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Hydrogen bonding in brucinium dihydrogen citrate trihydrate at 130 K

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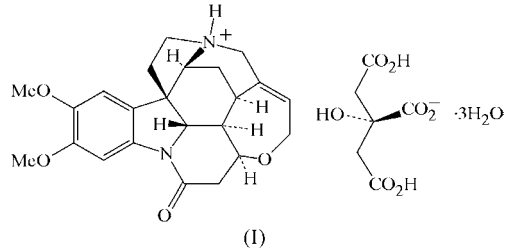
The structure of brucinium dihydrogen citrate trihydrate (systematic name: 2,3-dimethoxy-10-oxostrychnidinium dihydrogen citrate trihydrate), $C_{23}H_{27}N_2O_4^+\cdot C_6H_7O_7^-\cdot 3H_2O$, has been determined at 130 K. The crystallographic asymmetric unit comprises two brucinium cations, two dihydrogen citrate anions and six water molecules of solvation. The two citrate anions, which are conformationally dissimilar, associate through extensive hydrogen-bonding interactions with the common undulating brucinium cation layer substructures and the water molecules, forming a three-dimensional framework polymer.

Comment

Citric acid has been commonly employed to form water-soluble salts with organic compounds having little aqueous solubility. This has direct application in the preparation of pharmaceutical products where water solubility and biological compatibility are desirable. Because the ionization constants for the three carboxylic acid groups of citric acid are similar (pK_{a1-3} = 3.1, 4.8 and 6.4), stoichiometric reaction with strong bases readily results in possible formation of the full range of salts, *viz*. dihydrogen citrates, hydrogen citrates and normal citrates. However, the 1:1 interaction with compounds having nitrogen Lewis base functional groups, such as those commonly incorporated into drug molecules, will, depending on the number and base strength of the N-atom acceptor group, usually give dihydrogen citrate salts. This is the case with the antiestrogenic drug tamoxifen citrate (O′Neil, 2001) and sildenafil citrate monohydrate (Viagra), while with the opiate fentanyl citrate (O′Neil, 2001) (two N-atom acceptors), the citrate is dianionic. This tendency has been confirmed in the crystal structure determinations of tamoxifen citrate (Goldberg & Becker, 1987), fentanyl citrate [Peeters *et al.*, 1960; Duchamp *et al.*, 1977 (123 K)] and sildenafil citrate monohydrate (Yathirajan *et al.*, 2005). The strychnos alkaloids strychnine and brucine have two N-atom acceptors (pK_{a1} = 6.0 and pK_{a2} = 11.7), the widely separated values meaning that only with strong acids is the rare dication species formed. Crystallographically characterized examples include strychninium sulfate pentahydrate (Bokhoven *et al.*, 1951) and brucinium binaphtholphosphate dihydrate ethanol solvate (Bao *et al.*, 1996). Despite the fact that the structures of a large number of the proton-transfer compounds of both alkaloids are known, those with the α-hydroxy acids are rare, although both strychnine and brucine have been used for the resolution of a number of such acids (Wilen, 1972). The known crystal structures comprise two strychnine salts with resolved enantiomorphic tartrates, *viz*. strychninium hydrogen (2*S*,3*S*)-tartrate trihydrate and bis(strychninium) (2*R*,3*R*)-tartrate hexahydrate (Gould *et al.*, 1987), and brucinium L-glycerate 4.5-hydrate (Białońska *et al.*, 2005). No examples of compounds with achiral α-hydroxy acids have been reported. Therefore, the formation of large well formed crystals from the 1:1 stoichiometric interaction of brucine with citric acid in 80% ethanol–water was of interest, and this compound, brucinium dihydrogencitrate trihydrate, (I), which is reported here, represents the first example of its type. Because of the lability of the interstitial water molecules in many hydrated compounds of brucine (Gould *et al.*, 2002; Białońska *et al.*, 2005; Smith *et al.*, 2005), data collection using a CCD-detector diffractometer operating at low temperature [130 (2) K] was employed.



