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The Crystal and Molecular Structure of 1-(β-Aminoethyl)-4-hydroxy-5-iodo-3,6-benzoquinone, an Oxidation Product of 6-Hydroxydopamine

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The title compound was obtained on oxidation of 6-hydroxydopamine by potassium iodate. The crystal structure was determined by X-ray diffraction techniques. The crystals are monoclinic, space group $P2_1/c$ with $a = 7.074(3)$ Å, $b = 14.555(7)$ Å, $c = 8.264(2)$ Å, $\beta = 90.57(3)°$. Full-matrix least-squares refinements resulted in an R-factor of 0.048 for 1058 observed reflections. Standard deviations in bond lengths are 0.01 – 0.02 Å and in bond angles 1°. The molecules, which appear to have a zwitterionic structure, are observed in a conformation with $\tau_1 = 165°$ and $\tau_2 = -71°$. The ions are arranged in chains along the c-axis, and are stacked along the a-axis in the crystals. Intermolecular contacts consist of van der Waals' interactions, N–H···O hydrogen bonds, and a short I···O=C contact indicative of a charge-transfer interaction.

6-Hydroxydopamine is well-known as a chemical sympathectomic agent. A main theory concerning the neurodegenerative action of the compound is related to the binding of its oxidation products to intraneuronal macromolecules.[1,2] Extensive polarographic and spectroscopic studies have been performed in order to establish the oxidation pathways of 6-hydroxydopamine.[3,4] In view of the differences in the biological actions of 6-hydroxydopamine and chemically related sympathomimetic amines, such as adrenaline, it is considered of great importance to correlate the oxidation studies of these compounds.

The crystallographic data available for oxidation products of the amines are limited. From a previous study the crystal structure of a complex between 6-hydroxydopamine hydrochloride and its oxidized, p-quinonoid form was reported.[5] Recently, crystals of a cyclized oxidation product of adrenaline, 7-iodoadrenochrome, were attained using potassium iodate as an oxidizing agent.[6] This procedure proved to work also for the oxidation of 6-hydroxydopamine. In order to compare the oxidation products obtained, the present structure investigation was initiated.

EXPERIMENTAL

To 2 ml of a 0.004 M aqueous solution of 6-hydroxydopamine hydrobromide was added a few drops of a 0.1 M potassium iodate solution. By slow diffusion of an ethanol/ethyl ether mixture into the solution, thin, deep red, needle-formed crystals of the title compound appeared.

From the systematic absences of reflections the space group was determined to $P2_1/c$. Unit cell parameters and three-dimensional intensity data were obtained from a crystal of dimensions $0.18 \times 0.08 \times 0.03$ mm³ by the use of a SYNTEX $P\bar{1}$ automatic diffractometer with graphite crystal monochromated Mo$K\alpha$ radiation. Intensities of 1152 reflections with $2\theta \leq 55°$ were recorded using the $\omega - 2\theta$ scan technique. The scan speed varied between 1 and 1.5° min^{-1}, the scan range was 2°, and the ratio of background counting time to scan time was 0.7. 1058 reflections having net intensities larger than $2.5\sigma(I)$ were considered to be observed, the remaining reflections were excluded from the further calculations. The intensity data were corrected for Lorentz, polarization, and absorption effects. The computer programs employed during the present study are described in Ref. 7. Atomic form factors were obtained from Ref. 8 for the non-hydrogen atoms and from Ref. 9 for hydrogen.

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Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations for the non-hydrogen atoms. The anisotropic temperature factors are given by $\exp -2\pi^2(U_{11}a^{*2}h^2+U_{22}b^{*2}k^2+U_{33}c^{*2}l^2+U_{12}a^*b^*hk+U_{13}a^*c^*hl+U_{23}b^*c^*kl)$.

