SYNTHESIS AND CRYSTAL STRUCTURE OF HYDROGEN-BONDED LONG-CHAIN OF 1:1-METHANOL:1-[N-METHYLPYRIDOXYLIDENIUM]-2-[2^1-PYRIDYL]HYDRAZINE IODIDE

Schelly Avramovici-Grisaru[a], Shmuel Cohen[b], and Shalom Sarel[a(*)]

[a]Department of Pharmaceutical Chemistry, and [b]Chemical Crystallography Unit, The Hebrew University, P.O. Box 12065, Jerusalem 91120, Israel

Abstract - The synthesis and N-monomethylation [(5)—>(6a)] of 1-[pyridoxylidene]-2-[2^1-pyridyl]hydrazine (5) are herein described. The product, 1-[N-methylpyridoxylidenium]-2-[2^1-pyridyl]hydrazine iodide (6a), on recrystallization from methanol yielded hydrogen-bonded long-chains of 1:1-methanol:(6a) of crystal structure (8) [Figure 2]. The reaction of (6a) with aqueous $HClO_4$ afforded dimers of the corresponding diperchlorate of structure (6b) [Figure 1]. The formation of (8) is rationalized in terms of cooperative hydrogen-bonding, arising from the ability of the alcoholic OH group to function both as acceptor and donor. The dimeric crystal structure of (6b) is envisioned to arise from an alternative mode of H-bonding, namely, the "three- center" geometry, influenced by the ClO_4 oxygen acceptors.

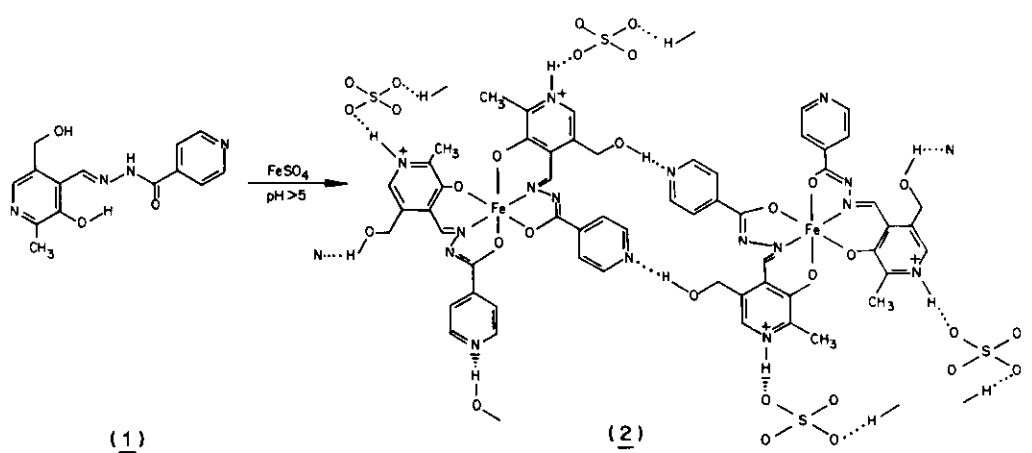
INTRODUCTION

1-[Pyridoxylidene]-2-[isonicotinoyl]hydrazine, [pyridoxal isonicotinoyl hydrazone, PIH, (1)],[1] is a representative of a new class of orally active iron chelators which are capable of removal of toxic accumulation of iron from the body. Its discovery a decade ago has opened new vista of its biochemistry,[2] pharmacological and medicinal chemistry,[3] physical organic chemistry,[4] coordination chemistry,[5] and cell biology.[6]

