

The Crystal and Molecular Structure of 7-Iodoadrenochrome

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The structure investigation of a deep red-coloured compound obtained on oxidation of adrenaline with potassium iodate shows that the oxidation product is 7-iodoadrenochrome. The crystal structure was determined by X-ray methods using 886 observed reflections collected by counter diffractometer techniques. The crystals are monoclinic, space group $P2_1$ with $a = 8.407(4)$ Å, $b = 6.942(3)$ Å, $c = 9.171(4)$ Å, $\beta = 118.78(3)^\circ$. Least-squares refinements yielded a conventional R -factor of 0.058. Standard deviations in bond lengths are 0.01–0.04 Å and in bond angles 1–5°. The molecules are arranged in the crystals in stacks along the b -axis with an interplanar spacing of the almost parallel, overlapping, quinonoid six-rings of 3.55 Å. The interactions between neighbouring stacks consist of a rather short $I \cdots O = C$ contact of 3.20 Å, and a $O \cdots O$ contact of 2.81 Å corresponding to a hydrogen bond.

Aminochromes belong to a class of deep red-to violet-coloured compounds which are obtained on oxidation of catecholamines.¹ The aminochromes have attracted considerable attention for many years being intermediate products in the formation of dark polymeric pigments known as melanins.² The studies performed in order to elucidate the chemistry of aminochromes are numerous. The main information concerning this class of compounds is obtained from solution studies using spectroscopic methods.¹ Procedures have been reported for the synthesis of some aminochrome derivatives in the solid state,^{1,3,4} among them iodo-adrenochrome.⁵ The compounds isolated, however, have to the author's knowledge never been studied by X-ray methods. This is probably because the oxidation of catecholamines occurs very rapidly so that isolation of crystalline oxidation products is rather difficult. During the present study, deep red-coloured

crystals were successfully obtained from an adrenaline solution by the use of potassium iodate as an oxidizing agent. The crystals were not ideal for an X-ray study, being extremely thin needles, but the structural study seemed worthwhile in view of the lack of corresponding data for catecholamine oxidation products.

EXPERIMENTAL

(–) Adrenaline (1.5 mg) was suspended in water (2 ml) and a few drops of 1 M HCl added so that all the solid was dissolved. Oxidation of the solution was performed by adding 2 ml of a 0.04 M potassium iodate solution. After standing for some days at about 4°C, thin, deep red, needle-formed crystals of the title compound had separated from the reaction mixture. A crystal of dimensions $0.36 \times 0.04 \times 0.01$ mm³ was used for the X-ray study.

The systematic absence of reflections $0k0$ with k odd indicated space group $P2_1$, which was in accordance with the results of a Wilson plot demonstrating a non-centrosymmetric space group. Unit cell parameters and three-dimensional intensity data were obtained from measurements on a SYNTEX P1 automatic diffractometer. Intensities were recorded using graphite crystal monochromated $MoK\alpha$ radiation and the $\omega - 2\theta$ scan technique. Scan speed was 1° min^{-1} , scan range 2.4° , and background counting time/scan time was 0.7. The measurements included 968 reflections with $2\theta \leq 55^\circ$. Of these, 82 reflections having $I < 2\sigma(I)$ were defined as unobserved and were excluded from the structure analysis.

Corrections for Lorentz, polarization, and absorption effects were performed. The computer programs employed during the present work are described in Ref. 6. The atomic scattering factors used were obtained from Ref. 7 for non-hydrogen atoms and from Ref. 8 for the hydrogens.

CRYSTAL DATA

7-Iodoadrenochrome, $C_9H_9O_3NI$
 Space group $P2_1$, monoclinic
 $a = 8.407(4) \text{ \AA}$, $b = 6.942(3) \text{ \AA}$, $c = 9.171(4) \text{ \AA}$,
 $\beta = 118.78(3)^\circ$,
 $V = 469.1 \text{ \AA}^3$, $M = 305.07$, $F(000) = 292$, $Z = 2$,
 $D_{\text{obs}}(\text{floatation}) = 2.10 \text{ g cm}^{-3}$, $D_{\text{calc}} = 2.161 \text{ g cm}^{-3}$

STRUCTURE DETERMINATION

Coordinates of the iodine atom were determined by use of the Patterson function. A subsequent weighted Fourier synthesis⁹ revealed the positions of all non-hydrogen atoms. Fourier and least-squares refinements yielded an R -factor of 0.070. The electron density of a difference Fourier map calculated at this stage showed local maxima near the positions expected for all hydrogen atoms. The result of the difference map was, however, rather uncertain, showing peaks and troughs distributed all over in an irregular manner. When introducing the hydrogen atoms in the structure factor calculations, an improvement of the R -factor was obtained. Hydrogen contributions were, therefore, included in the final least-squares calculations, but hydrogen parameters were not refined. The parameters used for the hydrogen atoms are given in Table 2. The refinements yielded a conventional R -factor of 0.058 and a weighted R -factor of 0.055.