(I)

The structure of (I) shows the presence of two independent brucinium cations (molecules *A* and *B*) (Fig. 1), two dihydrogen citrate anions (molecules *C* and *D*) and six water molecules of solvation (Fig. 2) in the triclinic (*P*1) asymmetric unit. Protonation occurs as expected at atom N19 of the brucine cage in each molecule, the invoked Peerdeman (1956) absolute configuration giving the overall Cahn–Ingold–Prelog stereochemistry of the cations (Eliel, 1962) as C7(*S*), C8(*S*), C12(*S*), C13(*R*), C14(*R*), C16(*S*) and N19(*S*). The central carboxylic acid group of citric acid [associated with the first dissociation constant (pK_{a1} = 3.1)] is deprotonated in both residues, this being consistent with what is found in the structures of tamoxifen citrate (Goldberg & Becker, 1987), sildenafil citrate (Yathirajan *et al.*, 2005) and the alkali metal dihydrogen citrates, *e.g.* the Na salt (Glusker *et al.*, 1965). O atoms of the same central carboxylate groups in both anion *C* and anion *D* act as acceptors in intramolecular hydrogen bonds with the O3 hydroxy groups, resulting in near coplanarity of the carboxylate anion group and the C3—O3 bond vector [O3···O31 = 2.640 (4) (anion *C*) and 2.678 (4) Å (*D*); O3—C3—C31—O31 = 10.6 (4) (*C*) and −0.5 (5)° (*D*)]. The structure also features extensive intermolecular hydrogen bonding (Table 2) involving all molecular species.

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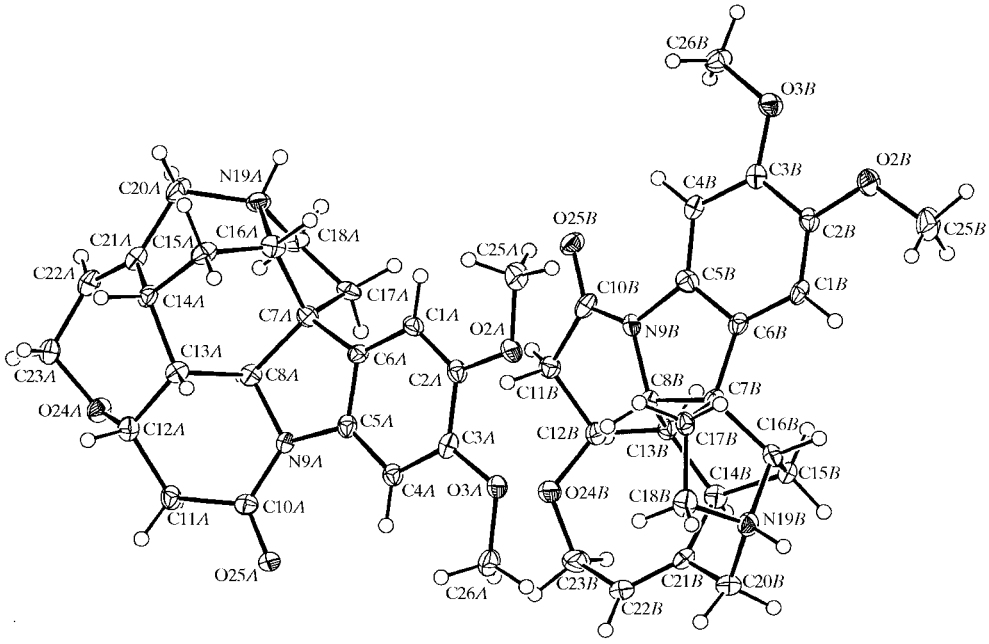

Figure 1
The molecular configuration and atom-numbering scheme for the two independent brucinium cations (*A* and *B*) in the asymmetric unit in (I). Non-H atoms are shown as 40% probability displacement ellipsoids.

