Cinchoninium L-tartrate tetrahydrate

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The title compound, (3R,4S,8R,9S)-cinchoninium (2R,3R)-tartrate tetrahydrate, $C_{19}H_{23}N_2O^+ \cdot C_4H_5O_6^- \cdot 4H_2O$, is a hydrated salt of cinchonine. In the cinchoninium cation, the geometry around the quinuclidinic N atom is typical of a protonated N atom, and the bond lengths and angles in the tartrate moiety clearly indicate the mono-ionized form. The relative orientation of the quinoline and quinuclidine systems is that most frequently observed in structures of cinchona salts and corresponds to one of the energy minima calculated for this type of molecule in the gas phase. An extended network of intermolecular hydrogen bonds spreads parallel to the bc plane separating apolar layers.

Comment

Compounds containing heterocyclic nitrogen systems are very important to mankind as they are often associated with substances that show physiological activity. In particular, naturally occurring alkaloids of the cinchona group have for a long time been used as antimalarial, antibacterial and cardioactive agents (Verpoorte et al., 1988; Carroll et al., 1991; Karle & Karle, 1992; Oleksyn & Serda, 1993; Chiou et al., 1996). Many factors can influence the biological activity of these substances and the action mechanism is still not completely understood. In particular, the activity seems to be strongly correlated with the stereochemistry of the adjacent C8 and C9 chiral centres and the 8,9-threo-isomers have been shown to possess minimal biological activity (Dijkstra et al., 1989; Karle & Karle, 1992; Oleksyn & Serda, 1993; Fujii et al., 2000). In addition, the ability of the amino and hydroxyl groups at C8 and C9 to form intermolecular hydrogen bonds with the receptors is also considered essential for biological activity, which is completely lost when these groups are engaged in intramolecular hydrogen bonds. Apart from their biological activity, this class of substances has been used, after the pioneering studies of Pasteur (1853) and McKenzie (1899), as effective resolving agents of racemic mixtures of carboxylic acids (Fogassy et al., 1986; Dijkstra et al., 1989; Ryttersgaard & Larsen, 1998) and, more recently, as chiral control elements in various asymmetric processes (Corey et al., 1997; Thiel et al., 2001, and references therein).

(I)
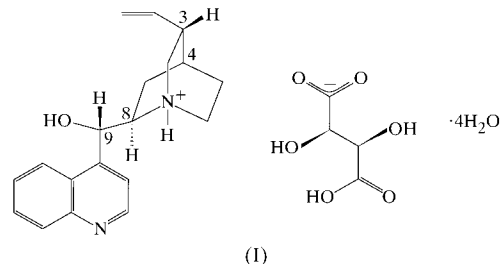
Several adducts formed by cinchona alkaloids with carboxylic acids have been studied crystallographically in the last decade (Larsen et al., 1993; Oleksyn & Serda, 1993; Gjerløv & Larsen, 1997a,b; Ryttersgaard & Larsen, 1998). The present structure of (3R,4S,8R,9S)-cinchoninium (2R,3R)-tartrate tetrahydrate, (I), underlines the stereochemical features of the alkaloid moiety and its characteristic mode of interaction with other molecules in the crystal.