Studies have shown that whereas the crystal structure of (1) is dimeric,[7] involving hydrogen contacts between the hydrazinic NH, a molecule of water, and the pyridoxylidenic OH (phenolic), as an acceptor group, the crystal structure of $[PIH]_2Fe$ complex[5c] is characterized by a hydrogen-bonded long-chain of supramolecular alignment of structure (2) (see, Scheme 1). In contrast to (1), the hydrogen contacts in (2) involve the pyridoxylidenic alcoholic OH as a donor,

and the isonicotinoyl ring nitrogen, as an acceptor. There is another hydrogen contact in (2), which involves the counter-ion oxygen acceptor, SO_4^{2-}, and the proton attached to the pyridoxylidenic ring nitrogen. This suggested that the alcoholic hydroxyl group in (2) may play a pivotal role in stabilizing the hydrogen-bonded long-chain crystal structure. Lately, we have observed[8] that the biological properties of the pyridoxal-based chelators could be improved considerably if the acyl-carbonyl group in (1) is eliminated. This provided a new generation of iron mobilizers which are: therapeutically safe, orally active, displaying high affinity to iron, of which 1-[pyridoxylidene]-2-[2^1-pyridyl]-hydrazine (5) is a representative. We sought, therefore, to examine the effects of aromatic ring-nitrogen quaternizations (i.e. methiodination) of (5) on its biological property and chemical structure. Towards this end we attempted the syntheses of 1-[N-methylpyridoxylidenium]-2-[2^1-pyridyl]hydrazine iodide (6a), and of 1-[N-methylpyridoxylidenium]-2-[2^1-N-methylpyridylium]hydrazine diiodide (7). This paper describes the formation, properties, and single crystal X-ray diffraction anaylsis of (6b) and (8) which are the major product of the synthesis. Product (7) is minor, and an account of which will be a subject of a consecutive paper.

Scheme 1



(1) (2)

EXPERIMENTAL

Materials. 2-Hydrazinopyridine (4) was prepared according to literature.[9] Infrared spectra were measured on a Perkin-Elmer Model 457 Grating infrared spectrophotometer. Ultraviolet spectra were run on a Varian Techtron Model 635 UV-Vis spectrphotometer. ^{1}H-Nmr spectra were obtained on a WH-300 Bruker spectrometer with TMS as an internal standard, and Me_2SO-d_6 as solvent. Mass spectra were recorded with a LKB 90 21 spectrometer.

1-[Pyridoxylidene]-2-[2^1-pyridyl]hydrazine (5). (a) Hydrochloride. To a solution of pyridoxal hydrochloride (3) (2.5 g, 0.0125 mol) in 10 ml of H_2O was added dropwise with stirring a solution of 2-hydrazinopyridine (4) (1.1 g, 0.01 mol) in 10 ml of methanol at room temperature. Within a few minutes a yellow-orange precipitate was formed (2.5 g, 95%) which recrystallized from ethanol. The resulting yellow crystals of the hydrochloride of (5) melted at 298°C. Ir (KBr, ν, cm^{-1}): 3360, 3040, 2960, 2650, 2370, 2030, 1960, 1730, 1615, 1490, 1475, 1448, 1422, 1340. Uv (λ, nm, MeOH, c. $1\cdot10^{-3}$M): 376.9 (log ϵ 4.31), 239.8 (4.19), 212.9 (4.21); (c. 2.10^{-3}M): 398 (4.14), 370.6 (4.27), 239.1 (4.18), 215.2 (4.14). ^{1}H-Nmr (δ, ppm, Me_2SO-d_6): 8.52 (1H, s), 8.28 (1H, t, J=1.2 Hz), 8.15 (1H, s), 7.77 (1H, t. J=1.4 Hz), 6.98 (2H, m), 4.76 (2H, s), 2.60 (3H, s). Ms m/z = 260 (M^++2, 30%), 259 (M^++1, 100). Anal. Calcd for $C_{18}H_{15}N_4O_2Cl$: C, 52.92; H, 5.09; N, 19.00; Cl, 12.03. Found: C, 53.12; H, 4.97; N, 18.96; Cl, 12.43.

