those of the amide proton, H(1). We note the following important features:

(1) The observed N–H(1) bond length of 0·90 (2) Å is reasonable for a distance determined by X-rays (Churchill, 1973).

(2) The steric interaction between the phenyl and acetyl groups is reflected in the angles subtended at the N atom, with C(1)–N–H(1) = 115 (1)° and C(7)–N–H(1) = 117 (1)°. The C(1)–N–C(7) angle is 127·6 (1)°.

(3) The hydrogen bond is, as expected, nearly linear, with N–H(1)–O′ = 171 (1)°. The intermolecular H(1)···O′ distance is 2·02 (2) Å.

In conclusion, we have shown that the temperature dependency of the vibrational spectrum of acetanilide results from factors unrelated to gross structural changes in crystals of the molecule, *e.g.* phase changes. It is interesting to note that the largest difference [0·015 (4) Å] between room- and low-temperature molecular species occurs in the carbonyl bond and that an increase in the C–O distance, while not inconsistent with the amide-I shift to lower frequency at low temperature (Careri *et al.*, 1983), would not explain the appearance of two amide-I frequencies.

We plan to carry out further studies, especially single-crystal neutron analyses, on isotopically substituted species, to determine if there is a structural basis for additional spectral anomalies (Johnston & Swanson, 1984) that occur in these molecules.

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Synthesis and Structure of (*E*)-3-Fluoro-4-pyridinecarbaldehyde Oxime, $C_6H_5FN_2O$, and Conversion to its Quaternary Methyl Iodide Derivative

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Abstract. $M_r = 140·12$, monoclinic, $P2_1/a$, $a = 14·225$ (2), $b = 11·742$ (1), $c = 3·9852$ (6) Å, $\beta = 92·48$ (1)°, $V = 665·1$ (2) Å^3, $Z = 4$, $D_x = 1·399$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1·5418$ Å, $\mu = 9·148$ cm^{-1}, $F(000) = 288$, room temperature, $R = 0·050$ for 1217 independent observed reflections. Compound synthesized by oxidation of 3-fluoro-γ-picoline with iodine/dimethyl sulfoxide to give the corresponding aldehyde, which was then treated *in situ* with hydroxylamine. The oxime group and pyridine ring are coplanar but the fluorine atom does not participate in any hydrogen bonding. Quaternization with iodomethane gave (*E*)-3-fluoro-4-hydroxyiminomethyl-1-methylpyridinium iodide; this oxime group has a pK_a of 8·2, which is 0·4 pK_a units lower than that of the nonfluorinated parent compound, as expected from the electron-withdrawing effect of fluorine.

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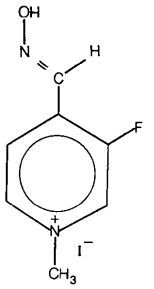
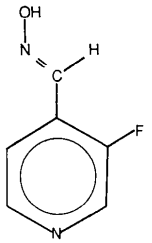
Introduction. Nucleophilic 1-alkyl-hydroxyiminomethylpyridinium halides (generally referred to as PAM compounds) reactivate phosphonate-inhibited acetylcholinesterase by attacking the phosphorus center of the phosphonate and displacing the free enzyme (Poziomek, Hackley & Steinberg, 1958). Thus, these compounds, such as 2-PAM, are potentially important as antidotes for chemical warfare agents involving phosphonate groups. Extensive studies (Hagedorn, Stark & Lorenz, 1972) indicate a pK_a optimum near 8·0–8·2 for the maximum rate of reactivation of enzyme, but the optimum structural parameters for most efficient reactivation have not yet been identified. The PAM compound 3-fluoro-4-hydroxyiminomethyl-1-methylpyridinium iodide (I) contains F substitution on the pyridine ring of the relatively slow enzyme reactivator 4-hydroxyiminomethyl-1-methylpyridinium

iodide, also called 4-PAM (Ginsburg & Wilson, 1957). As a result of this substitution the pK_a of the oxime group is lowered from 8·6 to near the optimum (8·0–8·2)* while the stereochemistry of 4-PAM is minimally disturbed. It was reasoned that if the 4-configuration represents a structural optimum, 3-fluoro-4-PAM should surpass the classical reactivator 2-PAM (Ginsburg & Wilson, 1957) in rate of reactivation. A structure determination of the immediate unquaternized precursor of 3-fluoro-4-PAM was carried out with the specific aim of establishing the relative orientation of the fluorine and oxime group and also in order to investigate the mode of hydrogen bonding of the oxime group. The formula of the compound studied is given as (II).