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I	−.2344(1)	.1987(1)	.1538(1)	.0335(4)	.0232(4)	.0316(4)	−.0022(6)	−.0064(3)	−.0039(6)
O1	.3701(13)	−.1648(6)	.1647(10)	.033(5)	.022(5)	.019(5)	−.000(4)	−.011(4)	.002(4)
O2	.3867(13)	.0036(6)	.2976(9)	.039(5)	.023(3)	.013(5)	−.001(4)	−.012(4)	.000(4)
O3	.1204(14)	.1146(6)	−.1883(10)	.059(7)	.022(5)	.018(3)	.004(5)	−.024(3)	.005(4)
N	.3997(21)	−.1357(7)	−.4733(18)	.033(7)	.014(6)	.027(7)	−.001(6)	−.014(6)	−.003(6)
C1	.2034(16)	−.0410(8)	−.1773(13)	.013(6)	.025(7)	.010(6)	−.003(5)	.001(5)	−.005(5)
C2	.2634(17)	−.1128(9)	−.0866(14)	.018(7)	.022(7)	.013(6)	−.004(5)	−.002(5)	−.003(5)
C3	.3235(16)	−.0998(9)	.0814(13)	.015(6)	.024(7)	.012(6)	−.000(6)	.000(5)	−.000(6)
C4	.3232(17)	−.0035(9)	.1551(14)	.018(6)	.023(7)	.016(7)	−.002(6)	.004(6)	.002(6)
C5	.2557(16)	.0671(8)	.0567(14)	.017(6)	.018(7)	.012(6)	.001(5)	−.004(5)	−.005(5)
C6	.1875(16)	.0540(8)	−.1079(14)	.013(6)	.021(7)	.019(7)	−.003(5)	−.002(5)	.001(5)
C7	.1383(21)	−.0486(9)	−.3504(16)	.031(8)	.018(7)	.024(8)	.003(6)	−.003(6)	.006(6)
C8	.1943(22)	−.1345(11)	−.4392(17)	.040(9)	.030(9)	.014(7)	−.006(7)	−.006(7)	−.001(6)

Table 2. Fractional coordinates with estimated standard deviations and isotropic thermal parameter for hydrogen atoms.

Atom	x	y	z	B(Å²)
HC2	.272(16)	−.182(7)	−.136(13)	1.4
H1C7	.175(18)	−.001(9)	−.394(15)	1.9
H2C7	−.020(18)	−.048(8)	−.358(14)	1.9
H1C8	.163(17)	−.186(9)	−.378(15)	2.2
H2C8	.144(18)	−.119(9)	−.542(16)	2.2
H1N	.434(17)	−.100(9)	−.549(15)	1.6
H2N	.423(23)	−.170(9)	−.465(19)	1.6
H3N	.466(17)	−.110(9)	−.407(15)	1.6

CRYSTAL DATA

$C_8H_8O_3NI$

Space group $P2_1/c$, monoclinic

$a = 7.074(3)$ Å, $b = 14.555(7)$ Å, $c = 8.264(2)$ Å, $\beta = 90.57(3)°$

$V = 850.8$ Å³, $M = 293.06$, $F(000) = 560$, $Z = 4$

D_{obs}(flotation) $= 2.25$ g cm^{-3}, $D_{calc} = 2.289$ cm^{-3}.

STRUCTURE DETERMINATION

The coordinates of the iodine atom were determined from a sharpened Patterson function. From a following weighted Fourier map [10] the positions of all non-hydrogen atoms were obtained. Subsequent Fourier and least-squares

Table 3. Bond angles (°; estimated standard deviations are 1°) and bond lengths involving hydrogen atoms (Å).

C1 – C2 – C3	121	C2 – HC2	1.08(11)
C2 – C3 – C4	120	C7 – H1C7	0.83(13)
C3 – C4 – C5	117	C7 – H2C7	1.12(12)
C4 – C5 – C6	124	C8 – H1C8	0.93(13)
C5 – C6 – C1	117	C8 – H2C8	0.94(13)
C6 – C1 – C2	122	N – H1N	0.85(12)
C7 – C1 – C6	114	N – H2N	0.55(14)
C7 – C1 – C2	124	N – H3N	0.81(13)
C1 – C6 – O3	120		
C5 – C6 – O3	123		
C6 – C5 – I	117		
C4 – C5 – I	119		
C5 – C4 – O2	127		
C3 – C4 – O2	116		
C4 – C3 – O1	119		
C2 – C3 – O1	121		
C1 – C7 – C8	116		
C7 – C8 – N	111		