The final parameters for non-hydrogen atoms are given in Table 1. The numbering of the atoms follows the convention commonly adopted for aminochromes. This is shown in Fig. 2, which also presents bond lengths in the molecule. Bond angles are listed in Table 3.

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

DISCUSSION

The present study demonstrates a cyclization of the adrenaline molecule in accordance with the reaction scheme commonly accepted for catecholamine oxidation,¹ which is illustrated in Fig. 1. The reaction product obtained by oxidation of adrenaline with potassium iodate has previously been described as 2-iodoadrenochrome.⁵ From later NMR studies¹⁰

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

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I	.4194(1)	.2140(0)	.0975(2)	.0288(5)	.0627(9)	.0403(6)	-.0041(24)	.0171(4)	.0084(25)
O(1)	.462(2)	.286(2)	.444(2)	.043(8)	.081(17)	.048(9)	.014(8)	.012(7)	-.006(8)
O(2)	.161(1)	.238(8)	.193(1)	.039(6)	.060(19)	.025(6)	.006(16)	.019(6)	.004(16)
O(3)	.192(1)	.215(10)	.285(1)	.033(6)	.104(15)	.029(6)	.006(29)	.015(5)	-.013(27)
N(1)	.011(2)	.228(7)	.300(2)	.044(8)	.071(19)	.036(9)	.027(19)	.021(7)	-.050(19)
C(2)	-.171(3)	.261(7)	.440(2)	.047(11)	.085(43)	.026(10)	.008(15)	.005(9)	-.017(15)
C(3)	-.303(2)	.202(12)	.387(2)	.036(10)	.100(25)	.017(8)	-.031(33)	.003(8)	-.019(33)
C(4)	-.249(2)	.208(11)	.087(2)	.039(8)	.034(11)	.039(9)	-.026(38)	.024(7)	-.013(35)
C(5)	-.118(2)	.204(10)	.086(2)	.036(19)	.036(19)	.019(7)	.012(20)	.010(8)	-.000(20)
C(6)	.086(2)	.214(6)	.134(2)	.064(11)	.068(15)	.059(11)	.052(20)	.037(10)	.057(20)
C(7)	.142(2)	.245(2)	.015(2)	.041(7)	-.042(8)	.015(7)	.000(6)	.019(6)	-.007(5)
C(8)	.005(2)	.209(6)	.154(1)	.045(9)	-.012(9)	.011(6)	.020(20)	.010(6)	-.009(20)
C(9)	-.193(2)	.198(8)	.201(2)	.031(7)	.019(18)	.025(7)	.002(16)	.010(6)	-.015(16)
C(10)	.143(3)	.233(14)	.347(3)	.108(16)	.074(28)	.070(13)	-.033(33)	.083(13)	-.045(28)

Table 2. Fractional coordinates for hydrogen atoms. Isotropic thermal parameters are given with values equal to those of the atoms to which the hydrogens are covalently bonded.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> (Å ²)
H1C(2)	-.19	.41	-.47	5.4
H2C(2)	-.19	.18	-.54	5.4
HC(3)	-.36	.07	-.44	4.5
HC(4)	-.39	.22	-.12	2.8
H1C(10)	.09	.23	-.48	4.7
H2C(10)	.22	.13	-.30	4.7
H3C(10)	.22	.35	-.31	4.7
HO(1)	-.57	.20	-.47	4.2

it has been reported that the iodine atom is in the 7-position, which is confirmed by the present structure analysis.

A quinonoid character of the adronochrome molecule is inferred by the values of the bonds C(4)–C(9), C(4)–C(5) and C(5)–O(2) of 1.34, 1.44 and 1.22 Å, respectively. These are normal values for C=C, C–C and C=O bonds in benzoquinones.¹¹ The bond distances C(6)–O(3) (1.24 Å) and C(5)–C(6) (1.56 Å) are further-

Table 3. Bond angles (°) with estimated standard deviations in parentheses.