(I)



(II)

Experimental. Commercial 2-amino-γ-picoline (Aldrich Chemical Co.) was converted by a known sequence of reactions (Roe & Seligman, 1955) to 3-amino-γ-picoline, which in turn was converted to 3-fluoro-γ-picoline (Roe & Seligman, 1955) by a modified Schiemann reaction employing ethyl nitrite (Semon & Damerell, 1930) as the diazotization agent. Oxidation of the 3-fluoropicoline with iodine/dimethyl sulfoxide (Markovac, Stevens, Ash & Hackley, 1970) gave 3-fluoro-4-pyridinecarbaldehyde, which was treated *in situ* with aqueous hydroxylamine (pH 7·4) to give the crystalline oxime (40%). High-pressure liquid chromatographic analysis of this product indicated a trace amount (<4%) of a companion product, assumed to be the (*Z*) isomer of the title oxime but this was not isolated. Recrystallization from hot H_2O/EtOH (3/1 *v/v*) gave the pure (*E*) isomer (II), as pale-yellow crystals, m.p. 399–401 K, mass spectrum *m/e* [rel. intensity, species]: 141 [17,$(M+1)^+$], 140 [100, M^+], 122 [72, $M^+ - H_2O$]. The ^1H NMR spectrum [δ values, 0·04 *M* $CDCl_3$ solution: H(2) at 8·52, H(6) at 8·43, H(5) at 7·69, aldehydic proton H(8) at 8·35, oxime hydroxyl proton H(10) at 8·96] and elemental analysis (calc. for $C_6H_5FN_2O$: C 51·43, H 3·59, N 20·00, F 13·56%; found: C 51·54, H 3·59, N 20·28, F 13·50%) were consistent with the assigned structure.

The quaternary (enzyme-dephosphonylating) species of this oxime (I) was synthesized by refluxing (*E*)-3-fluoro-4-pyridinecarbaldehyde oxime (II) with excess iodomethane in methanol for 18 h (91% yield). After removal of excess reagent and solvent, crystallization from hot 2-propanol gave dark-orange crystals of (I),* m.p. 395–405 K (decomp.). The elemental analysis (calc. for $C_7H_8FIN_2O$: C 29·81, H 2·86, N 9·93, F 6·74, I 44·99; found: C 29·90, H 3·10, N 9·45, F 7·03, I 44·71%) and ^1H NMR spectrum [δ values, D_2O, DSS int. std: methyl group singlet at 4·37, aldehydic proton H(8) at 8·45, plus pyridine ring protons H(5) at 8·35, H(6) at 8·70, H(2) at 9·00] were consistent with the expected (*E*)-3-fluoro-4-hydroxyiminomethyl-1-methylpyridinium iodide [(*E*)-3-F-4-PAM] structure. Assignment of (*E*) geometry is consistent with (*a*) previous proof that quaternization of 4-pyridinecarbaldehyde oxime occurs without alteration of the oxime configuration (Poziomek, Kramer, Mosher & Michel, 1961) and (*b*) a single aldehydic proton resonance in the NMR spectrum. Crystals were not of sufficient quality for an X-ray structure determination.

Yellow equidimensional crystal of oxime (II), 0·2 mm edge, mounted on glass fiber. Nicolet $P2_1$ diffractometer. Space group $P2_1/a$ from systematic absences (*h*0*l*, *h* odd; 0*k*0, *k* odd). Unit cell: 15 centered reflections, least-squares fit. Three-dimensional X-ray intensity data collected with θ–2θ scan technique (bisecting mode), graphite-monochromated Cu $K\alpha$ radiation. 1226 unique reflections in range $(\sin\theta)/\lambda = 0{\cdot}05$ to $0{\cdot}61$ Å^{-1} ($2\theta = 138°$); variable scan mode, depending on intensity, 2·0 to 29·3° min^{-1}. 1217 reflections with $I > \sigma(I)$ [$\sigma(I)$ derived from counting statistics] used in structure solution and refinement. $-16 \le h \le 17$, $0 \le k \le 14$, $0 \le l \le 4$. Four check reflections measured every 60 reflections; no decay in intensity. $\sigma(F) = (F/2)\{[\sigma^2(I)/I^2] + \delta^2\}^{1/2}$, δ is instrumental uncertainty ($\delta = 0{\cdot}0256$) determined from variation in measured intensities in periodically scanned standard reflections. Reflection data converted to structure amplitudes by Lorentz and polarization factors and placed on absolute scale with Wilson plot; no absorption correction. Structure solved by Patterson superposition and Fourier syntheses. Hydrogen atoms found from a difference Fourier map after refinement of non-hydrogen atomic parameters. Atomic positions, anisotropic thermal parameters of non-hydrogen atoms and isotropic thermal parameters of hydrogen atoms refined by full-matrix least-squares procedure. $\sum w[|F_o| - |F_c|]^2$ minimized, $w = 1/\sigma^2(F)$. Final $R = 0{\cdot}050$; av. shift in atomic parameters $<0{\cdot}085\sigma$.

