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Absolute configuration of (*R*)-synephrine hydrochloride

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.006 Å
R factor = 0.067
wR factor = 0.120
Data-to-parameter ratio = 16.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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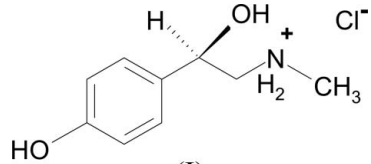
The title compound, 2-hydroxy-2-(4-hydroxyphenyl)-*N*-methylethanaminium chloride, $C_9H_{14}NO_2^+\cdot Cl^-$, has been isolated for the first time from the genus *Harrisonia*. Its structure is stabilized by extensive intra- and intermolecular hydrogen bonds of type O—H···O, N—H···O, N—H···Cl and C—H···Cl, resulting in a three-dimensional network. Additional weak π–π stacking interactions between adjacent molecules further stabilize the crystal structure.

Comment

Harrisonia abyssinica Oliv. (*Simaroubaceae*) is widely used in various African folk remedies. Its roots and stem bark are used throughout Africa in the treatment of gonorrhea, dysentery, skin diseases, tuberculosis, bilharzia infections and as an ascaricide (Balde *et al.*, 1989; Chhabra *et al.*, 1984; Sofowora, 1982). The plant has also been reported to show antifeedant activity against the most common East African crop pests, the monophageous *Sophoptera exempta* (African army worm) and *S. eridania* (Southern army worm), and antibacterial activity against Gram-positive microorganisms, as well as cytotoxic and plant-growth inhibitory activities (Kubo *et al.*, 1976). The butanolic extract of the fruit of *Harrisonia abyssinica* was phytochemically investigated to give the compound synepherine hydrochloride, (I). The natural occurrence of synepherine has been reported in various genera, such as *Citrus*, *Coryphantha*, *Ficus* and *Haloxylon* (Stewart & Wheaton, 1964; Stewart *et al.*, 1964; Ranieri & Mclaughlin, 1976; Smith, 1977). However, this is the first time that synepherine hydrochloride has been isolated from the genus *Harrisonia*.



(I)

Synepherine is a sympathomimetic agent showing vasoconstrictor, hypertensive and bronchial muscle relaxant properties (Chen *et al.*, 1980; Stewart *et al.*, 1964). The absolute stereochemistry of synepherine was determined by X-ray diffraction studies of its synthetic salt as the (−)-3-bromocamphor-8-sulfonate (Midgley *et al.*, 1989). In this paper, we report the absolute stereochemistry of naturally occurring (*R*)-synepherine hydrochloride, (I).

The bond lengths and bond angles in (I) (Fig. 1) are within normal ranges (Allen *et al.*, 1987). Atoms C7 and O1 are

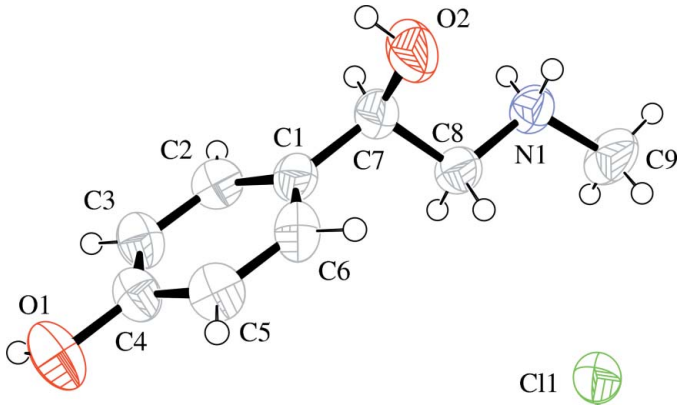


Figure 1
An *ORTEPII* (Johnson, 1976) drawing of (I), showing 50% probability displacement ellipsoids and the atomic numbering scheme.

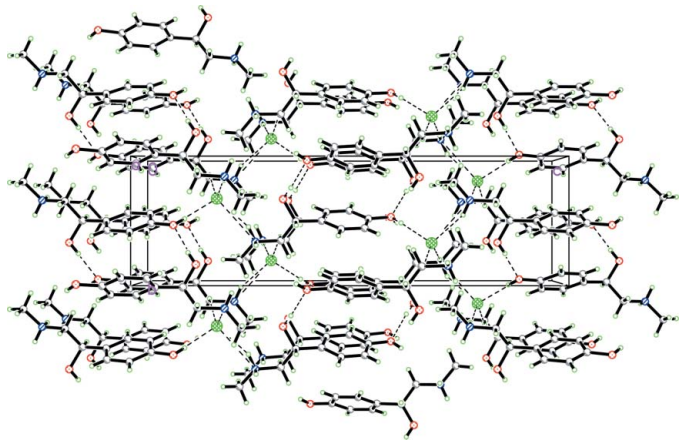


Figure 2
A packing diagram of (I). Hydrogen bonds are represented by broken lines.

essentially in the plane of the benzene ring. The hydroxyl group at C7 is twisted away from the benzene ring, the O2—C7—C1—C2 torsion angle being 131.5 (4)°. The side chain comprising atoms C1, C7, C8, N1 and C9 is fully extended and its mean plane is inclined at an angle of 71.9 (2)° with respect to the mean plane of the benzene ring.