Fig. 1 shows a perspective view of the asymmetric unit in the cell. All the bond lengths and angles are in the expected ranges (Pniewska & Suszko-Purzycka, 1989, and references therein; Ryttersgaard & Larsen, 1998). In particular, the geometry around N1 in the quinuclidinic moiety is typical of a protonated N atom (Oleksyn et al., 1978, 1979). Likewise, the values of the bond lengths and angles in the tartrate anion clearly indicate that only the C4A carboxyl group is ionized. In the cinchona cation, N1$^+$ is oriented anti with respect to the quinoline ring and the orientation of the quinoline and quinuclidine moieties is described by the torsion angles N1—C8—C9—C16 and C8—C9—C16—C15 of −170.9 (2) and
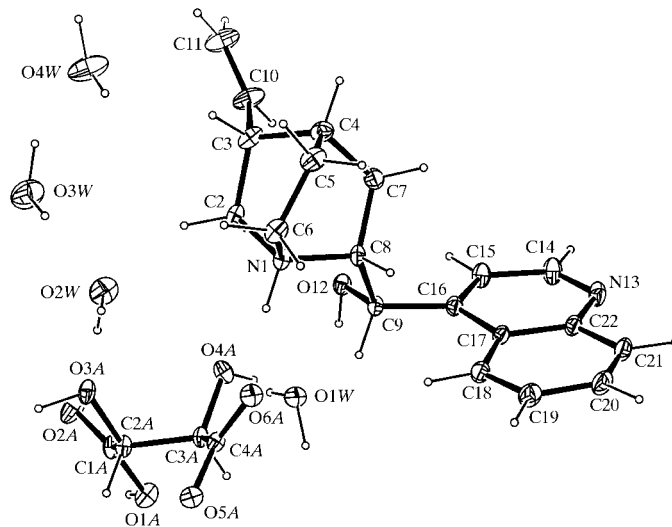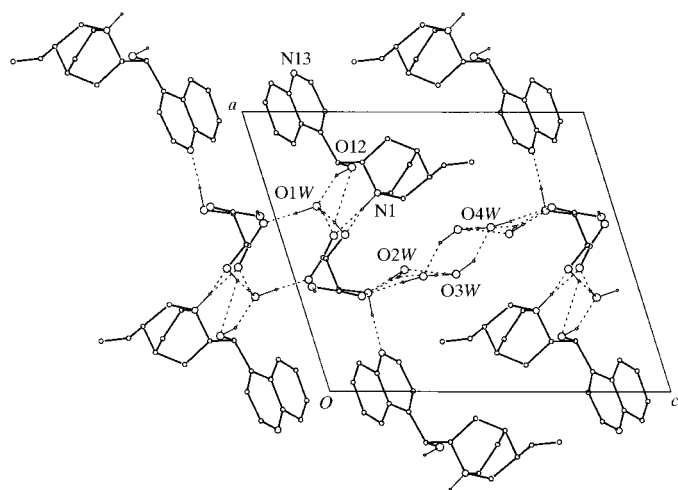

Figure 1
Perspective view of the asymmetric unit of (I) with the atomic labelling for non-H atoms. Displacement ellipsoids are drawn at the 30% probability level.

$-108.8\ (3)°$, respectively. This conformation corresponds to one of the energy minima calculated in the gas phase for this alkaloid family (Dupont *et al.*, 1985; Carroll *et al.*, 1991) and is the most frequently observed in the crystal structures of cinchona salts (Oleksyn & Serda, 1993). The quinoline system is only roughly planar. With respect to the best plane through the non-H atoms of the bicyclic system, the deviations are within 0.054 (3) Å. This finding, together with the values of the bond lengths and angles, is consistent with the low aromaticity of the bicyclic system (Gdaniec *et al.*, 1989; Oleksyn & Serda, 1993). The bicyclic rings of the quinuclidine system are in a boat conformation, slightly distorted toward a twist-boat form, so that the methylene groups are twisted by $\sim12°$ around the $N1\cdots C4$ line. This twisting is more pronounced in the N1-protonated cinchona alkaloids (Oleksyn *et al.*, 1992; Oleksyn & Serda, 1993). The vinyl group is oriented to form a torsion angle of $137.6\ (4)°$ with the C2—C3 bond, according to the experimental and theoretical results for correlated structures (Karle & Karle, 1981; Carroll *et al.*, 1991; Ryttersgaard & Larsen, 1998). The hydroxyl O atom at C9 forms an O12—C9—C8—N1 torsion angle of $68.5\ (2)°$.

The tartrate anion adopts the usual extended *trans* conformation (Ryttersgaard & Larsen, 1998). The value of $-175.4\ (2)°$ for the backbone torsion angle (C1A—C2A—C3A—C4A) is well within the variance of $\pm16°$ around $180°$ found for 90 tartrate structures in a search of the Cambridge Structural Database (Version 5.21, April 2001; Allen & Kennard, 1993).

