

7,8-Dihydroxy-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolinium bromide monohydrate, a dopamine agonist

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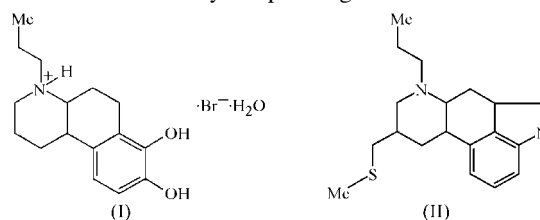
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In the crystal structure of the title dopaminergic compound, C₁₆H₂₄N₂O₂⁺·Br⁻·H₂O, protonation occurs at the piperidine N atom. The piperidine ring adopts a chair conformation and the cyclohexene ring adopts a half-chair conformation; together with the planar benzene ring, this results in a relatively planar shape for the whole molecule. Classical hydrogen bonds (N—H···Br, O—H···Br and O—H···O) produce an infinite three-dimensional network. Hydrogen bonds between water molecules and Br⁻ anions create centrosymmetric rings throughout the crystal structure. Structural comparison of the molecule with the ergoline dopamine agonist pergolide shows that it is the hydrogen-bond-forming hydroxy or imino group that is necessary for dopaminergic activity, rather than the presence of a phenyl or a pyrrole ring *per se*.

Comment

TL140, (I) (Fig. 1), was synthesized and shown to be a potent dopamine agonist (Cannon *et al.*, 1979). Bond distances and angles are within the normal ranges. Protonation of the molecule occurs at atom N1 of the piperidine ring and the sum of the angles at this atom is 335°. The piperidine ring adopts a chair conformation, with puckering parameters (Cremer & Pople, 1975) of $Q = 0.558(4) \text{ \AA}$, $\Theta = 175.4(4)^\circ$ and $\Phi = 129(5)^\circ$. The cyclohexene ring adopts a half-chair conformation, with puckering parameters of $Q = 0.537(4) \text{ \AA}$, $\Theta = 49.1(4)^\circ$ and $\Phi = 213.3(5)^\circ$. The benzene ring, including its hydroxy atoms O18 and O19, is planar. Despite the saturated and partly saturated nature of two of the rings, the whole molecule displays a high degree of planarity. The r.m.s. deviation from the plane through all non-H atoms of the molecule is 0.2378 Å and the largest deviation is -0.541(4) Å for atom C8. Classical hydrogen bonds (N—H···Br, O—

H···Br and O—H···O) produce an infinite three-dimensional network (Table 1 and Fig. 2). Layers of a hydrophobic character (cyclohexene and benzene rings) are interspersed with hydrophilic layers (water molecules, Br⁻ anions and hydroxy groups) running parallel to the *bc* plane. The significant difference in the C11—O18—H18 (108.9°) and C12—O19—H19 (121.5°) angles can be explained by considering the hydrogen bonding involved. The intramolecular O18—H18···O19 hydrogen bond forces H18 towards O19, thus decreasing the angle, and the intermolecular O19—H19···O20 hydrogen bond to the water molecule forces H19 towards O20 due to the position of the water in the crystal lattice, thus increasing the angle. Hydrogen bonding of the water molecules and Br⁻ anions creates centrosymmetric rings throughout the crystal structure; van der Waals interactions also contribute to the crystal packing.



The identification of the dopamine pharmacophore in ergoline compounds such as pergolide, (II), was questioned when dopaminergic analogues lacking the phenyl *A* ring were synthesized. This led to suggestions (Bach *et al.*, 1980; Nordmann & Petcher, 1985) that the pyrrolylethylamine moiety, rather than the dopamine-like phenylethylamine, was the ergoline dopaminergic entity. However, if the electronegative *meta*-O atom of dopamine and the pyrrole N atom of pergolide are necessary for dopamine activity, rather than a particular ring structure (Camerman & Camerman, 1981), the distinction is academic. TL140 presents a means of testing the pharmacophore models as it resembles the overall ring structure of pergolide but lacks a pyrrole ring. Fig. 3 shows a stereoscopic superposition of TL140 with pergolide (Ma *et al.*, 1987); the atoms of the three six-membered rings in each molecule were used in the least-squares fitting procedure. The structures of the two molecules overlap closely at all atoms in common, including the propyl groups. The functional groups superpose well, *viz.* the two piperidine N atoms, and the *meta*-

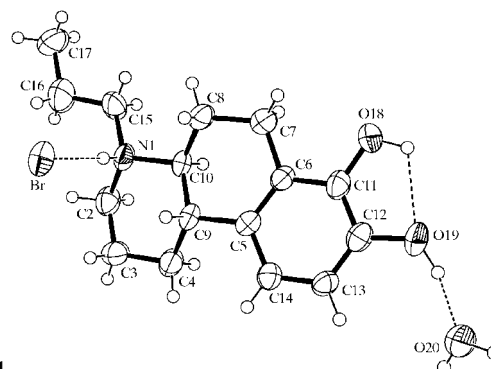


Figure 1
The molecular structure of the title compound, showing 50% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii.

† Deceased.

