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Structure of (3,4-Dihydroxyphenethyl)trimethylammonium Bromide (Coryneine Bromide)*

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Abstract. $C_{11}H_{18}NO_2^+.Br^-$, $M_r = 276{\cdot}2$, monoclinic, $P2_1/c$, $a = 9{\cdot}730\ (1)$, $b = 10{\cdot}141\ (3)$, $c = 12{\cdot}989\ (2)$ Å, $\beta = 101{\cdot}55\ (5)°$, $Z = 4$, $D_c = 1{\cdot}461$ Mg m^{-3}, μ(Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å) $= 3{\cdot}17$ mm^{-1}. Final $R = 0{\cdot}041$ for 1638 observed counter amplitudes. The ethylammonium side chain is in the extended conformation, C–C–C–N$^+$ torsion angle 179·8 (6)°. The plane of these atoms is inclined at 76 (1)° to the plane of the phenyl ring.

Introduction. Coryneine, the trimethylammonium derivative of dopamine, has high nicotine-like ganglion-stimulant activity and is also a potent neuromuscular blocking agent (Barlow, Bowman, Ison & McQueen, 1974). It is of interest, therefore, to compare its dimensions and conformation with those of the closely related epinine (Giesecke, 1976), dopamine (Giesecke, 1980) and other sympathomimetic phenethylamines (Carlström, Bergin & Falkenberg, 1973).

Single crystals were obtained from aqueous solution. After preliminary examination by photographic methods, a crystal 0·4 × 0·3 × 0·05 mm was mounted on an Enraf–Nonius CAD-4 diffractometer. Cell dimensions were obtained by least squares from the setting angles of 25 reflections measured with graphite-monochromated Mo $K\alpha$ radiation. 2206 reflections ($2° < 2\theta < 50°$) were scanned in the ω–2θ mode, of which 1638 [$I > 2{\cdot}5\sigma(I)$] were considered observed and used in the analysis. Two standard reflections, remeasured every hour, showed no significant variation with time. The intensities were not corrected for absorption.

The structure was solved by Patterson and Fourier methods and refined by least-squares methods with anisotropic temperature factors for all non-H atoms. H

Table 1. *Fractional atomic coordinates* (×10^4) *and equivalent isotropic temperature factors* (Å^2 ×10^3)

$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$.

	x	y	z	U_{eq}
C(1)	4151 (4)	4292 (4)	1380 (3)	36 (2)
C(2)	5421 (4)	3628 (4)	1629 (3)	33 (2)
C(3)	6237 (4)	3696 (4)	2645 (3)	26 (2)
C(4)	5744 (4)	4396 (4)	3411 (3)	35 (2)
C(5)	4497 (4)	5056 (4)	3168 (3)	43 (2)
C(6)	3693 (5)	5011 (4)	2161 (3)	42 (2)
C(7)	3309 (5)	4267 (4)	258 (3)	46 (2)
C(8)	2558 (4)	2967 (4)	26 (3)	35 (2)
C(9)	1060 (4)	1506 (4)	−1210 (4)	42 (2)
C(10)	2536 (5)	3084 (5)	−1892 (3)	49 (3)
C(11)	498 (4)	3842 (4)	−1239 (3)	42 (2)
N	1688 (4)	2860 (3)	−1079 (3)	32 (2)
O(1)	7525 (3)	3118 (3)	2924 (2)	56 (2)
O(2)	6517 (3)	4488 (4)	4412 (2)	43 (2)
Br	8914 (1)	2329 (1)	966 (1)	44 (2)

* Contribution from the Crystallography Unit, Universities of Aston and Birmingham.

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atoms were located from a difference synthesis and fixed in their observed positions with an isotropic temperature factor, $U = 0.05$ Å^2.

Refinement was terminated when all calculated shifts were $<0.1\sigma$ with $R = 0.041$ and $R_w = 0.045$. Weights were assigned as $w = [\sigma^2(F) + 0.004F^2]^{-1}$. Computations were performed with *SHELX* (Sheldrick, 1978), using complex neutral-atom scattering factors taken from *International Tables for X-ray Crystallography* (1974). Final atomic parameters are listed in Table 1.*

Discussion. The stereochemistry of the cation and the atomic numbering are shown in Fig. 1. Bond lengths and angles, and selected torsion angles are in Table 2.