In the crystal, the molecular arrangement is governed by numerous intermolecular hydrogen bonds involving all the potential donor groups. The geometry of the hydrogen-bonding interactions is given in Table 2 and Fig. 2. In particular, the tartrate anions are interconnected through a short hydrogen bond between the carboxylic acid hydroxyl and carboxylate carbonyl groups, giving rise to anion chains parallel to the b axis and encircling the screw axis at $a = \frac{1}{2}, c = 0$. Such a head-to-tail chain arrangement is rather common in

tartrate structures with a translational period of about 7 Å (Fogassy *et al.*, 1986, and references therein). Further hydrogen-bonding interactions interconnect, along the a direction, cinchoninium and tartrate ions in an infinite sequence of alternating cations and anions. In both chain motifs, the crystal water O1W is involved as a donor and acceptor in four hydrogen bonds. The remaining water molecules are arranged around the screw axis at a and $c = \frac{1}{2}$, and are joined by a network of hydrogen bonds which act as a bridge along the c direction between the screw-related tartrate moieties. In this manner, the molecular arrangement forms, along the a axis, an alternating sequence of polar ($a = \frac{1}{2}$) and apolar layers ($a = 0$). In the hydrophobic layers, all distances are greater than the sum of the van der Waals radii (>3.5 Å). The vinyl groups point towards the quinoline systems of neighbouring screw-related cations, with a $C11\cdots N13(2 - x, \frac{1}{2} + y, 1 - z)$ distance of 3.688 (4) Å.

Experimental

Single crystals of (I) were selected directly from the Artificial Crystal Collection of the mineralogist Arcangelo Scacchi (1810–1893) preserved in the 'Real Museo Mineralogico' of Naples. Identical crystals were obtained by dissolving a fraction of the original sample in methanol followed by slow evaporation (about three weeks) at 277 K. Crystals of compound (I) were also obtained from equimolar amounts of cinchonine and L-tartaric acid (Fluka products) dissolved in a methanol–water (5:1) mixture.

Crystal data

$C_{19}H_{23}N_2O^+\cdot C_4H_5O_6^-\cdot 4H_2O$	$D_x = 1.332$ Mg m^{-3}
$M_r = 516.54$	Cu $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 25
$a = 12.802\ (7)$ Å	reflections
$b = 7.0425\ (10)$ Å	$\theta = 25.4$–$31.3°$
$c = 14.970\ (10)$ Å	$\mu = 0.90$ mm^{-1}
$\beta = 107.44\ (3)°$	$T = 291$ K
$V = 1287.6\ (11)$ Å^3	Rectangular prism, light brown
$Z = 2$	$0.42 \times 0.22 \times 0.09$ mm

Data collection

Enraf–Nonius CAD-4 diffractometer	5096 independent reflections
ω–θ scans, as suggested by peak-shape analysis implemented in *CAD*-4 Software (Enraf–Nonius, 1989)	4833 reflections with $I > 2.5\sigma(I)$
	$R_{int} = 0.030$
	$\theta_{max} = 75.7°$
	$h = 0 \rightarrow 16$
	$k = -6 \rightarrow 8$
Absorption correction: ψ scan (North *et al.*, 1968)	$l = -18 \rightarrow 17$
$T_{min} = 0.764, T_{max} = 0.922$	3 standard reflections
5316 measured reflections	frequency: 200 min
	intensity decay: none

Refinement

Refinement on F	Extinction correction: Stout & Jensen (1968)
$R = 0.046$	
$wR = 0.054$	Extinction coefficient:
$S = 0.99$	$1.6\ (2) \times 10^{-6}$
4833 reflections	The absolute configuration was chosen according to that of the known cinchonine (Oleksyn *et al.*, 1978) and is supported by the refined Rogers parameter (Rogers, 1981)
326 parameters	
H-atom parameters constrained	
$w = 1/[\sigma^2(F_o) + (0.02F_o)^2 + 1.0]$ (Killean & Lawrence, 1969)	
$(\Delta/\sigma)_{max} = 0.013$	
$\Delta\rho_{max} = 0.24$ e Å^{-3}	Rogers parameter for absolute structure determination = 0.998 (6)
$\Delta\rho_{min} = -0.24$ e Å^{-3}	

Figure 2
The crystal packing projected onto the *ac* plane. Only the H atoms involved in hydrogen bonding are shown. Dotted lines indicate hydrogen bonds.

Table 1
Selected geometric parameters (Å, °).

