3-Substituted 2-Pyridinecarbaldoximes [1]

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A series of 2-pyridinecarbaldoximes and salts derived from them by methylation of the pyridine nitrogen, all of which are substituted at the 3-position with carbon (*i.e.*, derivatives of nicotinic acid and its homologues) or oxygen, have been prepared.

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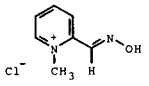
Introduction.

Aldoximes [5], and in particular 2-pyridinecarbaldoxime methochloride [2-PAM] (**1**, [oxime geometry unspecified]) [6], have been successfully employed in the regeneration of activity of cholinesterase enzymes (EC 3.1.1.7 and EC 3.1.1.8) *in vivo*, after the activity has been lost through organophosphorus derivatization. The effectiveness of this treatment to regenerate enzyme activity decreases as time passes (the phosphorus bearing enzyme having said to have "aged") presumably because of hydrolysis of a phosphorus ligand *other than the one* with which the binding to the enzyme has been made [7] and a reduced rate of reaction of this new, partially hydrolyzed, phosphorus bearing enzyme with 2-PAM (or its analogues) compared to that originally present.



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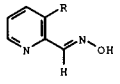


2a: R = CO_2CH_3
2b: R = $CO_2CH_2CH_3$
2c: R = $CO_2CH(CH_3)_2$
2d: R = $CO_2C(CH_3)_3$
2e: R = $CH_2CO_2CH_2CH_3$
2f: R = $CH_2CH_2CO_2CH_3$
2g: R = $CH_2CH(CO_2CH_2CH_3)_2$
2h: R = OH
2i: R = O_2CCH_3
2j: R = $CH_2O_2CCH_3$
2k: R = $CH_2CH_2O_2CCH_3$

With the expectation that hydrolysis of the enzyme to phosphorus bond might be made more facile in the partially hydrolyzed phosphorus bearing enzyme if coordination to a second site on the pyridine ring (to which the oxime is already attached) could be effected, a series of 3-substituted derivatives of 2-pyridinecarbaldoximes, *i.e.* methyl 2-(carbaldoxime)nicotinate (**2a**), ethyl 2-(carbaldoxime)nicotinate (**2b**), isopropyl 2-(carbaldoxime)nicotinate (**2c**), *t*-butyl 2-(carbaldoxime)nicotinate (**2d**), ethyl pyridine-2-(carbaldoxime)-3-acetate (**2e**), methyl 3-[2-(carbaldoxime)-3-pyridyl]propionate (**2f**), 3-(diethyl methylpropanedioate)pyridine-2-carbaldoxime (**2g**), 3-hydroxypyridine-2-carbaldoxime (**2h**), 3-acetoxypyridine-2-carbaldoxime (**2i**), 3-(acetoxymethyl)pyridine-2-carbaldoxime (**2j**), and 3-(2-acetoxy)ethylpyridine-2-carbaldoxime (**2k**) have been prepared and some of them converted to salts related to 2-PAM (**1**) for testing. The syntheses are reported here [8].

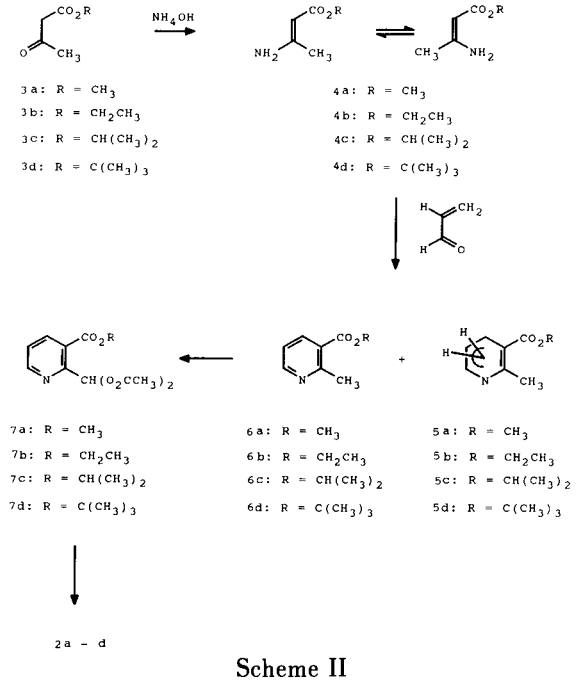
Results and Discussion.