The free-base, pale yellow crystals of mp 288°C, was obtained from the crude hydrochloride after its exposure to the action of dilute aqueous ammonium hydroxide. Ir (KBr, ν, cm^{-1}): 3320, 3040, 2980, 2870, 1610, 1580, 1555, 1448, 1385, 1350. Uv (λ, nm, MeOH, c. 1.10^{-3}M): 352.7 (4.39), 331.3 (4.33), 236.3 (4.24), 211 (4.31). ^{1}H-Nmr (δ, ppm, Me_2SO-d_6): 11.82 (1H,s), 11.44 (1H, s), 8.54 (1H, s), 8.23 (1H, t, J=1.2 Hz), 7.93 (1H, s), 7.72 (1H, t, J=1.5 Hz) 6.90 (1H,s), 6.87 (1H, t, J=0.6 Hz), 5.31 (1H, s), 4.60 (2H, d, J=0.9 Hz), 2.41 (3H, s). Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 60.42; H, 5.42; N, 21.69; Found. C, 60.15; H, 5.33; N, 21.79.

The reaction of free-base (5) with methyl iodide. Formation of (6a and (7). To a solution of (5) (mp 288°C) (0.93 g, 3.5 mmol) in dry ethanol (100 ml), was added methyl iodide (2.0 g, 14 mmol), and the resulting mixture was refluxed with stirring for 48 h. After partial removal of the solvent, it was cooled, the solid red precipitate (1.1 g) was collected, and subjected to fractional crystallization from methanol to yield three colored products: (a) mustard-yellow (about 70% of total yield); (b) red product, containing some of (a); (c) mixed crystals of red

and orange products. Repeated recrystallizations of each of the three fractions from methanol provided essentially two main products: a major one: comprising yellow colored of related products (6a) and (8), and a minor one, comprising red colored geometric isomers of the corresponding N^1,N^4-dimethyl monoiodide (7) which will be elaborated in a consecutive communication.

1-[N-Methylpyridoxylidenium]-2-[2[1]-pyridyl]hydrazine iodide (6a). When the major product was recrystallized from ethanol, orange-yellow needles of mp 235-236°C were obtained. Ir (FT, KBr, ν, cm^{-1}): 3300, 3186, 2895, 2659, 2605, 1605, 1577, 1557, 1507, 1482, 1299, 1147. Uv (λ, nm, MeOH, c. 5.10^{-5}M): 399.2 (4.41), 339.6 (3.90), 219.8 (4.43). ^{1}H-Nmr (δ, ppm, Me_2SO-d_6): 12.11 (1H, s), 8.47 (1H, s,), 8.31 (1H, d, J=0.84 Hz), 7.79 (1H, t, J = 1.5 Hz), 7.04 (2H, d, J = 2.94 Hz), 5.87 (1H, m), 4.78 (2H, s), 4.22 (3H,s), 3.33 (1H,s), 2.65 (3H, s). Ms m/z = 273 (M^+-I, 70%), 95 ($C_5H_7N_2^+$, 100). Anal. Calcd for $C_{14}H_{17}N_4O_2I$: C, 42.00; H, 4.25; N, 14.00; I, 31.75. Found: C, 42.05; H, 4.27; N, 13.77; I, 31.68.

1-[N-Methylpyridoxylidenium]-2-[2[1]-pyridyl]hydrazine iodide: MeOH-compound (8). When the major reaction product was recrystallized from methanol, yellow-mustard cubic crystals of mp 246°C were isolated. Ir (FT, KBr, ν, cm^{-1}): 3292, 3246, 3156, 3143, 3133, 3122, 3097, 3040, 3000, 2984, 2951, 2944, 2917, 2888, 1598, 1571, 1546, 1474, 1455, 1438, 1420. Uv (λ, nm, MeOH, c. 5.10^{-5}M): 390.5 (4.48), 339.6 (4.08), 299.6 (3.85), 218.6 (4.52). ^{1}H-Nmr (δ, ppm, Me_2SO-d_6): 12.50 (1H, m), 8.46 (2H, s),8.44 (1H, s), 8.29 (1H, d, J=0.5 Hz), 7.80 (1H, m), 6.99 (2H, m), 4.76 (2H, s), 4.27 (3H, s), 3.21 (3H, s), 2.70 (3H, s). Ms m/z = 273 (M^+-I, 100%). Anal. Calcd for $C_{15}H_{21}N_4O_3I$: C, 41.67; H, 4.86; N, 12.96; I, 29.40. Found: C, 41.27; H, 4.64; N, 12.49; I, 29.45.