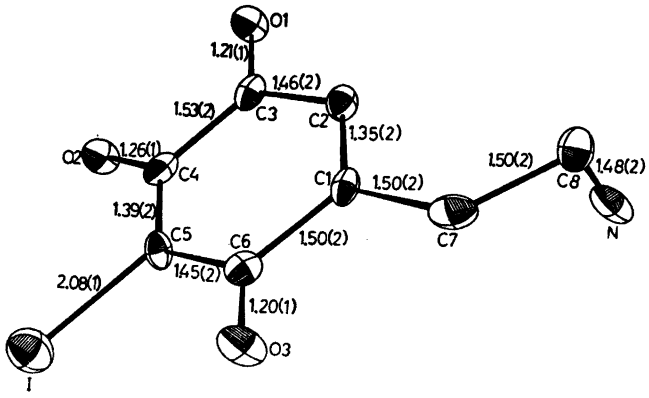

Fig. 1. 50 % probability ellipsoids and bond lengths (Å).

refinements yielded an R-factor of 0.06. A difference Fourier map calculated at this stage indicated the positions of all of the eight hydrogen atoms. Although the map showed relatively large electron density fluctuations, the electron density observed near carbon, nitrogen, and oxygen atoms was consistent with the localization of five hydrogen atoms bonded to carbons and the remaining three hydrogen atoms bonded to the nitrogen. The positional parameters of the H atoms were included in the final cycles of least-squares refinements. The isotropic thermal parameters of the hydrogens were kept constant with values equal to those of the atoms to which they were bonded. The refinements resulted in a conventional R-factor of 0.048 and a weighted R-factor of 0.053.

The final parameters for non-hydrogen atoms are listed in Table 1 and for hydrogen atoms in Table 2. The numbering of the atoms is indicated in Fig. 1, which also presents the ellipsoids of thermal motion and bond lengths. Bond angles, and also the bond lengths involving hydrogens, are given in Table 3.

The structure factor list may be obtained from this institute upon request.

DISCUSSION

The present study shows that an oxidation of 6-hydroxydopamine with potassium iodate has yielded a 5-iodo-3,6-quinone derivative of the compound. Formation of a corresponding quinonoid oxidation product of 6-hydroxydopamine has been reported from a previous structure investigation.[5] These studies confirm that 6-hydroxydopamine oxidation proceeds *via* formation of an open-chain *p*-quinone. The studies also seem to support the proposal that the quinone formed does not readily undergo an intramolecular cyclization reaction,[3]

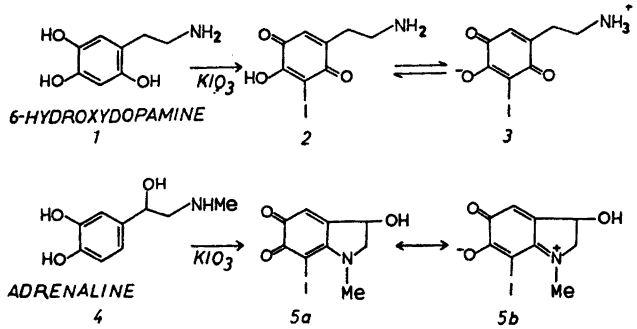

Fig. 2. Oxidation of 6-hydroxydopamine and adrenaline with potassium iodate.

which is reported to occur rapidly during oxidation of adrenaline and related catecholamines.[3,11] As illustrated in Fig. 2, the oxidation of 6-hydroxydopamine and adrenaline [6] solutions with potassium iodate has resulted in the formation of iodinated open-chain and cyclized oxidation products, respectively. The iodo-substituted *p*-quinonoid derivative of 6-hydroxydopamine is obtained in the base form. The molecules in the crystals appear to exist in the zwitterionic form *3* (Fig. 2), which corresponds to the proposed red chromophore appearing in oxidized solutions of 6-hydroxydopamine.[3]