Bond lengths and angles are normal and are generally in good agreement with those in dopamine hydrochloride (Giesecke, 1980). Only the N–C(8) length differs by more than 0.02 Å, 1.479 (4) Å in dopamine compared with 1.517 (5) Å in the title compound and this difference is presumably due to the quaternary nature of the 'onium group in the latter compound. The phenyl ring is planar to within ±0.01 Å (Table 3). The ethylamine chain is in the fully extended conformation, torsion angle C(1)–C(7)–C(8)–N 179.8 (6)°, and these four atoms are coplanar to within ±0.001 Å. The angle between this plane and the plane of the phenyl ring is 76.3 (6)°, torsion angle C(6)–C(1)–C(7)–C(8) being −105.1 (6)°. In dopamine hydrochloride the corresponding torsion angles are −173.2 (2) and 100.4 (3)°.† The conformations of the coryneine and dopamine cations are therefore virtually identical in the solid state. The epinine cation (Giesecke, 1976) also has a similar conformation, with these torsion angles having values of −177 and 110°. Most of the related sympathomimetic phenethylamines reviewed by Carlström *et al.* (1973) also adopt similar conformations and there does not seem to be a simple stereochemical explanation for the differences in biological properties between coryneine on the one hand and dopamine and epinine and the related sympathomimetic amines on the other.

The crystal packing involves two hydrogen bonds, between the phenolic groups and bromide ions, linking the coryneine cations into chains parallel to **c**. Pertinent distances and angles are in Table 4. Other contact

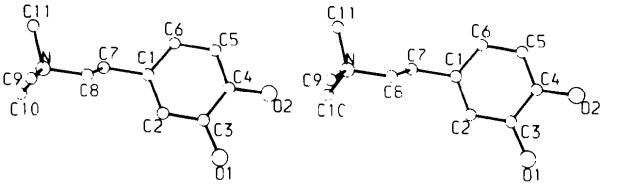

Fig. 1. Stereoscopic view of the coryneine cation in a direction perpendicular to the plane of the phenyl ring. H atoms have been omitted.

Table 2. *Molecular dimensions*

(*a*) Bond lengths (Å)

C(1)–C(2)	1.388 (5)	C(4)–O(2)	1.368 (5)
C(2)–C(3)	1.399 (5)	C(1)–C(7)	1.522 (6)
C(3)–C(4)	1.385 (6)	C(7)–C(8)	1.509 (6)
C(4)–C(5)	1.366 (6)	C(8)–N	1.517 (5)
C(5)–C(6)	1.384 (6)	C(9)–N	1.499 (5)
C(6)–C(1)	1.393 (6)	C(10)–N	1.482 (5)
C(3)–O(1)	1.365 (5)	C(11)–N	1.509 (5)

(*b*) Bond angles (°); e.s.d.'s are *ca* 0.4°

C(6)–C(1)–C(2)	119.0	C(4)–C(5)–C(6)	120.7
C(7)–C(1)–C(2)	119.9	C(5)–C(6)–C(1)	120.2
C(7)–C(1)–C(6)	121.1	C(1)–C(7)–C(8)	110.6
C(1)–C(2)–C(3)	120.4	C(7)–C(8)–N	114.1
C(2)–C(3)–C(4)	119.4	C(8)–N–C(9)	108.1
O(1)–C(3)–C(2)	123.1	C(8)–N–C(10)	112.2
O(1)–C(3)–C(4)	117.5	C(8)–N–C(11)	110.5
C(3)–C(4)–C(5)	120.3	C(9)–N–C(10)	109.4
O(2)–C(4)–C(3)	120.9	C(9)–N–C(11)	107.8
O(2)–C(4)–C(5)	118.7	C(10)–N–C(11)	108.8

(*c*) Selected torsion angles (°); e.s.d.'s are *ca* 0.6°

C(2)–C(1)–C(7)–C(8)	77.2	C(7)–C(8)–N–C(9)	177.5
C(6)–C(1)–C(7)–C(8)	−105.1	C(7)–C(8)–N–C(10)	56.9
C(1)–C(7)–C(8)–N	179.8	C(7)–C(8)–N–C(11)	−64.8

Table 3. *Mean-plane calculations*

Deviations (Å) of atoms from least-squares planes are given. E.s.d.'s are *ca* 0.008 Å for non-H atoms.