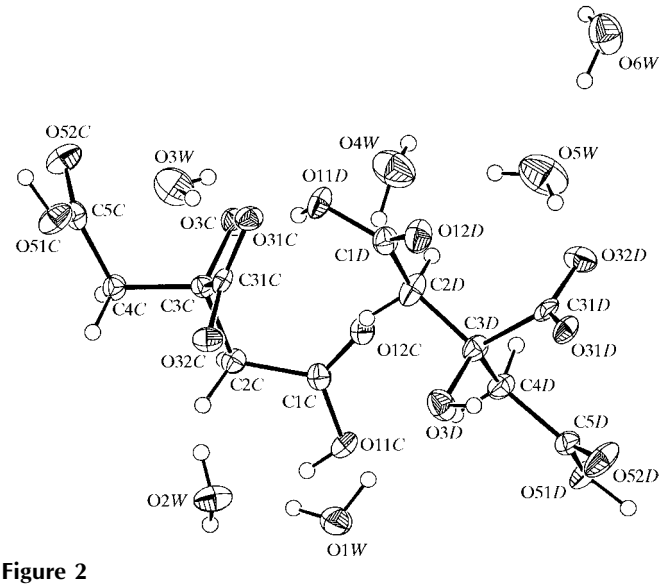

Figure 2
The molecular configuration and atom-numbering scheme for the two independent dihydrogen citrate anions (*C* and *D*) and the six water molecules in (I). Non-H atoms are shown as 40% probability displacement ellipsoids.

The brucinium cations in (I) form into undulating sheet host substructures, which are the reason for the molecular recognition peculiar to brucine (Gould & Walkinshaw, 1984; Gould *et al.*, 1985; Dijksma *et al.*, 1998; Oshikawa *et al.*, 2002; Białońska & Ciunik, 2004*a*,*b*). In (I), these structures extend through the crystal along the *b* cell direction (Fig. 3), with the dihydrogen citrate anions and the water molecules occupying the interstitial spaces. The protonated N19 centres of cation *A* give a single hydrogen-bonding interaction with an O-atom acceptor of the central carboxylate group of a *C*-citrate residue [N19*A*$\cdots$O31*C* = 2.645 (4) Å; symmetry code: (i) $x+1, y-1, z+1$], while cation *B* forms a three-centred interaction with a *D*-citrate O atom [N19*B*$\cdots$O31*D*^{i} = 2.824 (4) Å; symmetry code: (i) $x+1, y-1, z+1$] and a water molecule [N19*B*$\cdots$O6*W*^{ii} = 2.873 (5) Å; symmetry code: (ii) $x+1, y, z+1$]. However, the molecules within the brucinium host structures do not give either the $2_12_12_1$ propagation in the orthorhombic ($P2_12_12_1$) examples, *e.g.* the brucinium bicyclo[2.2.1]hept-5-ene-2-cyanohydrins (Pinkerton *et al.*, 1993), or the 2_1 propagation in the monoclinic ($P2_1$) examples, *e.g.* bruncine benzoyl-D-alanine (Gould & Walkinshaw, 1984) and brucinium glucuronate and galacturonate (Dijksma *et al.*, 1998), which constitute the majority of structural types in this series. Instead, there is a pseudo-2_1 structural framework, similar to that in the low-temperature brucinium L-glycerate 4.75-hydrate structure (Białońska *et al.*, 2005). The similarity extends also to space group *P*1 ($Z = 2$), cell parameters (a = 9.31 Å, b = 9.58 Å, c = 16.13 Å, α = 77.21°, β = 87.36° and γ = 81.57°) and the general pseudo-2_1 propagation of the basic undulating brucinium cation substructural framework.

The terminal carboxylic acid residues of anions *C* and *D* also extend the structure in the *c* cell direction through interactions with brucinium carbonyl O-atom acceptors [O51*C*—H51*C*$\cdots$O25*B* = 2.685 (4) Å and O51*D*—H51*D*$\cdots$O25*A*^{v} = 2.647 (4) Å; symmetry code: (v) $x, y, z-1$]. The six water molecules of solvation complete an extensive secondary hydrogen-bonding framework, through both water–water and water–anion interactions (Table 2), which associates with the brucinium-cation host structure, resulting in a three-dimensional polymer.

