

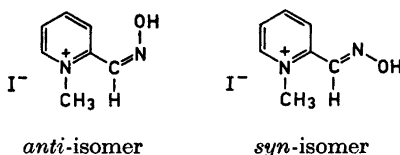
A Crystallographic Study of N-Methyl-pyridine-2-aldoxime (2-PAM) Halides

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Crystal data of three halides of the "nerve gas" antidote 2-PAM are presented. A crystal structure determination carried out on the iodide shows that the molecules are in the *syn*-form. The planar molecules form a layered structure which explains the mechanical and optical properties of the crystals. Whereas the bond distances and bond angles of the pyridine ring are quite normal, the C—N bond in the oxime part shows a less pronounced double bond character than usually found in oximes. This feature may depend on the interaction of the iodide ion which is closer to the oxime oxygen than a normal van der Waals distance.

The excellent antidotal activity of N-methyl-pyridine-2-aldoxime iodide (usually denoted pralidoxime or 2-PAM) for "nerve gas" poisoning¹ was simultaneously discovered by Davies and Green² and Wilson and Ginsburg.³ The effect of 2-PAM depends on its ability to reactivate acetylcholinesterase which has been blocked by toxic organophosphates through phosphorylation of the enzyme's active site. Wilson⁴ advanced a molecular complementary theory on the reactivation of inhibited acetylcholinesterase which predicted that the *anti*-isomer of 2-PAM was the effective reactivator whereas the *syn*-isomer should be inactive.



This concept was not supported by Poziomek *et al.*⁵ who found that the molecular magnetic resonance spectra of 4-PAM indicated that the *syn*-form was the active one. In which of the two isomers the antidote really exists seems not yet to have been established.

EXPERIMENTAL

Crystal data. Well-crystallized samples of the chloride, the bromide, and the iodide of the antidote were obtained from Department I, Research Institute of National Defence, Sundbyberg. X-Ray data were determined from rotation and Weissenberg photographs in a Nonius integrating Weissenberg camera. In addition, more accurate unit cell dimensions of the iodide were gained from rotation photographs in a 190 mm diameter cylinder camera. For calibration the crystals were coated with silicon powder ($a_0 = 5.4306$ Å). Ni-filtered Cu-radiation was used throughout. The density was determined by flotation in mixtures of organic fluids. The crystal data of the three halides are collected in Table 1.

Table 1. Crystal data of 2-PAM halides.

Formula: M.W.	$C_7H_9N_2O \cdot Cl$ 172.6	$C_7H_9N_2O \cdot Br$ 217.1	$C_7H_9N_2O \cdot I$ 264.1
Colour and form:	colourless prisms elongated along b	colourless prisms elongated along b	yellow prisms or needles elongated along b
Crystal system and class:	triclinic, $\bar{1}$	triclinic, $\bar{1}$	monoclinic, $2/m$
Unit cell dimensions:			
axes (Å)			
a	7.13 ± 0.01	7.28 ± 0.01	7.475 ± 0.001
b	7.19 ± 0.01	7.32 ± 0.01	6.518 ± 0.001
c	8.88 ± 0.01	9.04 ± 0.01	9.316 ± 0.002
angles			
α	$75.9^\circ \pm 0.1^\circ$	$75.4^\circ \pm 0.1^\circ$	—
β	$94.7^\circ \pm 0.1^\circ$	$95.0^\circ \pm 0.1^\circ$	$95.01^\circ \pm 0.01^\circ$
γ	$113.9^\circ \pm 0.1^\circ$	$114.5^\circ \pm 0.1^\circ$	—
Axial ratio ($a:c$):	1:1.245	1:1.242	1:1.246
Volume (Å ³):	403.6	424.7	452.14
Z:	2	2	2
D_m (g·cm ⁻³):	1.42	1.70	1.94
D_x (g·cm ⁻³):	1.42	1.70	1.940
Absent spectra:	none	none	($0k0$) when k is odd
Space group:	$P\bar{1}$	$P\bar{1}$	$P2_1/m$

The three 2-PAM salts all exhibited a very strong birefringence and a perfect cleavage parallel to {010}. In addition, the iodide had a less pronounced cleavage parallel to {001}. From Table 1 it is evident that the chloride and the bromide are isomorphous. These triclinic compounds show many similarities to the monoclinic iodide. So, for example, is the β -angle and the a to c ratio closely the same in the three halides. Multiple twinning on (010) was frequently observed in the bromide and such twins thus simulated the higher monoclinic symmetry of the iodide.