Scheme I provides an overview of the generalized synthetic pathway for the generation of the oximes **2a-2d** while Scheme II provides the same information about oximes **2e-2k**. Thus, for the oximes **2a-2d**, as the archtypical 3-substituted derivatives of the parent 2-pyridinecarbaldoxime [the progenitor of 2-PAM (**1**)] the readily available esters of acetoacetic acid [methyl acetoacetate (**3a**), ethyl acetoacetate (**3b**), isopropyl acetoacetate (**3c**) and, *t*-butyl acetoacetate (**3d**)], were converted to the corresponding aminocrotonate esters **4a-d** with ammonium hydroxide [9].

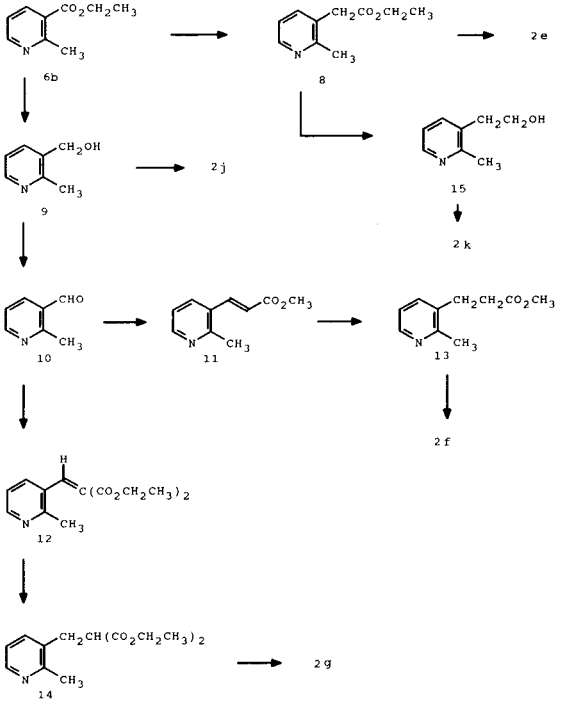
Then, the aminocrotonates **4a-d** were individually allowed to react with an excess of acrolein to generate, respectively, a mixture of corresponding 2-methylnicotinate ester **6a-d** and one or more dihydronicotinates **5a-d**, in modest yields (about 30-50% overall) essentially independent of esterifying alcohol. Purification of this crude mixture away from a resinous residue by simple vacuum distillation was attended by partial further oxidation of the dihydropyridine nucleus in the esters **5a-d** to the fully aromatic heterocycle (as shown by gas chromatography) but these oxidations were incomplete and the yield of pyridine varied from batch to batch. Thus, initially following the older literature [10] but later, the more convenient and more recent work [9], oxidation of the partially purified condensation product **5a-d** (albeit that some oxidation had already occurred) was effected without complete identification of the crude mixture by utilizing an excess of nitric acid as oxidant.

The well known technology [11] for specific oxidation of 2-methylpyridines to the corresponding 2-pyridinecarboxaldehydes (as the diacetates, **7a-d**, of the corresponding hydrates) *via* oxidation first to the corresponding *N*-oxides

Scheme I



Scheme II



and subsequent rearrangement with acetic anhydride was successfully applied on the purified esters **6a-d** using either hydrogen peroxide [12] or 3-chloroperoxybenzoic acid [11]. The diacetates, generated by two applications of the oxidation-rearrangement process, were directly converted to the corresponding oximes **2a-2d** with hydroxylamine hydrochloride and without the necessity of first producing the intermediate aldehyde.