Although the *C* and *D* dihydrogen citrate residues adopt similar extended conformations, the two are conformationally dissimilar (Table 1), particularly with respect to the terminal

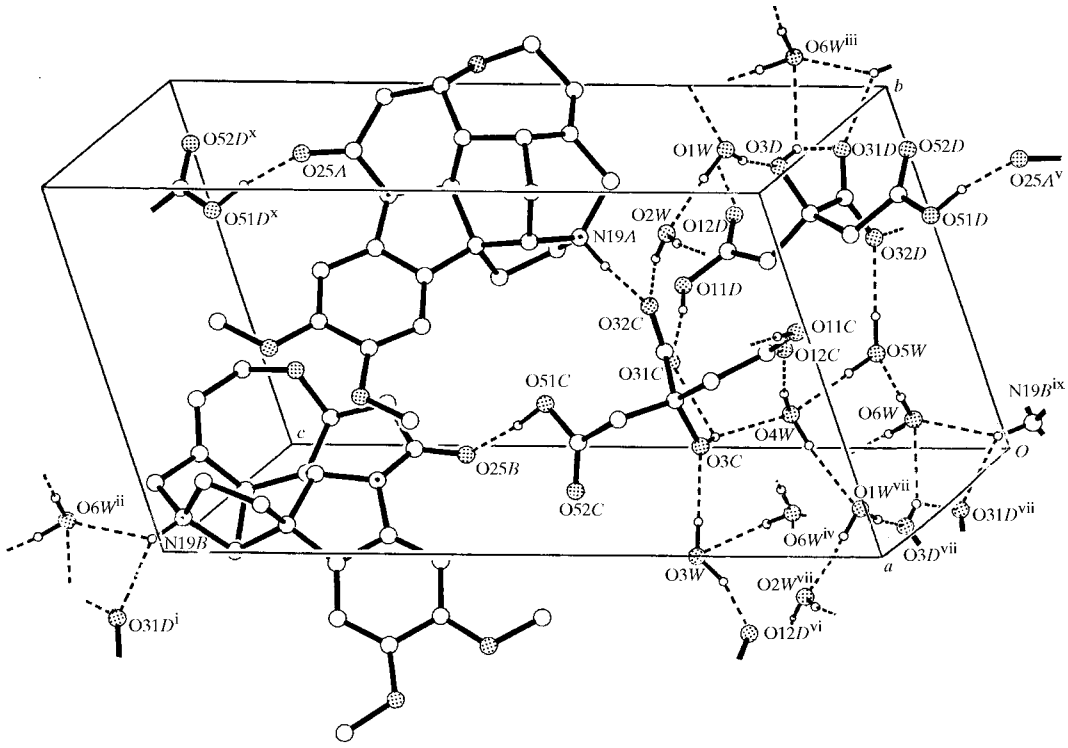

Figure 3
A perspective view of the packing of (I) in the unit cell, viewed approximately down the *a* axial direction. Hydrogen-bonding associations are shown as broken lines; H atoms not involved in hydrogen bonding have been omitted. [Symmetry codes: (ix) $x-1, y, z-1$; (x) $x, y, 1+z$; for other codes, see Table 2.]