Intensity data collection of 2-PAM iodide. For the collection of three-dimensional data an acicular 2-PAM iodide crystal bounded by the forms {100}, {001}, and {010}, having a cross-section of 0.040×0.042 mm, was cut parallel to the {010}-cleavage so that a 0.039 mm long fragment of almost cubic shape was obtained. The choice of the iodide was made because of its monoclinic symmetry and its use as an antidote. Intensity data were collected from equi-inclination Weissenberg photographs with the usual multiple film technique. Six layers on the b -axis ($k = 0-5$) with the zero-layer of the a -axis for cross correlation were recorded with Ni-filtered $CuK\alpha$ radiation. The photographic density of the reflexions and corresponding background was determined in a microdensitometer. A satisfactorily consistent set of intensity data for 706 independent reflexions (representing 79 % of the total possible in the recorded layers) was derived from about 1600 observed intensities. The non-observed reflexions were given half the

Table 2. Observed and calculated structure factors.

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0	1	15.1	13.1	0	2	16.6	-80.6	0	3	18.0	-172.2	0	4	19.4	-312.2	0	5	20.8	-462.2	0	6	22.2	-612.2	0	7	23.6	-762.2	0	8	25.0	-912.2	0	9	26.4	-1062.2	0	10	27.8	-1212.2	0	11	29.2	-1362.2	0	12	30.6	-1512.2	0	13	32.0	-1662.2	0	14	33.4	-1812.2	0	15	34.8	-1962.2	0	16	36.2	-2112.2	0	17	37.6	-2262.2	0	18	39.0	-2412.2	0	19	40.4	-2562.2	0	20	41.8	-2712.2	0	21	43.2	-2862.2	0	22	44.6	-3012.2	0	23	46.0	-3162.2	0	24	47.4	-3312.2	0	25	48.8	-3462.2	0	26	50.2	-3612.2	0	27	51.6	-3762.2	0	28	53.0	-3912.2	0	29	54.4	-4062.2	0	30	55.8	-4212.2	0	31	57.2	-4362.2	0	32	58.6	-4512.2	0	33	60.0	-4662.2	0	34	61.4	-4812.2	0	35	62.8	-4962.2	0	36	64.2	-5112.2	0	37	65.6	-5262.2	0	38	67.0	-5412.2	0	39	68.4	-5562.2	0	40	69.8	-5712.2	0	41	71.2	-5862.2	0	42	72.6	-6012.2	0	43	74.0	-6162.2	0	44	75.4	-6312.2	0	45	76.8	-6462.2	0	46	78.2	-6612.2	0	47	79.6	-6762.2	0	48	81.0	-6912.2	0	49	82.4	-7062.2	0	50	83.8	-7212.2	0	51	85.2	-7362.2	0	52	86.6	-7512.2	0	53	88.0	-7662.2	0	54	89.4	-7812.2	0	55	90.8	-7962.2	0	56	92.2	-8112.2	0	57	93.6	-8262.2	0	58	95.0	-8412.2	0	59	96.4	-8562.2	0	60	97.8	-8712.2	0	61	99.2	-8862.2	0	62	100.6	-9012.2	0	63	102.0	-9162.2	0	64	103.4	-9312.2	0	65	104.8	-9462.2	0	66	106.2	-9612.2	0	67	107.6	-9762.2	0	68	109.0	-9912.2	0	69	110.4	-10062.2	0	70	111.8	-10212.2	0	71	113.2	-10362.2	0	72	114.6	-10512.2	0	73	116.0	-10662.2	0	74	117.4	-10812.2	0	75	118.8	-10962.2	0	76	120.2	-11112.2	0	77	121.6	-11262.2	0	78	123.0	-11412.2	0	79	124.4	-11562.2	0	80	125.8	-11712.2	0	81	127.2	-11862.2	0	82	128.6	-12012.2	0	83	130.0	-12162.2	0	84	131.4	-12312.2	0	85	132.8	-12462.2	0	86	134.2	-12612.2	0	87	135.6	-12762.2	0	88	137.0	-12912.2	0	89	138.4	-13062.2	0	90	139.8	-13212.2	0	91	141.2	-13362.2	0	92	142.6	-13512.2	0	93	144.0	-13662.2	0	94	145.4	-13812.2	0	95	146.8	-13962.2	0	96	148.2	-14112.2	0	97	149.6	-14262.2	0	98	151.0	-14412.2	0	99	152.4	-14562.2	0	100	153.8	-14712.2

minimum observed intensity when included in the calculations. Lorentz and polarization correction was applied in the usual way. No correction was made for absorption on account of the minute size and the almost equidimensional shape of the specimen. The data were placed on a common scale by correlations among the reflexions recorded more than one time.