1-[N-Methylpyridoxylidenium]-2-[2[1]-pyridyl]hydrazine diperchlorate (6b). This diquaternary salt was produced following exposure of either (6a), or (8), to the action of 5% $HClO_4$. Repeated recrystallizations from ethanol afforded yellow prismatic needles, mp 215°C. Ir (FT, KBr, ν, cm^{-1}): 3411, 3403, 3394, 3323, 3307, 3271, 3257, 3238, 3081, 2976, 2937, 2917, 2897, 2878, 2850, 2801, 2718, 2672, 2665, 1642, 1623, 1579, 1472, 1461. ^{1}H-Nmr (δ, ppm, Me_2SO-d_6): 12.30 (1H, m), 8.49 (2H, s), 8.22 (1H, d, J=4.2 Hz), 7.94 (1H, t, J=1.7 Hz), 7.08 (2H, t, J=0.77 Hz), 4.81 (2H, s), 4.23 (3H, s), 2.66 (3H, s). The elemental composition is implicit from the single crystal structure (Figure 1).

CRYSTAL DATA

Compound (6b). $[C_{14}H_{17}N_4O_2]^+ \cdot HClO_4 \cdot ClO_4$, M=473.2, a=23.102(5), b=14.844(4), c=11.583(4)Å, V=3972(1)Å^3, z=8, $D_{calcd.}$ 1.58 g cm^{-1}, $\mu(MoK_\alpha)$=3.33 cm^{-1}, no. of unique reflections = 2959, reflections with $I \geq 3\sigma(I)$=1481, R=0.096, space group Pbca.

Compound (8). $C_{14}H_{17}N_4O_2I \cdot CH_3OH$, M=432.26, a=9.225(3), b=13.518(5), c=14.994(5)Å, β=106.98(8)°, V=1788.3(7)Å^3, z=4, $D_{Calcd.}$ = 1.61 g cm^{-1}, $\mu(MoK_\alpha)$=16.70 cm^{-1}, no. of unique reflections = 2441, no. of reflections with $I \geq 2\sigma(I)$=1991, R=0.040, R_w=0.052, $w=(\sigma^2_F+0.000375.F^2)^{-1}$, space group $P2_1/C$.

X-RAY CRYSTAL STRUCTURE ANALYSIS

Data were measured on a PW1100/20 Philips Four-Circle Computer-Controlled Diffractometer. MoK_α (λ =0.71069A) radiation with a graphite crystal monochromator in the incident beam was used. The unit cell dimensions were obtained by a least-square fit of 20 centered reflections in the range of $10° \leq \theta \leq 13°$. Intensity data were collected using the w-2θ technique to a maximum 2θ of 46°. The scan width, Δw, for each reflection was 1.00+0.358 tan θ with a scan speed of 3.0 deg/min. Background measurements were made for a total of 20 seconds at both limits of each scan. Three standard reflections were monitored every 60 minutes. No systematic variations in intensities were found. Intensities were corrected for Lorenz and polarization effects. All non-hydrogen atoms were found by using the results of the SHELXS-86 direct method analysis.[10] After several cycles of refinements[11] the positions of the hydrogen atoms were found and added with a constant isotropic temperature factor of 0.5A^2 [11] to the refinement process. Refinement proceeded to convergence by minimizing the function $\Sigma w(|F_o|-|F_c|)^2$. A final difference Fourier synthesis map showed several peaks less than 0.5 e/A^3 scattered about the unit cell without a signficant feature. The discrepancy indices, $R=\Sigma[|F_o|-|F_c|]/\Sigma|F_o|$ and $R_w=[\Sigma_w(|F_o|-|F_c|)^2/\Sigma|F_o|]^{1/2}$ are presented with other pertinent crystallographic date in Tables 1 and 2.