* This pK_a optimum range is based on $pK_a = 8{\cdot}0$ for 2-hydroxyiminomethyl-1-methylpyridinium iodide, 2-PAM (Ginsburg & Wilson, 1957), and $pK_a = 8{\cdot}2$ for 1,1′-trimethylenebis(4-hydroxyiminomethyl bromide), TMB-4 (Poziomek, Hackley & Steinberg, 1958; Wilson & Ginsburg, 1958). Both of these compounds are fast reactivators.

* Prolonged exposure to air results in discoloration, and therefore this compound has to be stored *in vacuo*.

Table 1. *Refined atomic parameters*

Positional parameters are listed as fractions of cell edges. E.s.d.'s with respect to the last digit listed are given in parentheses.

$$B_{eq} = \tfrac{1}{3}\sum_{i=1}^{3} B_{ii}.$$

	x	y	z	B_{iso}/B_{eq}(Å^2)
N(1)	0·01225 (9)	0·20313 (12)	−0·1810 (3)	5·99 (6)
C(2)	0·01891 (11)	0·31414 (16)	−0·2365 (4)	6·14 (7)
C(3)	0·09442 (10)	0·37658 (14)	−0·1167 (4)	5·54 (7)
C(4)	0·16801 (9)	0·32838 (12)	0·0720 (3)	5·00 (6)
C(5)	0·15965 (10)	0·21220 (14)	0·1270 (4)	5·52 (7)
C(6)	0·08233 (11)	0·15412 (14)	−0·0012 (4)	5·97 (7)
F(7)	0·09715 (8)	0·48940 (9)	−0·1861 (3)	7·91 (6)
C(8)	0·24691 (10)	0·39643 (13)	0·2048 (4)	5·62 (7)
N(9)	0·31210 (8)	0·34883 (12)	0·3821 (3)	5·57 (6)
O(10)	0·37963 (8)	0·42580 (11)	0·4923 (3)	6·95 (6)
H(2)	−0·0275 (14)	0·3477 (18)	−0·370 (5)	7·8 (5)
H(5)	0·2079 (11)	0·1732 (16)	0·262 (4)	6·3 (4)
H(6)	0·0786 (13)	0·0771 (17)	0·033 (5)	6·6 (4)
H(8)	0·2461 (15)	0·4751 (19)	0·161 (5)	8·0 (5)
H(10)	0·4225 (19)	0·381 (3)	0·613 (7)	11·7 (8)

Max., min. height in final difference Fourier synthesis 0·25, −0·19 e Å^{-3}. Computer programs: locally modified version of *UCLALS*4 (Carrell, 1975; Gantzel, Sparks, Long & Trueblood, 1969) and other programs written in the Institute for Cancer Research laboratory. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974).

Discussion. Final refined coordinates and average equivalent isotropic temperature factors are listed in Table 1.* Bond lengths and interbond angles are in the range expected for heteroaromatic (*E*)-oximes (Martínez-Ripoll & Lorenz, 1976; Jerslev, 1983). The molecule is illustrated in Fig. 1. This diagram shows that the oxime conformation is (*E*) or *syn* [the torsion angle C(4)C(8)N(9)O(10) lies near 180° at −178·7°]. The molecule is approximately planar, in contrast to the nonfluorinated parent compound whose oxime group is twisted 13·7° from the plane of the pyridine ring (Martínez-Ripoll & Lorenz, 1976). Increased coplanarity is consistent with an electron-withdrawing effect of the fluorine atom favoring resonance between the pyridine ring and the oxime group. There is no apparent interaction between the oxime hydroxyl group and the fluorine atom. The ring angles at the site of oxime substitution are different in the unsubstituted and fluoro compounds (Martínez-Ripoll & Lorenz, 1976) [117·7 (5) *vs* 114·8 (2)° for C(3)C(4)C(5), 122·7 (5) *vs* 123·5 (2)° for C(5)C(4)C(8) and 119·6 (5) *vs* 121·7 (2)° for C(3)C(4)C(8)]. Thus, the oxime is more symmetrically bound to the aromatic ring in the 3-fluoro compound.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39953 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

The crystal structure, illustrated in Fig. 2 (Carrell, 1979), is held together by hydrogen bonding of the oxime hydroxyl group to N(9) of another molecule (at $\frac{1}{2}+x, \frac{1}{2}-y, 1+z$). This is the most common type of hydrogen bonding found in oxime groups in crystals (Bertolasi, Gilli & Veronese, 1982). The hydrogen-bond dimensions are H(10)···N(1′) 1·79 (3), O(10)···N(1′) 2·708 (2) Å, and the angle O(10)–H(10)···N(1′) 175 (2)°. The fluorine atom is not involved in any hydrogen bonding.