From the systematic absence alone the space group could not be uniquely determined; both the non-centric $P2_1$ and the centric $P2_1/m$ were possible. Since iodine is an anomalous scatterer to $\text{CuK}\alpha$ radiation the intensities of the hkl and $\bar{h}\bar{k}l$ reflexions of the non-centric projection (100) in space group $P2_1$ should be non-equivalent. However, no such effect was detected implying that the centric space group $P2_1/m$ was the most probable. A careful examination of the faces of well-developed crystals showed that they were holohedral leaving $P2_1/m$ as the only possible space group.

DETERMINATION OF THE STRUCTURE OF 2-PAM IODIDE

A Patterson map was calculated for the projection down [010]. The iodine position was readily located at: $x/a = 0.960$, $z/c = 0.804$. The iodine alone, given, an isotropic temperature factor $B = 2.5 \text{ \AA}^{-2}$, gave an agreement index $R = 0.192$ ($R = \sum |F_o - F_c| / \sum |F_o|$). A two-dimensional electron density map of the same projection was calculated with the phases determined by the iodine. All the atoms except hydrogens were immediately identified. A new set of structure amplitude calculations with the isotropic temperature factors of $B = 3.5 \text{ \AA}^{-2}$ for the light atoms and $B = 2.8 \text{ \AA}^{-2}$ for the iodine atom resulted in an R -value = 0.129 for the 156 observed $h0l$ reflexions. Corresponding electron-density projection along the b axis gave a good resolution enabling the determination of preliminary x and z coordinates. These calculations were carried out on the computers WEGEMATIC 1000 and IBM 1401.

Table 3. Atomic and thermal parameters and their estimated standard deviation. The positional coordinates for light atoms ($\times 10^4$) and for iodine ($\times 10^6$) are in fractions of the unit cell axes; $y = 1/4$.

Atom	x	σ_x	z	σ_z	B	σ_B
C(1)	7095	26	1504	21	3.27	0.44
C(2)	5593	30	562	24	4.29	0.55
C(3)	3880	38	1067	32	6.28	0.38
C(4)	3779	29	2569	23	4.00	0.53
C(5)	5321	24	3500	19	2.72	0.40
C(6)	8657	26	3879	21	3.33	0.43
C(7)	5280	24	5075	20	2.86	0.40
N(1)	6930	17	2919	14	2.02	0.28
N(2)	3649	25	5535	21	4.76	0.49
O	3796	21	7028	18	4.89	0.40
I	96098	16	80476	14	*	*

* Anisotropic thermal parameters ($\times 10^4$) for iodine are:

$$\begin{array}{cccc} \beta_{11} & \beta_{22} & \beta_{33} & \beta_{13} \\ 135 \pm 2 & 217 \pm 11 & 78 \pm 1 & -17 \pm 1 \end{array}$$

β_{ij} are the coefficients in the expression: $\exp \{ -(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{13}hl) \}$.

THREE-DIMENSIONAL REFINEMENT

The three-dimensional refinement of all parameters including individual temperature factors as well as six scale factors was carried out on an IBM 7090 computer with a full matrix least squares program.⁶ The hydrogen atoms were omitted throughout the calculations. Structure factors were calculated with the scattering factors tabulated in *International Tables for X-ray Crystallography*.⁷ Using only observed structure factors and isotropic temperature factors a discrepancy index of $R = 0.076$ was obtained after 3 cycles of refinement. When the iodine atom alone was assigned anisotropic thermal parameters the R -index dropped to 0.071 with an improvement of the standard deviations of all the atomic coordinates. Corresponding R -value with non-observed reflexions included was 0.092. The introduction of anisotropic temperature factors also for the light atoms resulted in a slight drop of the R -value to 0.068 but did not improve the positional coordinates significantly. The final observed and calculated structure amplitudes in Table 2 and the positional coordinates in Table 3 are taken from the last cycle in which the light atoms were isotropic ($R = 0.071$).

An attempt was also made to refine the structure on the noncentric space group $P2_1$ instead of the initially chosen $P2_1/m$. The iodine was kept fixed whereas the light atoms were displaced randomly by a small amount from the mirror plane. The R -value did not improve past the corresponding value in $P2_1/m$ and the shifts in the position of the atoms was not systematic but the y -coordinates oscillated around the mirror plane. Since the non-centric structure contains more parameters than the centric one, the standard deviation for the positional coordinates actually increased. It was concluded that