RESULTS AND DISCUSSION

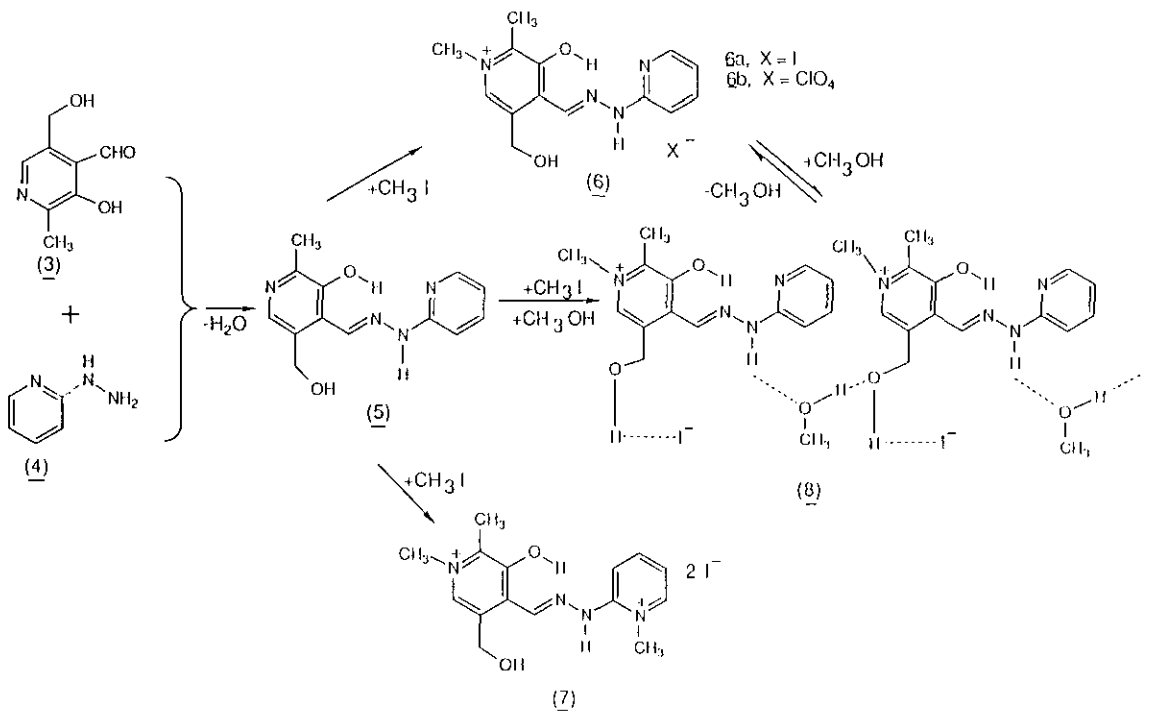
In distinction to N-methylation in (1), occurring non-selectively at both aromatic ring nitrogens,[12] the similar reaction of (5) with boiling MeI for 48 h provided preponderantly the respective monomethiodide of structure (6a). The

corresponding dimethiodide (7) could not be isolated probably because of its ready tendency to undergo facile dehydroiodination to yield an isolable isomeric mixture of N^1,N^4-dimethyl monoiodides.[13]

Crystals of (6a), suitable for X-ray analysis, could not be produced from ethanol. However, recrystallization from methanol afforded 1:1-methanol:(6a) complex of structure (8) (see, Figure 2). To understand factors underlying (6a) ⇌ (8) interconversion, we have undertaken an analysis of the single crystal X-ray diffractions of these products. Towards this end we have synthesized the respective diperchlorate salt (6b), the crystals of which proved amenable to X-ray analysis.

Chemically the N-methylpyridoxylidenium system is capable of carrying multiples of positive charge, being embedded in a surrounding of two ligands. Thus, (8) contains one neutral species (MeOH) and one negatively charged ionic species (I-), whereas (6b) contains two negatively charged species as counter-ions (ClO_4). In the former, the mono-cation is almost flat, but in the latter (6b) the dication framework is bend, forming a 38°C dihydral angle between

Scheme 2



the two heteroaromatic ring planes. The melecules in (8) are aligned in pairs of mirror-image structures with the alcoholic hydroxyls in-plane, orienting away of the azomethinic moiety. The case is just the opposite for the corresponding hydroxyls in (6b), which are both out of the N-methylpyridoxylidenium ring plane and pointing towards the azomethinic group. Sterically, flattened molecules require a lesser space in the lattice of (8) than the respective bended molecules in the lattice of (6b).