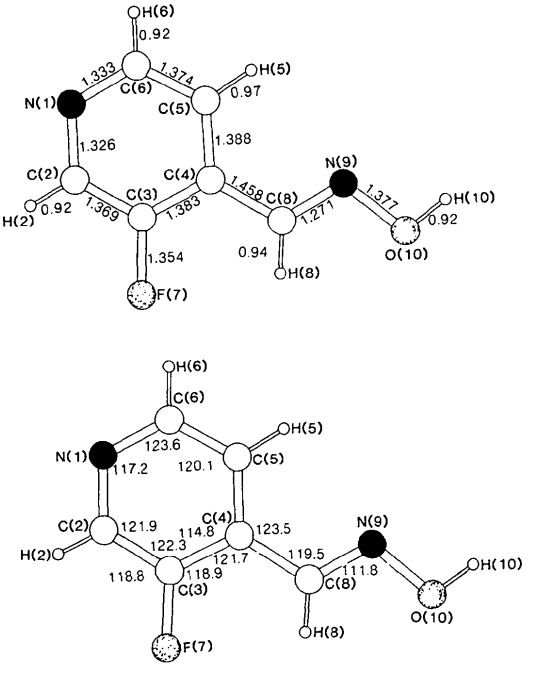


Fig. 1. *syn*-3-Fluoro-4-pyridinecarbaldehyde oxime. E.s.d. for non-hydrogen bond lengths is 0·002 Å and for those involving hydrogen 0·03 Å. E.s.d.'s for bond angles are 0·2 and 1·5°, respectively. [Torsion angles (e.s.d.'s 0·2–0·3°) C(3)–C(4)–C(8)–N(9) 178·7°, C(5)–C(4)–C(8)–N(9) 0·3°, C(4)–C(8)–N(9)–O(10) −178·7°.]

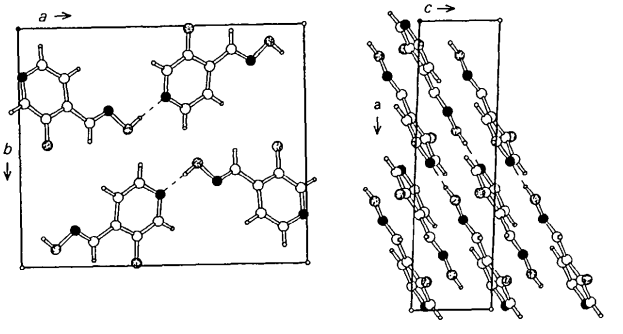


Fig. 2. Packing in the unit cell. Fluorine and oxygen atoms are stippled, nitrogen atoms are black. The hydrogen bonds are indicated by dashed lines.

The pK_a value for (*E*)-3-fluoro-4-PAM was found by potentiometric titration to be 8·2. Therefore, this compound meets the empirical pK_a requirement for rapid reactivation of phosphonylated acetylcholinesterase. Since the corresponding pK_a value of the nonfluorinated analog (4-PAM) is 8·6 (Ginsburg & Wilson, 1957; Poziomek, Kramer, Mosher & Michel, 1961), substitution of fluorine for hydrogen at the 3-position of the pyridine ring decreases the pK_a by 0·4 pK_a units, an effect expected from the electron-withdrawing properties of the fluorine atom. Preliminary studies indicate that the fluorine-substituted compound has an increased rate of dephosphonylation of enzyme relative to the unsubstituted parent compound, but less than that of 2-PAM (in spite of the similarities in pK_a values). Thus, except for the fact that the fluorine substitution causes more stringent coplanarity between the oxime group and the pyridine ring, the effect of fluorine is confined to lowering the pK_a value.

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Structure of 6,6,10,10-Tetranitropentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane, $C_{10}H_8N_4O_8$

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Abstract. $M_r = 312{\cdot}20$, monoclinic, *Pc*, $a = 7{\cdot}761$ (1), $b = 11{\cdot}500$ (2), $c = 14{\cdot}277$ (2) Å, $\beta = 108{\cdot}63$ (2)°, $V = 1207{\cdot}5$ (3) Å^3, $Z = 4$, $D_x = 1{\cdot}717$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0{\cdot}113$ mm^{-1}, $F(000) = 640$, $T = 295$ K. Final $R = 0{\cdot}041$, $wR = 0{\cdot}042$, for 2457 independent observed reflections. The carbon skeleton (bishomocubane) consists of four puckered five-membered rings and two four-membered rings which are bent about their diagonals by approximately 20°. The two molecules in the asymmetric unit are nearly identical, with the primary difference being the orientations of the NO_2 groups.

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