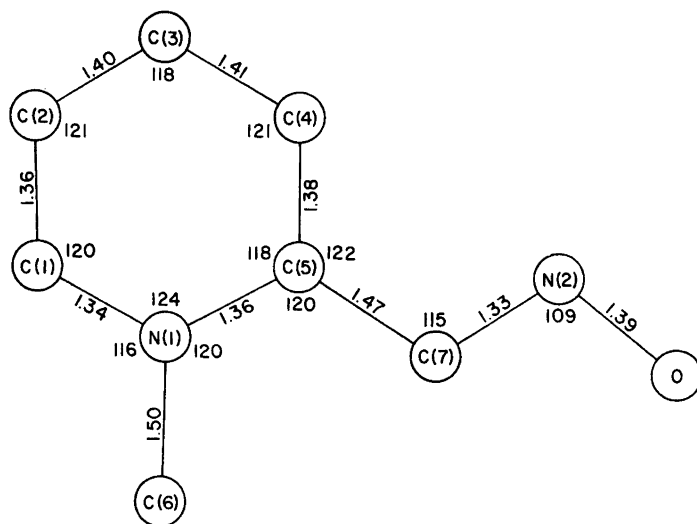


Fig. 1. Intramolecular bond lengths and angles.

the initially chosen centric space group was preferable and the following discussion is based on the parameters of the centrosymmetric structure listed in Table 3.

DISCUSSION

The bond lengths and bond angles were evaluated on an IBM 7090 computer and are shown in Fig. 1. As was expected by a structure of the present kind, where the major part of the intensity of most reflexions is determined by the contribution of the iodine atom, the accuracy in the bond lengths and bond angles is not very high. The estimated standard deviation in the bond lengths thus varied between 0.02 Å and 0.03 Å whereas the estimated standard deviation in the bond angles varied between 1.4° and 2.2°. Although the structure determination is not of a high degree of accuracy the general features of the molecule are clearly evident (Figs. 1 and 2). The antidote, 2-PAM iodine, thus appears in the *syn*-form which seems to be the most stable configuration. The shape and size of the pyridine ring is very close to that in other pyridine derivatives such as pyridine hydrochloride,⁸ nicotinic acid,⁹ nicotinamide,¹⁰ and α -pyridoin.¹¹ The size and configuration of the oxime part is also consistent with the bond lengths and bond angles found in other oximes.¹² The C(7)—N(2) bond (1.33 Å) is, however, longer

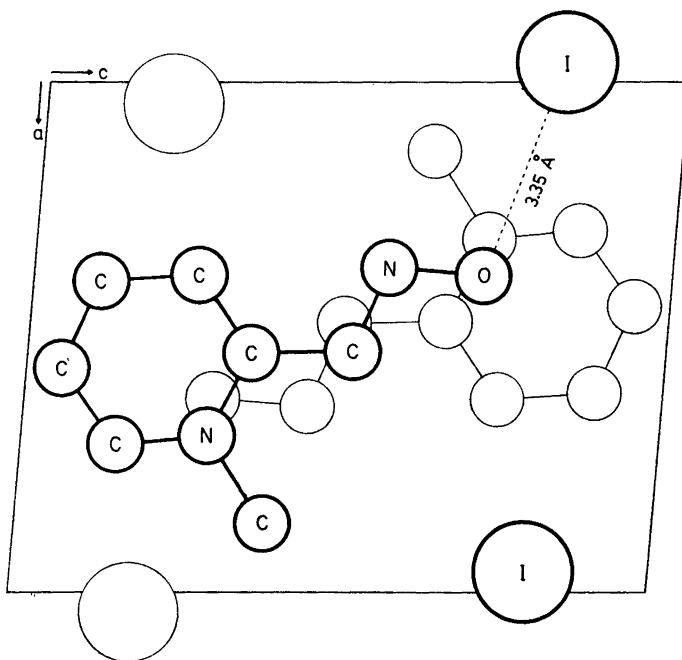
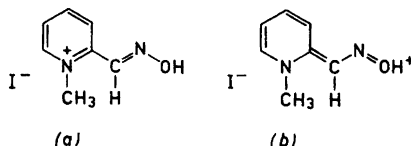


Fig. 2. Projection of the structure on (010). Atoms in heavier outlines at $y = \frac{1}{4}$, and lighter at $y = \frac{3}{4}$.

than that ordinarily found in oximes (1.23–1.29 Å) suggesting a less pronounced double bond character than is usually encountered. The N(2)—O bond is in addition slightly shorter (1.39 Å) than the corresponding bond (1.415 Å) in formamide oxime.¹³ The rather small C—N—O bond angle characteristic of oximes (110°–112°) is also found in the 2-PAM molecule (109°). The present structure determination suggests that 2-PAM essentially can be described in terms of resonance between the two structures (a) and (b) with a large predominance for the former. This is in agreement with infrared and dipole moment data of the basic form.¹⁴



The latter structure may explain the only short distance found in the structure, the O...I⁻ distance (3.35 Å) which is significantly shorter than the normal iodine-oxygen van der Waals contact (3.55 Å), indicating a weak charge-transfer bond.¹⁵

The crystal structure of 2-PAM iodide explains the extremely high birefringence of this compound as well as the pronounced perfect cleavage of the crystals parallel to the plane of the molecules.

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