carboxylic acid groups, as indicated by the comparative torsion angles C3—C2—C1—O12 [−5.8 (5)° (*C*) *cf.* 15.2 (6)° (*D*)] and C3—C4—C5—O52 [91.0 (5)° (*C*) *cf.* −0.4 (6)° (*D*)]. The previously mentioned intramolecularly hydrogen-bonded central carboxylate groups show a smaller variation. It is also of interest to note the presence of *anti*-related H atoms on the carboxylic acid atoms O11*C* and O11*D*. These provide both strong $A\cdots D$ intra-unit anion associations [O11*D*···O31*C* = 2.604 (4) Å] and catemeric $A\cdots D$ inter-unit associations [O11*C*···O32*D*^{iv} = 2.537 (4) Å; symmetry code: (iv) $x+1, y, z$], which extend down the *a* cell direction. This overall molecular flexibility is a characteristic feature of citrates, and in the case of (I) not only results in the conformational variation within anions *C* and *D* but subsequently contributes largely to the degeneration of the crystal space symmetry to *P*1. Probably also contributing to this is the presence of the six water molecules of solvation, which act both as proton donors and acceptors and also in a space-filling capacity. These aspects of the structure of (I) also resemble those of the brucinium L-glycerate structure (Bialońska *et al.*, 2005).

Experimental

The title compound, (I), was synthesized by heating 1 mmol quantities of brucine tetrahydrate and citric acid in 80% ethanol–water (50 ml) for 10 min under reflux. After concentration to *ca* 30 ml, partial room-temperature evaporation of the hot-filtered solution gave large colourless plate-shaped crystals (m.p. 489.9–494.1 K).

Crystal data

$C_{23}H_{27}N_2O_4^{2+}\cdot C_6H_7O_7^{2-}\cdot 3H_2O$
M_r = 640.63
Triclinic, *P*1
a = 9.2355 (8) Å
b = 9.6894 (8) Å
c = 17.1446 (15) Å
α = 75.775 (2)°
β = 80.917 (2)°
γ = 81.553 (2)°
V = 1459.1 (2) Å^3
Z = 2
D_x = 1.458 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 2391 reflections
θ = 2.3–25.5°
μ = 0.12 mm^{-1}
T = 130 (2) K
Cut block, colourless
0.45 × 0.40 × 0.30 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
7737 measured reflections
5129 independent reflections
4354 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.031
θ_{max} = 25.0°
h = −10 → 9
k = −11 → 11
l = −17 → 20

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.075
S = 0.92
5129 reflections
888 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0266P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.027
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

H atoms potentially involved in hydrogen-bonding interactions were located by difference methods and their positional and isotropic displacement parameters were refined. Other H atoms were included in the refinement at calculated positions (C—H = 0.95–1.00 Å) and treated as riding, with U_{iso}(H) values of 1.2U_{eq}(C) or 1.5U_{eq}(methyl

Table 1
Selected torsion angles (°).