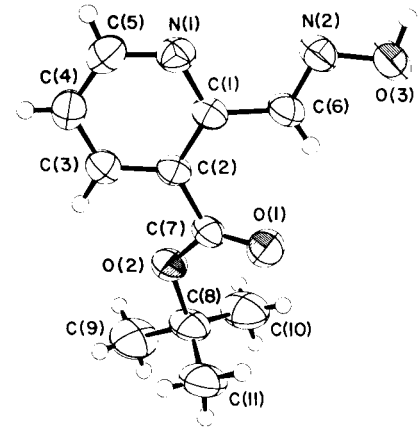


Figure. A representation of the X-ray crystal structure of *t*-butyl 2-(carbaldoxime)nicotinate, **2d**. Selected Interatomic Distances (Å) and Angles (degrees) are presented. Additionally, O(1) is apparently above the plane of the aromatic ring by about 0.37 Å, O(2) is below the plane of the aromatic ring by about 0.35 Å, and N(2) is also below the plane of the aromatic ring by about 0.20 Å.

Similarly, and as shown in Scheme II, ethyl 2-methylnicotinate (**6b**) (chosen only because the requisite ethyl acetoacetate (**3b**) was most readily available) was converted to its next higher homologue, ethyl 2-methylhomonicotinate **8** [12] and that too, without event and with the same techniques, to the corresponding oxime, *viz.* ethyl pyridine-2-(carbaldoxime)-3-acetate (**2e**). Alternatively, ethyl 2-methylnicotinate (**6b**) could be conveniently reduced with lithium aluminum hydride to the (commercially available) alcohol 2-methyl-3-(hydroxymethyl)pyridine (**9**) and the latter oxidized with manganese dioxide to the corresponding aldehyde, 2-methylpyridine-3-carbaldehyde (**10**). This convenient synthon was then available for a host of condensation reactions such as those exemplified, on the one hand, by reaction with methyl triphenylphosphoranylidineacetate, to produce methyl (*E*)-3-(2-methyl-3-pyridyl)propenoate (**11**) and, on the other, by condensation with diethyl malonate to produce the diester, diethyl 2-(2-methylpyridyl)ethylene-1,1-dicarboxylate (**12**).

After reduction to avoid potential (unwanted) double bond oxidation, the saturated esters methyl 3-(2-methyl-3-pyridyl)propionate (**13**) and diethyl 3-(2-methyl-3-pyridyl)-propanedioate (**14**) (derived from **11** and **12**, respectively) could also be converted to the corresponding oximes, *i.e.* methyl 3-[2-(carbaldoxime)-3-pyridyl]propionate (**2f**) and 3-(diethyl methylpropanedioate)pyridine-2-carbaldoxime (**2g**), uneventfully, with the oxidation-rearrangement process [11] which had successfully been applied to the simpler esters, followed by treatment with hydroxylamine hydrochloride.

Finally, the preparation of the oxime esters 3-acetoxypyridine-2-carbaldoxime (**2i**), 3-(acetoxymethyl)pyridine-2-carbaldoxime (**2j**), and 3-(2-acetoxy)ethylpyridine-2-carbaldoxime (**2k**) was also examined. The ester **2i** was obtained

Table

Selected Bond Lengths and Angles of *t*-Butyl 2-(carbaldoxime)nicotinate (2d)

Bond Lengths (Å)

C(1)-C(2)	1.399(2)	C(1)-C(6)	1.468(2)	C(1)-N(1)	1.345(2)	C(2)-C(3)	1.393(2)
C(2)-C(7)	1.489(2)	C(3)-C(4)	1.360(2)	C(4)-C(5)	1.369(2)	C(5)-C(1)	1.320(2)
C(6)-N(2)	1.252(2)	C(6)-H(C6)	0.84(2)	C(7)-O(1)	1.199(2)	C(7)-O(2)	1.322(2)
C(8)-C(9)	1.496(3)	C(8)-C(10)	1.506(3)	C(8)-C(11)	1.497(2)	C(8)-O(2)	1.499(2)
N(2)-O(3)	1.371(2)	O(3)-H(O3)	0.87(3)				

Bond Angles (degrees)