O1A—C1A	1.310 (3)	C9—C16	1.534 (3)
O2A—C1A	1.206 (3)	C10—C11	1.247 (5)
O5A—C4A	1.268 (3)	C14—C15	1.406 (4)
O6A—C4A	1.232 (3)	C15—C16	1.372 (3)
O12—C9	1.421 (3)	C16—C17	1.424 (4)
N1—C2	1.510 (3)	C17—C18	1.418 (4)
N1—C6	1.516 (3)	C17—C22	1.424 (3)
N1—C8	1.515 (3)	C18—C19	1.371 (4)
N13—C14	1.310 (4)	C19—C20	1.404 (4)
N13—C22	1.362 (3)	C20—C21	1.351 (4)
C3—C10	1.514 (4)	C21—C22	1.425 (4)
C8—C9	1.527 (3)		
C2—N1—C6	108.4 (2)	C7—C8—C9	115.1 (2)
C2—N1—C8	112.1 (2)	O12—C9—C8	110.1 (2)
C6—N1—C8	107.4 (2)	O12—C9—C16	110.2 (2)
C14—N13—C22	118.2 (3)	C8—C9—C16	108.3 (2)
O1A—C1A—O2A	124.3 (2)	C3—C10—C11	128.0 (3)
O1A—C1A—C2A	112.1 (2)	N13—C14—C15	123.6 (3)
O2A—C1A—C2A	123.5 (2)	C14—C15—C16	119.6 (3)
O5A—C4A—O6A	125.8 (2)	C9—C16—C15	119.5 (2)
O5A—C4A—C3A	114.7 (2)	C9—C16—C17	121.9 (2)
O6A—C4A—C3A	119.5 (2)	C15—C16—C17	118.6 (2)
N1—C2—C3	109.3 (2)	C16—C17—C22	117.1 (2)
N1—C6—C5	108.8 (2)	N13—C22—C17	122.6 (2)
N1—C8—C7	107.4 (2)	N13—C22—C21	118.0 (2)
N1—C8—C9	113.0 (2)		
O1A—C1A—C2A—C3A	57.1 (2)	C4—C5—C6—N1	17.2 (3)
O3A—C2A—C3A—O4A	−59.0 (2)	C4—C7—C8—N1	23.1 (3)
C1A—C2A—C3A—C4A	−175.4 (2)	N1—C8—C9—O12	68.5 (2)
C2A—C3A—C4A—O5A	52.3 (3)	N1—C8—C9—C16	−170.9 (2)
N1—C2—C3—C4	17.9 (3)	C8—C9—C16—C15	−108.8 (3)
C2—C3—C10—C11	137.6 (4)	C9—C16—C17—C18	5.8 (4)

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

D—H⋯A	D—H	H⋯A	D⋯A	D—H⋯A
O4A—H3A⋯O12	0.98	2.56	3.064 (3)	112
O4A—H3A⋯O1W	0.98	1.85	2.822 (3)	170
O12—H1⋯O1W	0.98	1.81	2.719 (2)	152
N1—H2⋯O4A	0.98	2.15	2.936 (3)	136
N1—H2⋯O6A	0.98	1.93	2.784 (3)	144
O2W—H4W⋯O3A	0.98	1.85	2.826 (3)	171
O3W—H5W⋯O4W	0.98	1.97	2.839 (4)	147
O3W—H6W⋯O2W	0.98	1.97	2.831 (4)	146
O2W—H3W⋯O4W^i	0.98	2.43	3.191 (4)	134
O4W—H7W⋯O2A^i	0.98	2.23	2.943 (4)	129
O4W—H7W⋯O3A^i	0.98	2.22	3.141 (3)	156
O4W—H8W⋯O3W^i	0.98	1.71	2.691 (4)	177
O2W—H3W⋯O2A^{ii}	0.98	2.26	3.136 (3)	148
O1W—H1W⋯O5A^{iii}	0.98	1.78	2.716 (3)	158
O1W—H2W⋯O6A^{iv}	0.98	1.76	2.705 (3)	162
O1A—H1A⋯O5A^{iv}	0.98	1.68	2.556 (2)	146
O3A—H2A⋯N13^v	0.98	1.73	2.693 (3)	169

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

All H atoms were observed in difference Fourier maps and included at idealized positions in the final refinements as fixed atoms, with $U_{iso}(H) = U_{eq}$(parent atom). Alkyl H atoms and hydroxyl and water H atoms were constrained to lie 1.02 and 0.98 Å, respectively, from their parent atoms.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *SDP* (Enraf–Nonius, 1985); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1993); program(s) used to refine structure: *SDP*; molecular graphics: *ORTEP*-3 (Farrugia, 1997); software used to prepare material for publication: *PARST* (Nardelli, 1983, 1995).