O11*C*—C1*C*—C2*C*—C3*C*	174.6 (3)
O12*C*—C1*C*—C2*C*—C3*C*	−5.8 (5)
C1*C*—C2*C*—C3*C*—O3*C*	70.5 (4)
O3*C*—C3*C*—C31*C*—O31*C*	10.6 (4)
O3*C*—C3*C*—C31*C*—O32*C*	−170.6 (3)
C4*C*—C3*C*—C31*C*—O31*C*	−108.2 (4)
C2*C*—C3*C*—C31*C*—O31*C*	134.3 (3)
C2*C*—C3*C*—C31*C*—O32*C*	−46.9 (4)
O3*C*—C3*C*—C4*C*—C5*C*	−58.3 (4)
C4*C*—C3*C*—C31*C*—O32*C*	70.6 (4)
C3*C*—C4*C*—C5*C*—O52*C*	91.0 (5)
C3*C*—C4*C*—C5*C*—O51*C*	−89.6 (4)
O11*D*—C1*D*—C2*D*—C3*D*	−165.4 (3)
O12*D*—C1*D*—C2*D*—C3*D*	15.2 (6)
C1*D*—C2*D*—C3*D*—O3*D*	68.2 (4)
O3*D*—C3*D*—C31*D*—O31*D*	−0.5 (5)
C4*D*—C3*D*—C31*D*—O32*D*	58.0 (4)
O3*D*—C3*D*—C31*D*—O32*D*	179.0 (3)
C2*D*—C3*D*—C31*D*—O31*D*	118.8 (4)
C2*D*—C3*D*—C31*D*—O32*D*	−61.7 (4)
C4*D*—C3*D*—C31*D*—O31*D*	−121.5 (4)
O3*D*—C3*D*—C4*D*—C5*D*	−67.4 (4)
C3*D*—C4*D*—C5*D*—O51*D*	178.8 (3)
C3*D*—C4*D*—C5*D*—O52*D*	−0.4 (6)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N19*A*—H19*A*···O32*C*	0.93 (4)	1.76 (4)	2.645 (4)	156 (4)
N19*B*—H19*B*···O31*D*^{i}	0.94 (4)	2.14 (4)	2.824 (4)	128 (3)
N19*B*—H19*B*···O6*W*^{ii}	0.94 (4)	2.12 (4)	2.873 (5)	135 (3)
O3*C*—H3*C*···O4*W*	0.73 (5)	2.36 (5)	3.051 (5)	159 (5)
O3*C*—H3*C*···O31*C*	0.73 (5)	2.28 (5)	2.640 (4)	111 (4)
O3*D*—H3*D*···O6*W*^{iii}	0.81 (6)	2.10 (6)	2.761 (4)	140 (6)
O3*D*—H3*D*···O31*D*	0.81 (6)	2.08 (7)	2.678 (4)	131 (5)
O11*C*—H11*C*···O32*D*^{iv}	0.84 (3)	1.70 (3)	2.537 (4)	173 (5)
O11*D*—H11*D*···O31*C*	0.94 (5)	1.69 (5)	2.604 (4)	167 (4)
O51*C*—H51*C*···O25*B*	0.90 (6)	1.78 (7)	2.685 (4)	179 (8)
O51*D*—H51*D*···O25*A*^{v}	0.96 (6)	1.72 (6)	2.647 (4)	162 (5)
O1*W*—H11*W*···O3*D*	0.92 (4)	1.86 (5)	2.764 (5)	169 (4)
O1*W*—H12*W*···O2*W*	0.92 (5)	1.83 (5)	2.740 (5)	170 (4)
O2*W*—H21*W*···O31*D*^{iv}	0.80 (5)	2.01 (5)	2.798 (4)	169 (5)
O2*W*—H22*W*···O32*C*	0.83 (7)	1.95 (7)	2.758 (4)	162 (7)
O3*W*—H31*W*···O12*D*^{vi}	0.91 (6)	2.35 (6)	3.218 (5)	161 (4)
O3*W*—H32*W*···O3*C*	0.91 (4)	2.02 (4)	2.920 (5)	179 (5)
O4*W*—H41*W*···O1*W*^{vii}	0.86 (4)	1.87 (4)	2.735 (6)	180 (6)
O4*W*—H42*W*···O12*C*	0.90 (4)	1.97 (4)	2.861 (5)	171 (5)
O5*W*—H51*W*···O4*W*	0.90 (3)	1.89 (3)	2.790 (6)	180 (4)
O5*W*—H52*W*···O32*D*	0.90 (3)	1.88 (3)	2.774 (5)	179 (4)
O6*W*—H61*W*···O5*W*	0.90 (3)	1.79 (3)	2.689 (5)	180 (4)
O6*W*—H62*W*···O3*W*^{viii}	0.87 (3)	2.01 (3)	2.806 (6)	153 (3)

Symmetry codes: (i) $x+1, y-1, z+1$; (ii) $x+1, y, z+1$; (iii) $x, y+1, z$; (iv) $x+1, y, z$; (v) $x, y, z-1$; (vi) $x+1, y-1, z$; (vii) $x, y-1, z$; (viii) $x-1, y, z$.

C). The atom-numbering scheme employed for the brucinium cation cages in (I) (Fig. 1) follows the original Robinson convention for strychnine (Holmes, 1952). The absolute configuration determined for the parent strychnidinin-10-one molecule (Peerdeman, 1956) was invoked.

Data collection: *SMART* (Bruker, 2000); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1999); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997) in *WinGX* (Farrugia, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997) in *WinGX* (Farrugia, 1999); 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: TA1515). Services for accessing these data are described at the back of the journal.

