	176
O6*W*—H62*W*···O6*W*^{vi}	0.83	2.29	2.756 (5)	116
O7*W*—H71*W*···O2*B*	0.93	2.27	2.986 (5)	133
O7*W*—H71*W*···O3*B*	0.93	2.26	3.096 (6)	148
O7*W*—H72*W*···O3*W*^{vii}	0.91	1.84	2.746 (8)	179
O8*W*—H81*W*···N19*B*	0.90	1.81	2.714 (5)	180
O8*W*—H82*W*···O2*W*^{viii}	0.91	1.82	2.727 (6)	179
O9*W*—H91*W*···O3*A*	0.87	2.16	2.987 (6)	158
O9*W*—H92*W*···O7*W*^{iii}	0.96	1.93	2.797 (7)	149
O10*W*—H13*W*···O1*W*	0.89	2.01	2.907 (11)	179
O10*W*—H14*W*···O24*A*^{vi}	0.90	1.81	2.711 (11)	179
O11*W*—H15*W*···O1*W*	0.89	1.89	2.777 (11)	179
O11*W*—H16*W*···O24*A*^{vi}	0.88	2.19	3.069 (11)	179
O12*W*—H17*W*···O5*W*^{iii}	0.90	1.75	2.646 (19)	179
O12*W*—H18*W*···O5*W*^{ix}	0.89	2.26	3.154 (19)	179

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

For both compounds, data collection: *SMART* (Bruker, 2000); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1999); program(s) used to solve structure: *SHELXL97* (Sheldrick, 1997) within *WinGX* (Farrugia, 1999) for (I) and *SHELXTL* (Bruker, 1997) for (II); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997) for (I) and *SHELXTL* for (II); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *PLATON*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GZ1028). Services for accessing these data are described at the back of the journal.

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