References

Allen, F. H. & Kennard, O. (1993). *Chem. Des. Autom. News*, **8**, 1, 31–37.
Altomare, A., Cascarano, G., Giacovazzo, C. & Guagliardi, A. (1993). *J. Appl. Cryst.* **26**, 343–350.
Carroll, F. I., Abraham, P., Gaetano, K., Mascarella, S. W., Wohl, R. A., Lind, J. & Petzoldt, K. (1991). *J. Chem. Soc. Perkin Trans.* 1, pp. 3017–3026.
Chiou, W.-F., Liao, J.-F. & Chen, C.-F. (1996). *J. Nat. Prod.* **59**, 374–378.
Corey, E. J., Xu, F. & Noe, M. C. (1997). *J. Am. Chem. Soc.* **119**, 12414–12415.
Dijkstra, G. D. H., Kellogg, R. M., Wynberg, H., Svendsen, J. S., Marko, I. & Sharpless, K. B. (1989). *J. Am. Chem. Soc.* **111**, 8069–8076.
Dupont, L., Konsur, A., Lewinski, K. & Oleksyn, B. (1985). *Acta Cryst.* C**41**, 616–619.
Enraf–Nonius (1985). *Structure Determination Package.* Version 3.0. Enraf–Nonius, Delft, The Netherlands.
Enraf–Nonius (1989). *CAD*-4 *Software*. Version 5.0. Enraf–Nonius, Delft, The Netherlands.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Fogassy, E., Acs, M., Faigl, F., Simon, K., Rohonczy, J. & Ecsery, Z. (1986). *J. Chem. Soc. Perkin Trans.* 2, pp. 1881–1886.
Fujii, I., Kobayashi, Y. & Hirayama, N. (2000). *Z. Kristallogr.* **215**, 762–765.
Gdaniec, M., Turowska-Tyrk, I. & Krygowski, T. M. (1989). *J. Chem. Soc. Perkin Trans.* 2, pp. 613–616.
Gjerløv, A. & Larsen, S. (1997a). *Acta Cryst.* B**53**, 708–718.
Gjerløv, A. B. & Larsen, S. (1997b). *Acta Cryst.* C**53**, 1505–1508.
Karle, I. L. & Karle, J. (1981). *Proc. Natl Acad. Sci. USA*, **78**, 5938–5941.
Karle, J. M. & Karle, I. L. (1992). *Acta Cryst.* C**48**, 1975–1980.
Killean, R. C. G. & Lawrence, J. L. (1969). *Acta Cryst.* B**25**, 1750–1752.
Larsen, S., Lopez de Diego, H. & Kozma, D. (1993). *Acta Cryst.* B**49**, 310–316.
McKenzie, A. (1899). *J. Chem. Soc.* **75**, 964–972.
Nardelli, M. (1983). *Comput. Chem.* **7**, 95–98.
Nardelli, M. (1995). *J. Appl. Cryst.* **28**, 659.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Oleksyn, B., Lebioda, L. & Ciechanowicz-Rutkowska, M. (1979). *Acta Cryst.* B**35**, 440–444.
Oleksyn, B. J. & Serda, P. (1993). *Acta Cryst.* B**49**, 530–535.
Oleksyn, B. J., Stadnicka, K. M. & Hodorowicz, S. A. (1978). *Acta Cryst.* B**34**, 811–816.
Oleksyn, B. J., Suszko-Purzycka, A., Dive, G. & Lamotte-Brasseur, J. (1992). *J. Pharm. Sci.* **81**, 122–127.
Pasteur, L. (1853). *C. R. Acad. Sci.* **37**, 110–114.
Pniewska, B. & Suszko-Purzycka, A. (1989). *Acta Cryst.* C**45**, 638–642.
Rogers, D. (1981). *Acta Cryst.* A**37**, 734–741.
Ryttersgaard, C. & Larsen, S. (1998). *Acta Cryst.* C**54**, 1698–1701.
Stout, G. H. & Jensen, L. H. (1968). *X-ray Structure Determination*, pp. 409–412. New York: Macmillan.
Thiel, J., Katrusiak, A. & Fiedorow, P. (2001). *J. Mol. Struct.* **561**, 131–143.
Verpoorte, R., Schripsenta, J. & Van der Leer, T. (1988). *Cinchona Alkaloids* in *The Alkaloids – Chemistry and Pharmacology*, Vol. 34, edited by A. Brossi, pp. 331–401. San Diego: Academic Press.