The data presented here clearly indicate the importance of modes of hydrogen bonding of OH groups [14-17] in stabilizing: a dimeric crystal structure for (6b) (see, Figure 1), and a long-chain, supramolecular structure, for the complex methanol: 1-[N-methylpyridoxylidenium]-2-[2^1-pyridyl]hydrazine iodide (8) (compare, Figure 2). In the sequence, it will be shown that the commonest modes of hydrogen bonding of the OH group play pivotal role in these stabilizations.

In the ionic crystal structure of (6b) there are three distinctly different donor groups (OH, NH, H-N), and three different acceptor groups (N, aromatic and non-aromatic, $OClO_3$), with respect to: (a) the electronegativity (or electron density) of the respective hetero atoms; (b) the geometrical patterns of contacts between the hydrogen and the acceptor atoms; and (c) the distribution of the corresponding hydrogen bond lengths.

Analysis shows that hydrogen-bond distances of (O^2)-H and (N^3)-H, in (6b), are strongly influenced by the two perchlorate counter-ions $OClO_3$. Thus, the (N^3)-H group is unsymmetrically H-bonded to the first $OClO_3$ oxygen acceptors with distances, 1.922 to 2.230A, whereas the (O^2)-H group is symmetrically distanced from both the (N^4) atom (1.839Å), and the oxygen acceptor of the second $OClO_3$ group (1.854Å). These lengthening of the primary H···O contacts induced by crystal-field environment categorizes this type of H-bonding as "three-center bonds".[14-16] The intramolecular H-bonding, (O^1)-H···(N^2), is of shorter distance (1.804Å), and has therefore the two-center ("linear") O-H···N bond.[17]

Unlike in (6b), the iodide counter-ion in (8) allows the respective (O^2)-H group, and the methanolic O-H, to manifest the most common mode of H-bonding, i.e., to function both as acceptor and donor. As with H_2O molecules, this is energetically favoured due to cooperative effect.[18-19] Thus, the symmetrical donor-acceptor relationship which is necessary for the formation of long-chains of H-bonds, implicit in cooperative hydrogen bonding, can effectively apply to crystal structure of (8).

Table 1. Bond Distances (Å), Angles (°) with e.s.d.'s in Parentheses of:
1 - [N-Methylpyridoxylidenium] - 2 - [2'-pyridyl] hydrazine Diperchlorate (6b)

O(1)	-- C(4)	1.36(2)		C(4)	-- C(5)	1.41(2)	
O(2)	-- C(7)	1.45(2)		C(5)	-- C(8)	1.47(2)	
N(1)	-- C(1)	1.35(2)		C(10)	-- C(14)	1.42(2)	
	-- C(5)	1.34(2)		C(11)	-- C(12)	1.37(2)	
	-- C(6)	1.49(2)		C(12)	-- C(13)	1.36(2)	
N(2)	-- N(3)	1.40(2)		C(13)	-- C(14)	1.39(2)	
	-- C(9)	1.26(2)		CL(1)	-- O(11)	1.42(1)	
N(3)	-- C(10)	1.36(2)			-- O(12)	1.41(1)	
N(4)	-- C(10)	1.33(2)			-- O(13)	1.38(1)	
	-- C(11)	1.36(2)			-- O(14)	1.38(2)	
C(1)	-- C(2)	1.37(2)		CL(2)	-- O(21)	1.31(2)	
C(2)	-- C(3)	1.39(2)			-- O(22)	1.36(2)	
	-- C(7)	1.50(2)			-- O(23)	1.33(2)	
C(3)	-- C(4)	1.39(2)			-- O(24)	1.35(2)	
	-- C(9)	1.46(2)					