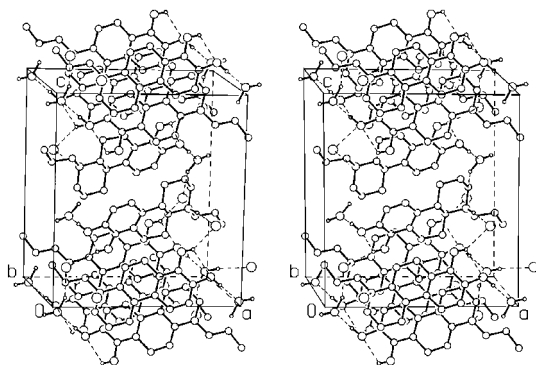


Figure 2
Stereodiagram of the molecular packing and hydrogen-bond scheme. For clarity, only H atoms involved in hydrogen bonding are shown.

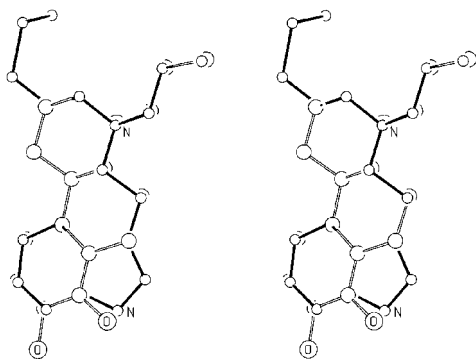


Figure 3
Stereodiagram of the superposition of the title compound and pergolide (filled bonds and small circles).

hydroxy O atom of TL140 with the pyrrole N atom of pergolide. Thus, as suggested previously, the ring phenyl and/or pyrrole structures in these compounds likely serve to position the functional electronegative atoms properly for acceptor interaction in these rigid dopamine agonists, and the nature of the ring itself, apart from planarity, is not critical.

Experimental

The crystal chosen for data collection was obtained by slow evaporation (over a period of 25 d) of a 10:1:1 (v/v/v) methanol-water-propanol solution at 294 K.

Crystal data

$C_{16}H_{24}NO_2^+ \cdot Br^- \cdot H_2O$
 $M_r = 360.29$
 Monoclinic, $P2_1/c$
 $a = 13.907(3) \text{ \AA}$
 $b = 7.856(2) \text{ \AA}$
 $c = 15.357(3) \text{ \AA}$
 $\beta = 93.21(2)^\circ$
 $V = 1675.2(6) \text{ \AA}^3$
 $Z = 4$

$D_x = 1.429 \text{ Mg m}^{-3}$
 Cu $K\alpha$ radiation
 Cell parameters from 32 reflections
 $\theta = 26\text{--}53^\circ$
 $\mu = 3.42 \text{ mm}^{-1}$
 $T = 294(2) \text{ K}$
 Prism, colorless
 $0.43 \times 0.28 \times 0.25 \text{ mm}$

Data collection

Picker FACS-1 four-circle diffractometer
 $\theta/2\theta$ scans
 Absorption correction: ψ scan (North *et al.*, 1968)
 $T_{\min} = 0.361$, $T_{\max} = 0.423$
 2858 measured reflections
 2854 independent reflections
 1439 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.017$
 $\theta_{\text{max}} = 65.0^\circ$
 $h = 0 \rightarrow 16$
 $k = 0 \rightarrow 9$
 $l = -18 \rightarrow 18$
 3 standard reflections every 100 reflections
 intensity decay: 2.1%

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.033$
 $wR(F^2) = 0.085$
 $S = 0.70$
 2854 reflections
 193 parameters

H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2)]$
 $(\Delta/\sigma)_{\text{max}} < 0.001$
 $\Delta\rho_{\text{max}} = 0.49 \text{ e \AA}^{-3}$
 $\Delta\rho_{\text{min}} = -0.45 \text{ e \AA}^{-3}$

Table 1

Hydrogen-bond geometry (\AA , $^\circ$).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
$N1-H1 \cdots Br^i$	0.91	2.36	3.265 (3)	177
$O18-H18 \cdots O19^j$	0.92	2.22	2.694 (4)	112
$O18-H18 \cdots Br^{ii}$	0.92	2.55	3.314 (3)	141 (1)
$O19-H19 \cdots O20^i$	0.94	1.79	2.620 (5)	146
$O20-H20A \cdots Br^{iii}$	0.92	2.52	3.384 (3)	158 (1)
$O20-H20B \cdots Br^{iv}$	0.92	2.44	3.222 (4)	143 (1)

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

The final difference map revealed the positions of all H atoms; however, due to the limited intensity data, all H atoms, except for those of the water molecule and the two hydroxy groups, were placed in calculated positions and allowed for riding. One overall isotropic displacement parameter was refined for the methyl H atoms [$U_{\text{iso}}(\text{H}) = 0.183(19) \text{ \AA}^2$] and another for the remaining H atoms [$U_{\text{iso}}(\text{H}) = 0.068(3) \text{ \AA}^2$]. The positions of the H atoms of the water molecule and the two hydroxy groups were taken from the final difference map. The positional parameters were not refined and the isotropic displacement parameters were fixed at $U_{\text{iso}}(\text{H}) = 0.14$ and 0.06 \AA^2 for the water and hydroxy H atoms, respectively. The range of C–H distances is 0.92–0.98 \AA and the N–H distance is 0.91 \AA .

Data collection: *Picker Operating Manual* (Picker, 1967); cell refinement: *Picker Operating Manual*; data reduction: *DATRDN: The X-ray System* (Stewart, 1976); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1288). Services for accessing these data are described at the back of the journal.

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