Plane (i) C(1)–(6)

C(1)	0.002	C(2)	0.006	C(3)	−0.012	C(4)	0.009
C(5)	−0.001	C(6)	−0.004	C(7)	−0.050	O(1)	−0.073
O(2)	−0.014	H(O1)	−0.214	H(O2)	0.014		

Plane (ii) C(1), C(7), C(8), N

C(1)	0.001	C(7)	−0.001	C(8)	−0.001	N	0.001

Angle: Plane (i)–Plane (ii) 76.3 (6)°

Table 4. *Hydrogen-bond geometry*

Distances (Å)		Angles (°)	
O(1)···Br$^-$	3.211 (3)	H(O1)–O(1)···Br$^-$	16
O(1)–H(O1)	1.01		
H(O1)···Br$^-$	2.25		
O(2)···Br$^{-(i)}$	3.320 (3)	H(O2)–O(2)···Br$^{-(i)}$	27
O(2)–H(O2)	0.99		
H(O2)···Br$^{-(i)}$	2.48		

Symmetry code: (i) $x, \frac{1}{2} - y, \frac{1}{2} + z$.

* Lists of structure factors, anisotropic thermal parameters, H coordinates and C–H bond lengths have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36453 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

† There is a difference in the signs of the torsion angles since the atomic coordinates arbitrarily chosen for coryneine correspond to the centrosymmetrically related rotamer. The rotamer with torsion angles of opposite sign (corresponding to those of dopamine) is also present in the crystal.

distances correspond to normal van der Waals interactions.

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Structure of Racemic *cis*-4-Phenylcyclophosphamide*

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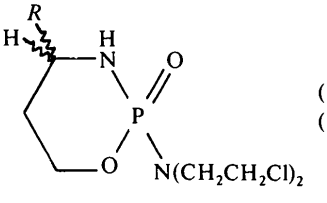
Abstract. $C_{13}H_{19}Cl_2N_2O_2P$, $M_r = 337{\cdot}2$, monoclinic, $P2_1/c$, $a = 8{\cdot}000\,(1)$, $b = 10{\cdot}279\,(2)$, $c = 20{\cdot}003\,(4)$ Å, $\beta = 102{\cdot}12\,(1)°$, $Z = 4$, $D_m = 1{\cdot}39\,(2)$ (flotation), $D_x = 1{\cdot}393$ Mg m^{-3}, μ(Mo $K\alpha$) = 0·507 mm^{-1}. The final R value after full-matrix least-squares refinement was 0·037 for 1206 observed reflections. The molecule was found to exist in a chair conformation with the phenyl substituent and the phosphoryl O atom in equatorial positions. The crystal structure consists of centrosymmetric dimers linked by hydrogen bonds between N—H and O=P.

Introduction. Cyclophosphamide (1) is a well-known drug which exhibits antineoplastic activity against a broad spectrum of human cancers. Consequently, the metabolism, mechanism of action, and the influence of structural modification upon the therapeutic activity of (1) are of considerable interest. The relationship between biological activity and molecular configuration and conformation has prompted X-ray structure analyses of (1) as well as of numerous metabolites and analogs of (1). Recently, the synthesis, anti-cancer screening, NMR data and other chemical information for 4-phenylcyclophosphamide (2) were reported by Boyd, Zon, Himes, Stalick, Mighell & Secor (1980). Two racemic geometrical isomers of (2) were synthesized and chromatographically separated into the faster and slower-eluting racemates. We report here the single-crystal X-ray diffraction analysis of the faster-eluting racemate of (2) which was recrystallized from a mixture of chloroform and diethyl ether.



(1), R = H
(2), R = Ph

Data were collected on a clear, hexagonally shaped crystal of dimensions 0·10 × 0·13 × 0·15 mm using an automated four-circle diffractometer with graphite-monochromated Mo $K\alpha$ radiation, $\lambda = 0{\cdot}71069$ Å. Cell dimensions were determined by a least-squares refinement of the setting angles of 15 reflections with 2θ

* (2*RS*,4*SR*)-2-[Bis(2-chloroethyl)amino]-4-phenyl-2*H*-1,3,2-oxazaphosphorinane 2-oxide.

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