Bond angle	
N(1)–C(2)–C(3)	108(2)
C(2)–C(3)–C(9)	103(2)
C(3)–C(9)–C(8)	109(1)
C(9)–C(8)–N(1)	106(1)
C(8)–N(1)–C(2)	111(1)
C(7)–C(8)–N(1)	131(2)
C(8)–N(1)–C(10)	137(2)
C(2)–N(1)–C(10)	112(2)
C(2)–C(3)–O(1)	122(5)
O(1)–C(3)–C(9)	114(3)
C(4)–C(5)–C(6)	118(2)
C(5)–C(6)–C(7)	122(1)
C(6)–C(7)–C(8)	115(2)
C(7)–C(8)–C(9)	121(1)
C(8)–C(9)–C(4)	122(1)
C(4)–C(9)–C(3)	129(2)
C(9)–C(4)–C(5)	120(2)
C(4)–C(5)–O(2)	122(2)
O(2)–C(5)–C(6)	119(2)
C(5)–C(6)–O(3)	115(1)
O(3)–C(6)–C(7)	123(2)
C(6)–C(7)–I	116(1)
I–C(7)–C(8)	123(1)

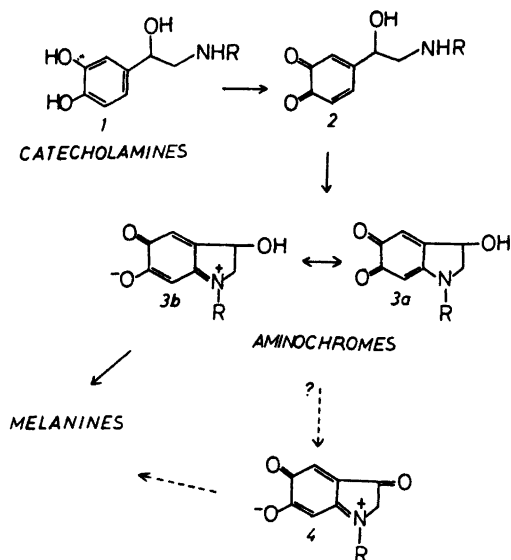


Fig. 1. Oxidation pathways of catecholamines.¹

more in agreement with those observed for diketonic compounds,¹¹ indicating an *o*-quinonoid character of the molecule corresponding to structure 3a in Fig. 1. However, the C(6)–C(7) and C(7)–C(8) bond lengths of 1.39 and 1.44 Å, respectively, indicate a contribution from resonance structure 3b, which is the one normally used to describe aminochrome compounds. The N(1)–C(8) bond length is shorter than the corresponding single-bond value, but

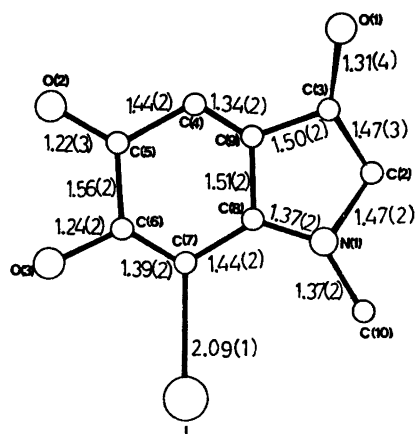


Fig. 2. Bond lengths (Å) with estimated standard deviations in parentheses.

Table 4. Deviation in Å of individual atoms from least-squares planes.

Atoms defining the plane		Other atoms	
(1)			
C(4)	0.075	O(2)	0.251
C(5)	-0.021	O(3)	-0.107
C(6)	-0.064	I	-0.254
C(7)	0.117	C(3)	0.047
C(8)	-0.066	N(1)	0.052
C(9)	-0.031	O(1)	0.712
		C(2)	0.374
(2)			
N(1)	0.009	C(2)	0.266
C(3)	-0.010	O(1)	0.639
C(8)	-0.016	C(10)	-0.087
C(9)	0.015		

the distance of 1.37 Å is closer to that commonly found for α,β -unsaturated nitrogen heterocyclic than for corresponding aromatic nitrogen compounds.¹³ Altogether, there seems to be a certain degree of π -delocalization extending through the entire O(3)-C(6)-C(7)-C(8)-N(1) region of the molecule. This is also suggested by the IR spectrum of the crystals showing peaks in the carbonyl region at 1600 and 1550 cm^{-1} , which have been attributed¹ to the conjugated system just mentioned, and appear at lower frequencies than the peaks assigned to the C(5)=O(2) and C(4)=C(9) bonds at 1665 and 1645 cm^{-1} . The nitrogen atom is situated in the plane of the aromatic ring, as seen from the calculations of least-squares planes given in Table 4. The sum of the bond angles about N(1), being 360°, is consistent with an sp^2 -hybridization of the atom. The N(1)-C(2) distance of 1.47 Å corresponds to a normal C-N single-bond. The N(1)-C(10) single-bond, on the other hand, is remarkably short being equal to the N(1)-C(8) bond. The methyl group appears to be somewhat displaced in the direction away from the C(7)-I bond, as indicated by the values of the exocyclic C-N-C angles.