N(1)-C(1)-C(2)	121.5(1)	N(1)-C(1)-C(6)	115.6(1)	C(2)-C(1)-C(6)	122.9(1)
C(1)-C(2)-C(3)	117.6(1)	C(1)-C(2)-C(7)	122.7(1)	C(3)-C(2)-C(7)	119.7(1)
C(2)-C(3)-C(4)	120.0(1)	C(3)-C(4)-C(5)	118.5(2)	C(4)-C(5)-N(1)	123.5(2)
C(1)-C(6)-N(2)	120.6(1)	C(1)-C(6)-H(C6)	121(1)	N(2)-C(6)-H(C6)	118(1)
C(2)-C(7)-O(1)	124.5(1)	O(1)-C(7)-O(2)	124.3(1)	C(9)-C(8)-C(10)	112.2(2)
C(9)-C(8)-C(11)	111.6(2)	C(9)-C(8)-O(2)	101.7(2)	C(10)-C(8)-C(11)	112.3(2)
C(10)-C(8)--O(2)	109.4(1)	C(11)-C(8)-O(2)	109.3(1)	C(1)-N(1)-C(5)	118.8(1)
C(6)-N(2)-O(3)	111.8(1)	C(7)-O(2)-C(8)	122.1(1)	N(2)-O(3)-H(O3)	102(2)
C(2)-C(7)-O(2)					

from the previously prepared [13] phenol derivative 3-hydroxypyridine-2-carbaldoxime (**2h**) by taking advantage of the (relative) acidity of the phenolic hydroxyl which, in the cold, with vigorous stirring of a biphasic solution, could be preferentially acetylated in the presence of the oximino hydroxyl. Other acetylation techniques yielded mixtures of unacetylated, partially acetylated, and bis-acetylated materials. Partial hydrolysis of the latter to give the desired **2i** could not be effected.

A similar difficulty was not encountered with preparation of the oximino esters **2j** and **2k** since their preparation did not involve a late stage acetylation. For them, the more traditional preparation of the alcohols, 2-methyl-3-(hydroxymethyl)pyridine (**9**) and 2-[3-(2-methylpyridyl)]-ethanol (**15**), by reduction of the corresponding esters (**6b** and **8**, respectively, whose syntheses have already been discussed) with lithium aluminum hydride followed by acetylation readily succeeded. For these esters, the conversion of the 2-methyl group to the oxime *via* the process already outlined, proceeded without untoward event.

EXPERIMENTAL

All commercial materials were used without further purification unless otherwise indicated. Tetrahydrofuran, diethyl ether, benzene and toluene were distilled from sodium benzophenone ketyl and stored under argon or nitrogen. Methanol was distilled from magnesium turnings and methylene chloride was distilled from calcium hydride.

Melting points, determined on a Thomas-Hoover melting point apparatus, and boiling points (obtained during distillation) are uncorrected. The ir spectra were recorded on Perkin-Elmer 137 CW and Digilab FTS-40 FT IR spectrometers. The ^{1}H nmr (pmr) were variously obtained on Varian EM360L (at 60 MHz), Perkin-Elmer R32 (at 90 MHz), or GE QE300 (at 300 MHz) and ^{13}C nmr (cmr) on Varian XL-100 equipped with a Nicolet 1180 FT Pulse System (at 25.16 MHz) or GE QE 300 (at 75.48 MHz) spectrometers depending upon equipment availability, sample size and whether or not the material had previously been reported. Deuteriochloroform (unless otherwise specified) was used as the nmr solvent and protiochloroform or tetramethylsilane (TMS) as internal reference. Values are reported as ppm (δ) downfield from TMS = 0.00. Low resolution mass spectrometry was accomplished with a Hewlett-Packard HP5995 GC/MS using the direct inlet mode. Analytical thin layer chromatography (tlc) was conducted using Analtech silica gel GF plates (0.25 mm) containing fluorescent indicator. Preparative tlc was carried out on 20 cm^2 silica gel GF plates (1000 micron). Flash column chromatography was performed using Merck silica gel 50 (230-400 mesh) and analytical gas chromatography on a Perkin-Elmer 900 GC equipped with an FID, helium as the carrier gas, and using a 6 ft x 1/8 in glass column packed with 5% OV-17 on acid washed Chromsorb W. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Ethyl 2-Methylnicotinate (**6b**) [9,14].

Method A [10].