References

Bao, J., Wulff, W. D., Dominy, J. B., Fumo, M. J., Grant, A. C., Whitcomb, M. C., Yeung, S.-M., Ostrander, R. L. & Rheingold, A. L. (1996). *J. Am. Chem. Soc.* **118**, 3392–3405.

Białońska, A. & Ciunik, Z. (2004*a*). *Acta Cryst.* C**60**, o853–o855.

Białońska, A. & Ciunik, Z. (2004*b*). *CrystEngComm*, **6**, 276–279.

Białońska, A., Ciunik, Z., Popek, T. & Lis, T. (2005). *Acta Cryst.* C**61**, o88–o91.

Bokhoven, C., Schoone, J. C. & Bijvoet, J. M. (1951). *Acta Cryst.* **4**, 275–280.

Bruker (1999). *SAINT*. Version 6.02. Bruker AXS Inc., Madison, Wisconsin, USA.

Bruker (2000). *SMART*. Version 5.55. Bruker AXS Inc., Madison, Wisconsin, USA.

Dijksma, F. J. J., Gould, R. O., Parsons, S., Taylor, J. & Walkinshaw, M. D. (1998). *Chem. Commun.* pp. 745–746.

Duchamp, J., Olson, E. C. & Chidester, C. G. (1977). *Am. Cryst. Assoc. Ser. 2*, **5**, 83.

Eliel, E. L. (1962). *Stereochemistry of Carbon Compounds*, pp. 92–94. New York: McGraw–Hill.

Farrugia, L. J. (1999). *J. Chem. Crystallogr.* **32**, 837–838.

Glusker, J. P., van der Helm, D., Love, W. E., Dornberg, M. L., Minkin, J. A., Johnson, C. K. & Patterson, A. L. (1965). *Acta Cryst.* **19**, 561–572.

Goldberg, I. & Becker, Y. (1987). *J. Pharm. Sci.* **76**, 259–264.

Gould, R. O., Kelly, R. & Walkinshaw, M. D. (1985). *J. Chem. Soc. Perkin Trans. 2*, pp. 847–852.

Gould, R. O., Taylor, J., Walkinshaw, M. D. & Bruins Slot, H. J. (1987). *Acta Cryst.* C**43**, 2405–2410.

Gould, R. O. & Walkinshaw, M. D. (1984). *J. Am. Chem. Soc.* **106**, 7840–7842.

Gould, R. O., Walkinshaw, M. D., Wimmer, N. & Kosma, P. (2002). *Acta Cryst.* A**58**, C-126.

Holmes, H. L. (1952). *The Alkaloids*, Vol. II, edited by R. H. F. Manske & H. L. Holmes, p. 514. New York: Academic.

O'Neil, M. J. (2001). Editor. *The Merck Index*, 13th ed., pp. 708, 709, 1614. Whitehouse Station, NJ: Merck and Co. Inc.

Oshikawa, T., Pochamroen, S., Takai, N., Ide, N., Takemoto, T. & Yamashita, M. (2002). *Heterocycl. Commun.* **8**, 271–274.

Peerdeman, A. F. (1956). *Acta Cryst.* **9**, 824.

Peeters, O. M., Blaton, N. M. & de Ranter, C. J. (1960). *Eur. Crystallogr. Meeting*, **13**, 144.

Pinkerton, A. A., Carrupt, P.-A., Claret, F. & Vogel, P. (1993). *Acta Cryst.* C**49**, 1632–1636.

Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.

Smith, G., Wermuth, U. D., Healy, P. C., Young, D. J. & White, J. M. (2005). *Acta Cryst.* E**61**, o2646–o2648.

Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.

Wilen, S. H. (1972). *Tables of Resolving Agents and Optical Resolutions*, edited by E. L. Eliel, pp. 68–75. London: University of Notre Dame Press.

Yathirajan, H. S., Nagaraj, B., Nagaraja, P. & Bolte, M. (2005). *Acta Cryst.* E**61**, o489–0491.