The zwitterionic character of the molecule was indicated by the localization of hydrogen atoms, and is further supported by the short distance observed for the C4 – O2 bond, 1.26 Å. This bond length is significantly shorter than correspondingly found for the phenolic hydroxyl group in the hydrochloride of the 6-hydroxydopamine-*p*-quinone.[5] Otherwise, the values of bond lengths and bond angles obtained from the two studies agree within the accuracy of the measurements. The C4 – O2 bond distance of the present study is close to that reported for the C – O^- groups in the anions of 2,5-dihydroxy-*p*-benzoquinone and related compounds.[12] The high degree of conjugation observed in the latter symmetrical anions is not found in the present molecule, although a certain extent of charge delocalization into the ring system is indicated both by the C4 – O^- distance and a relative lengthening of the C4 – C5 double bond. Corresponding bond distances are observed for 7-iodoadrenochrome,[6] in which there are contributions from the two resonance structures *5a* and *5b* (Fig. 2).

Table 4. Deviations in Å of individual atoms from a least-squares plane.

Atoms defining the plane		Other atoms	
C1	0.026	I	−0.066
C2	0.000	O1	−0.099
C3	−0.022	O2	0.070
C4	0.016	O3	−0.107
C5	0.009	C7	0.043
C6	−0.031	C8	0.438
		N	1.884

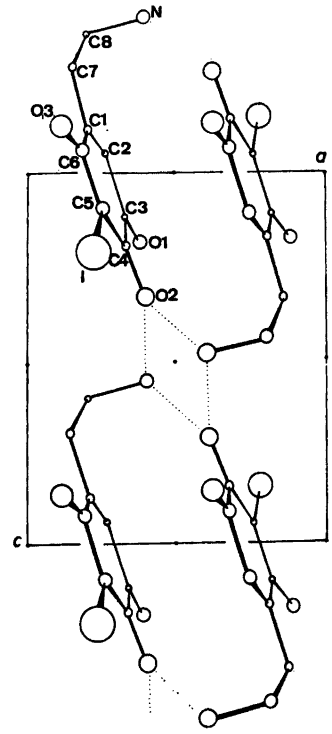

Fig. 3. The molecular arrangement in the (010) plane as viewed down the *b*-axis. Hydrogen bonds are indicated by dotted lines.

The quinone ring is planar within the error of the experiment. Atomic deviations from a least-squares plane are given in Table 4.

The conformation of the molecule deviates markedly from that commonly observed for crystalline phenylethylamine derivatives.[13–17] The torsion angle C6 – C1 – C7 – C8 (τ_1) is 165° and C1 – C7 – C8 – N (τ_2) is −71°. This means that the ethyl part of the side chain is situated close to the plane of the quinone ring, and the nitrogen atom in a *gauche* position relative to the ring system. The value of the τ_1 torsion angle corresponds to the one observed in the hydrochloride of the 6-hydroxydopamine-*p*-quinone,[5] but these are among the few crystal structures showing an exceptional conformation about the C1 – C7 bond.[13] The τ_1 angle is normally observed with a value of about ±90° in phenylethylamines, inclusive 6-hydroxydopamine when not being in the oxidized form.[5,14] It is, furthermore, a characteristic

feature to find this class of molecules with a maximally extended (*trans*) conformation in the crystals. The importance of a preference for the *trans* conformation has frequently been mentioned when discussing the mechanism underlying sympathomimetic activity.[13–18] Concerning the neurodegenerative action of 6-hydroxydopamine, one of the several theories proposed points to the significance of a molecular *gauche* conformation.[19] From a theoretical study performed on 6-hydroxydopamine and related polyhydroxyphenylethylamines it was indicated that the minimum energy conformation is a folded one, which was considered to be essential for the interaction of the molecules, or their ozidixed forms, with macromolecules.[19] A *gauche* conformation, however, is neither found in the crystals of pure 6-hydroxydopamine hydrochloride,[14] nor in the 1:1 complex with its oxidized, *p*-quinonoid form.[5] The *gauche* conformation observed in the present *p*-quinonoid molecule deviates from the one predicted from the theoretical computations,[19] having the exceptional small value of the τ_1 torsion angle. This conformation leads to a large N – O3 separation (4.78 Å), which excludes the possibility of an intramolecular hydrogen bond between the protonated amino group and the *ortho* oxygen atom. From the theoretical study such an intramolecular hydrogen bonding was suggested to provide a stabilization of a molecular *gauche* form.