C(1)	-N(1)	-C(5)	122(1)	N(2)	-C(9)	-C(3)	121(1)
		-C(6)	117(1)	N(3)	-C(10)	-N(4)	122(1)
C(5)	-N(1)	-C(6)	121(1)			-C(14)	117(1)
N(3)	-N(2)	-C(9)	116(1)	N(4)	-C(10)	-C(14)	121(1)
N(2)	-N(3)	-C(10)	118(1)		-C(11)	-C(12)	119(1)
C(10)	-N(4)	-C(11)	122(1)	C(11)	-C(12)	-C(13)	120(1)
N(1)	-C(1)	-C(2)	121(1)	C(12)	-C(13)	-C(14)	122(1)
C(1)	-C(2)	-C(3)	120(1)	C(10)	-C(14)	-C(13)	116(1)
		-C(7)	119(1)	O(11)	-CL(1)	-O(12)	110.3(8)
C(3)	-C(2)	-C(7)	121(1)			-O(13)	110.7(8)
C(2)	-C(3)	-C(4)	118(1)			-O(14)	107.6(9)
		-C(9)	121(1)	O(12)	-CL(1)	-O(13)	108.0(9)
C(4)	-C(3)	-C(9)	122(1)			-O(14)	107(1)
O(1)	-C(4)	-C(3)	124(1)	O(13)	-CL(1)	-O(14)	113(1)
		-C(5)	114(1)	O(21)	-CL(2)	-O(22)	98(1)
C(3)	-C(4)	-C(5)	122(1)			-O(23)	114(2)
N(1)	-C(5)	-C(4)	117(1)			-O(24)	109(1)
		-C(8)	121(1)	O(22)	-CL(2)	-O(23)	109(2)
C(4)	-C(5)	-C(8)	122(1)			-O(24)	113(1)
O(2)	-C(7)	-C(2)	109(1)	O(23)	-CL(2)	-O(24)	112(1)

Table 2. Bond Distances (Å), Angles (°) with e.s.d.'s in Parentheses of 1:1 – Methanol: 1- [N-Methylpyridoxylidenium]-2-[2'-pyridyl] hydrazine Iodide

O(1)	-- C(4)	1.352(7)		C(2)	-- C(3)	1.406(8)	
O(2)	-- C(7)	1.417(7)			-- C(7)	1.523(8)	
N(1)	-- C(1)	1.354(8)		C(3)	-- C(4)	1.400(9)	
	-- C(5)	1.336(7)			-- C(9)	1.46(1)	
	-- C(6)	1.49(1)		C(4)	-- C(5)	1.38(1)	
N(2)	-- N(3)	1.343(9)		C(5)	-- C(6)	1.511(9)	
	-- C(9)	1.278(7)		C(10)	-- C(14)	1.40(1)	
N(3)	-- C(10)	1.395(7)		C(11)	-- C(12)	1.37(1)	
N(4)	-- C(10)	1.337(9)		C(12)	-- C(13)	1.38(1)	
	-- C(11)	1.357(8)		C(13)	-- C(14)	1.365(9)	
C(1)	-- C(2)	1.37(1)		O(3)	-- C(15)	1.43(1)	

C(1)	-N(1)	-C(5)	121.7(5)	O(1)	-C(4)	-C(5)	116.7(6)
		-C(6)	117.3(6)	C(3)	-C(4)	-C(5)	121.5(7)
C(5)	-N(1)	-C(6)	121.0(5)	N(1)	-C(5)	-C(4)	119.0(6)
N(3)	-N(2)	-C(9)	120.5(6)			-C(8)	119.5(6)
N(2)	-N(3)	-C(10)	119.0(5)	C(4)	-C(5)	-C(8)	121.5(7)
C(10)	-N(4)	-C(11)	116.2(6)	O(2)	-C(7)	-C(2)	113.7(5)
N(1)	-C(1)	-C(2)	120.9(7)	N(2)	-C(9)	-C(3)	118.5(6)
C(1)	-C(2)	-C(3)	119.9(6)	N(3)	-C(10)	-N(4)	117.8(6)
		-C(7)	119.8(6)			-C(14)	118.2(6)
C(3)	-C(2)	-C(7)	120.3(5)	N(4)	-C(10)	-C(14)	124.0(7)
C(2)	-C(3)	-C(4)	116.8(5)			-C(11)	123.9(7)
		-C(9)	121.8(6)	C(11)	-C(12)	-C(13)	117.9(8)
C(4)	-C(3)	-C(9)	121.4(7)	C(12)	-C(13)	-C(14)	120.7(7)
O(1)	-C(4)	-C(3)	121.8(5)	C(10)	-C(14)	-C(13)	117.3(7)