The anions and the cations in (I) are linked together to form a three-dimensional network of hydrogen bonds (Fig. 2). In addition to N—H···O and C—H···Cl intramolecular hydrogen bonds, there are four intermolecular hydrogen bonds of the types O—H···Cl, N—H···Cl and O—H···O, which stabilize the crystal structure of (I); details of the hydrogen-bonding geometries are given in Table 1. The stability of the structure is also achieved by π–π stacking interactions between benzene rings from adjacent molecules. The mean planes of these rings are 3.150 (3) Å apart, indicating weak π—π interactions, with the distance between the ring centroids being 4.785 (3) Å.

Experimental

Powdered fruits of *Harrisonia abyssinica* (2.4 kg) were soaked and extracted with EtOH (10 l) for one week. The combined EtOH extracts were dried under vacuum to furnish a brown gum (150 g). Subsequent extraction of this EtOH extract afforded a hexane-soluble fraction (10 g), an ethyl acetate-soluble fraction (40 g) and a butanol-soluble fraction (5.5 g). The butanolic extract (5.5 g) was passed through a polyamine column and ten fractions were obtained. Fractions 3–5 were found to be similar by thin-layer chromatography and were combined (2.1 g). These combined fractions were again subjected to flash chromatography, using dichloromethane and methanol as the eluting solvents, and 14 fractions were obtained. Fractions 7–10 showed the formation of some needles which could not be separated by washing, so they were combined to give the sub-fraction HBR (200 mg). Sub-fraction HBR was again subjected to flash chromatography, using dichloromethane and methanol as the eluting solvents, to give compound (I) in a semi-purified form. This was further purified by recrystallization from methanol and dichloromethane (1:1) (10 mg, m.p. 508 K).

Crystal data

$C_9H_{14}NO_2^+\cdot Cl^-$
M_r = 203.66
Orthorhombic, $P2_12_12_1$
a = 6.7480 (13) Å
b = 6.9559 (13) Å
c = 23.450 (4) Å
V = 1100.7 (4) Å^3
Z = 4
D_x = 1.229 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 6750 reflections
θ = 1.7–25.0°
μ = 0.32 mm^{-1}
T = 293 (2) K
Needle, colourless
0.58 × 0.06 × 0.05 mm

Data collection

Siemens SMART CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.837, T_{max} = 0.984
5679 measured reflections
1928 independent reflections
1400 reflections with $I > 2\sigma(I)$
R_{int} = 0.058
θ_{max} = 25.0°
$h = -8 \rightarrow 7$
$k = -8 \rightarrow 8$
$l = -27 \rightarrow 25$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.067
$wR(F^2)$ = 0.120
S = 1.02
1928 reflections
120 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0489P)^2 + 0.1384P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Absolute structure: Flack (1983), with 764 Friedel pairs
Flack parameter: 0.07 (14)

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

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···Cl1^{i}	0.82	2.23	3.037 (3)	168
N1—H1A···Cl1^{ii}	0.90	2.22	3.091 (4)	163
N1—H1B···O2^{iii}	0.90	2.42	2.769 (4)	103
N1—H1B···Cl1^{iv}	0.90	2.31	3.161 (3)	157
O2—H2···O1^{v}	0.82	2.01	2.825 (5)	171
C8—H8A···Cl1	0.97	2.82	3.603 (4)	138

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

All H atoms were positioned geometrically and were allowed to ride on their parent atoms, with aromatic C—H = 0.93, methyl C—H = 0.96 Å, N—H = 0.90 Å and O—H = 0.82 Å, and with U_{iso}(H) =

$1.5U_{eq}$(C) for methyl H and $1.2U_{eq}$(parent) for other H atoms. The chirality of the structure was determined from the Flack (1983) parameter, the value for the inverted structure being 0.93 (14).

Data collection: *SMART* (Siemens, 1996); cell refinement: *SAINT* (Siemens, 1996); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 1997); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*, *PARST95* (Nardelli, 1995) and *PLATON* (Spek, 2003).

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