The zwitterions of the 6-hydroxydopaminequinone are arranged in the crystals with close

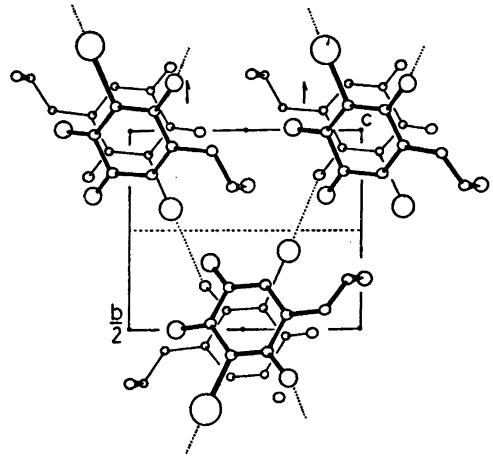

Fig. 4. The structure of half a unit cell as viewed down the *a*-axis. I···O3 interactions are indicated by dotted lines.

contacts between positively charged nitrogen atoms and negatively charged oxygen atoms, of 2.78 and 2.84 Å, respectively. The $N^+-H\cdots O^-$ interactions are representative of intermolecular hydrogen bonds, the depiction of which is given in Fig. 3 and Table 5. The hydrogen bond system in the crystals is linking the ions in chains along a crystallographic axis. This is an arrangement which is found to be characteristic for sympathomimetic amines existing in a zwitterionic form in the crystals.[15–17] The present crystal structure is built of chains of ions running nearly parallel to the

Table 5. Intermolecular distances.

a. Hydrogen bonded interactions	N---O (Å)	H---O (Å)	N – H---O(°)
N – H1N---O2($x,y,z-1$)	2.78	2.0	152
N – H3N---O2($-x+1,-y,-z$)	2.84	2.1	158
b. Other contacts (Å)			
N---O1($x,y,z-1$)	3.03		
N---O1($x,-y-\frac{1}{2},z-\frac{1}{2}$)	3.13		
I---C2($-x,-y,-z$)	3.77		
O1---C8($x,-y-\frac{1}{2},z+\frac{1}{2}$)	3.29		
O2---C8($x,y,z+1$)	3.26		
O2---C1($-x+1,-y,-z$)	3.12		
O3---C3($-x,-y,-z$)	3.28		
C1---C4($-x+1,-y,-z$)	3.41		
C3---C5($-x+1,-y,-z$)	3.23		
I---O3($x,-y+\frac{1}{2},z+\frac{1}{2}$)	3.12		

c-axis at $y=0$ and $y=\frac{1}{2}$. The ions are also stacked along the *a*-axis, so the crystals can be described as built of overlapping molecular chains extending in the (0 1 0) and (0 2 0) planes. The arrangement is shown in Fig. 3 for (0 1 0). As indicated in the figure are overlapping molecules linked in pairs through hydrogen bonds. The molecules are stacked with a separation between the ring centers of 3.47 and 3.73 Å. The ring planes are inclined at an angle of about 22° to the *a*-axis.

Van der Waals' interactions present in the crystals are given in Table 5. Additionally, there is observed an intermolecular I···O3 contact, 3.12 Å, being considerably shorter than the corresponding van der Waals' separation.[20] This indicates the presence of a charge-transfer interaction, as correspondingly suggested for the crystal structure of 7-iodoadrenochrome.[6] The system of I···O3 interactions (illustrated in Fig. 4) are connecting the molecular stacks of the (0 1 0) and (0 2 0) planes.

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