It should be noted that the standard deviations of the atomic parameters obtained in the present structure determination are rather large. This is probably mainly an effect of the iodine atom dominating the X-ray scattering. By examining the standard deviations it can be seen that the precision obtained in the bond

lengths and angles involving the C(3) and O(1) atoms is the least satisfactory. The value observed for the C(3)-O(1) distance (1.31 Å) lies between those commonly found for C-OH and C=O groups. Of these groups, the former should be present in aminochrome compounds, whereas the latter implies a 3-oxoaminochrome derivative corresponding to compound 4 in Fig. 1. As indicated in the figure, a catecholamine oxidation pathway leading to 3-oxoaminochromes has been a subject of discussion.¹ Thus, it would have been of value if an exact characterization of the C(3)-O(1) group of the present adrenaline oxidation product could have been given. It seems likely, however, that the reaction product obtained from the adrenaline solution is an iodo-substituted adrenochrome compound containing a 3-hydroxyl group. As shown in Table 4, the bonding arrangement about the C(3) atom seems to be non-planar in accordance with an sp^3 -hybridization of the atom. This was also suggested by the locations of hydrogen atoms, but as earlier mentioned, no definite conclusions could be reached in that connection. Support for the presence of a hydroxyl group in the 3-position arises from the building of the crystal structure. In the crystals the molecules are arranged with a short intermolecular O(1)···O(3) contact of 2.81 Å. This indicates the presence of a hydrogen bond, in which the O(1) atom should probably act as a hydrogen donor. Further evidence for a hydrogen-bonded -OH group is given by the IR spectrum of the crystals showing a strong peak at 3400 cm^{-1} . The spectrum does not give evidence for the presence of any oxidized form corresponding to a 3-oxoadrenochrome derivative in the crystals. Although the carbonyl region is rather complex, one should have expected a C=O group in the five-ring to give a peak at a higher frequency than the conjugated aromatic C=O groups.

The molecular arrangement in the crystals is illustrated in Fig. 3. The crystals are built of almost parallel molecules stacked along the *b*-axis. The molecules in the stacks are arranged with an overlap between the quinonoid six-rings. The distance between the ring centers is 3.55 Å. The only short intermolecular contact within the stacks, apart from the ring interactions mentioned, is a C(4)···I separation

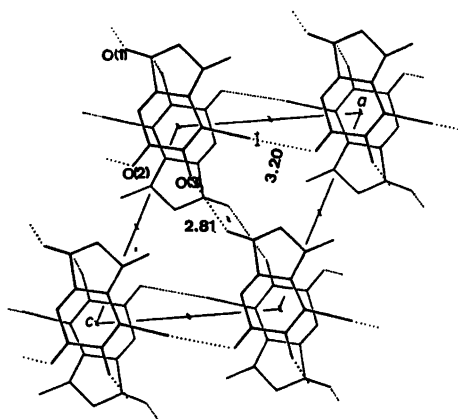


Fig. 3. The structure as viewed down the b -axis.

of 3.70 Å. Between the stacks are two intermolecular distances shorter than commonly found for van der Waals' contacts. One is between the O(1) oxygen atom and the O(3) atom of the neighbouring molecule situated in the relative position. $x-1, y, z-1$. This contact corresponds to a normal O—H...O hydrogen bond, the presence of which has been discussed above. The second is a I...O(2) ($x+1, y, z$) contact of 3.20 Å, which is more than 0.3 Å shorter than the corresponding van der Waals' separation given by Pauling.¹³ The C(7)—I...O(2) angle is 170°. This arrangement indicates the presence of a charge transfer interaction in the crystals, of the type suggested to occur between a halogen atom bonded to carbon and a lone-pair donor atom.¹⁴ Such a linear C—I...O arrangement is reported to constitute a charge transfer bond in the addition compound between iodoform and 1,4-dioxane.¹⁵ The I...O separation observed in the latter crystal structure, however, is markedly shorter, being 3.04 Å.

The arrangement of I...O(2) and O(1)...O(3) interactions in the crystals of 7-iodoadrenochrome, which are linking adjacent stacks of molecules, is depicted in Fig. 3. In view of a contribution from a zwitterionic structure corresponding to resonance structure 3b, one might possibly have expected to observe an approach between N(1) and O(3) atoms of neighbouring molecules in the crystals. A close contact between positively charged nitrogen atoms and negatively charged oxygen atoms

is found to constitute a characteristic feature of the crystal structures where sympathomimetic amines are existing in a zwitterionic form.¹⁶⁻¹⁸ In the present study, however, there are no intermolecular N...O contacts observed with a value less than 3.60 Å.

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Received October 18, 1978.