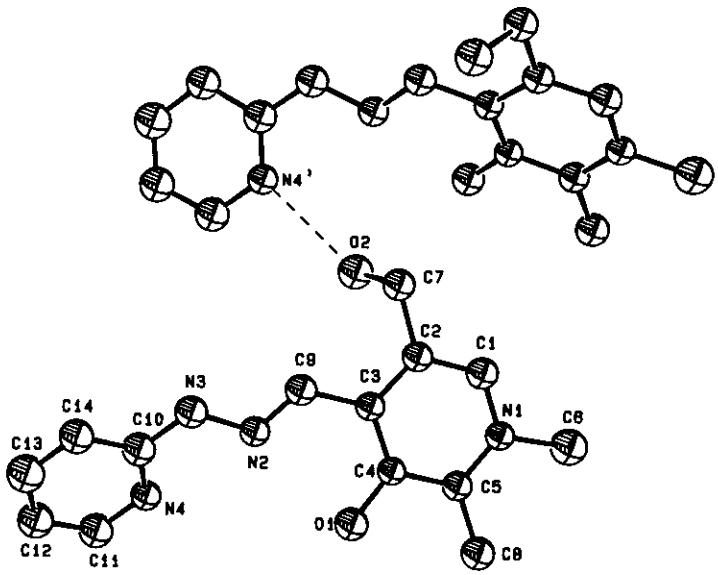


Figure1. Ortep Drawing of (6 b) With The Atom-Numbering Scheme And Thermal Ellipsoids At The 50% Probability Level[20]

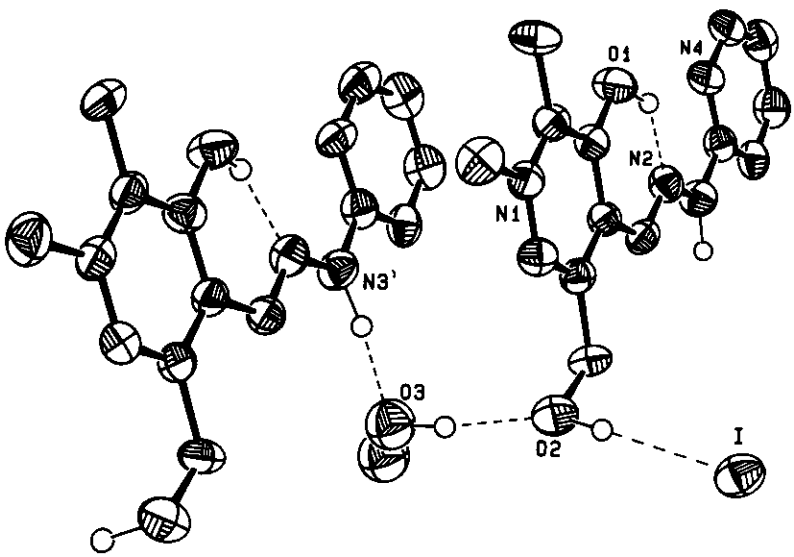


Figure 2. Ortep Drawing of (8) With the Atom-Numbering Scheme And Thermal Ellipsoids At The 50% Probability Level[20]

An interesting consequence of decreasing electron density on the pyridoxylidene ring system is reflected in the appearance of a new low-field resonance, at δ 12.5, in the nmr spectra in all quaternary salts: (6a), (6b) and (8), attributable to one of the OH protons in the molecule.

A demonstration of an opposite effect, namely, of destabilization effect in the expected di-iodide product (7), will be given in a following communication.

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