To a stirred mixture of ethyl 3-aminocrotonate [11] (80 ml, 74.9 g, 0.58 mole), 2-propanol (140 ml), and piperidine (3 ml) at 30° was added acrolein (54 ml, 45.3 g, 0.81 mole) in the course of 2 hours. The reaction mixture was heated at reflux for 3.5 hours, cooled to room temperature, a second portion of acrolein (54 ml) added, and the mixture reheated to reflux for an additional 3.5 hours. The solvent was removed by simple distillation and the residue, while being heated at 100°, was treated with powdered sulfur (61.0 g, 1.90 moles) added in small portions (**CAUTION: ADEQUATE VENTILATION REQUIRED**); hydrogen sulfide vigorously evolved. When the addition was complete, the reaction mixture was heated for an additional 2 hours at 100° and then 1.5 hours at 150°. After cooling to room temperature, chloroform (100 ml) was added and the precipitated sulfur removed by filtration. The chloroform solution was extracted with aqueous hydrochloric acid (2*N*, 300 ml in two portions) and the acidic aqueous solution backwashed with fresh chloroform (3 x 100 ml). With cooling, the aqueous acid was basified with aqueous sodium hydroxide (2*N*) and the ester so liberated extracted into chloro-

form (2 x 100 ml), the solvent removed at reduced pressure and the residue distilled *in vacuo* to obtain the title compound (46.6 g, 0.28 moles, 49%), bp 107° (10 torr); lit [9,14] 126-127° at 24 torr; ir (neat): 1720 cm^{-1} (C=O); pmr: 8.50 (1H, dd, $J_{6,4}$ = 1.5 Hz, $J_{6,5}$ = 6 Hz), 8.10 (1H, dd, $J_{4,6}$ = 1.5 Hz, $J_{4,5}$ = 6 Hz), 7.06 (1H, dd, $J_{5,4}$ = 6 Hz, $J_{5,6}$ = 6 Hz), 4.38 (2H, q, J = 8 Hz), 2.82 (3H, s), 1.40 (3H, t, J = 8 Hz); cmr: 150.8, 137.2, 125.1, 119.8, 60.2, 23.8, 13.5; ms: 92, 120 (100), 136, 150, 165.

Method B [9].

To a stirred mixture of ethyl 3-aminocrotonate [9] (80 ml, 74.9 g, 0.58 mole), absolute ethanol (170 ml) and piperidine (3 ml) at 0° was added acrolein (54 ml, 45.3 g, 0.81 mole) over 3 hours. After the addition was complete, the reaction mixture was heated at reflux for 24 hours, the solvent removed by simple distillation, and the residue distilled in vacuum to yield a mixture of ethyl 2-methylnicotinate (**6b**) and the corresponding dihydroderivative(s) (56.1 g, bp 70-150° at 1 torr). The crude distillation product was oxidized by cautiously adding it to a mixture of concentrated sulfuric acid (32.7 g, 23.4 ml), concentrated nitric acid (35.1 g, 18.7 ml), and water (105 g, 105 ml) and gently (**CAUTION**) warming the reaction mixture, with occasional stirring, on the water bath for about 10 minutes, during which effervesence occurred. The resulting mixture was cooled to room temperature, extracted with ether (100 ml), made basic with saturated sodium bicarbonate and the basic solution extracted with ether again (5 x 50 ml). The combined ether extracts were dried over sodium sulfate, the ether removed at reduced pressure, and the residue distilled as above to yield the title compound (28.9 g, 0.18 moles, 30%).

Methyl 2-Methylnicotinate (**6a**) [15].

Prepared as above (Method B, 35%) from methyl aminocrotonate has bp 90-95° (5 torr); ir (neat): 1740 cm^{-1} (C=O); pmr: 8.60 (1H, dd, $J_{6,4}$ = 1.8 Hz, $J_{6,5}$ = 5 Hz), 8.17 (1H, dd, $J_{4,6}$ = 1.8 Hz, $J_{4,5}$ = 8 Hz), 7.20 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 8 Hz), 3.91 (3H, s), 2.83 (3H, s); cmr: 166.9, 159.8, 151.7, 138.4, 125.3, 120.8, 52.2, 24.7.

Isopropyl 2-Methylnicotinate (**6c**).

Prepared as above (Method B, 41%) from isopropyl aminocrotonate has bp 115° (5 torr); ir (neat): 1720 cm^{-1} (C=O); pmr: 8.50 (1H, dd, $J_{6,4}$ = 1.8 Hz, $J_{6,5}$ = 5 Hz), 8.07 (1H, dd, $J_{4,6}$ = 1.8 Hz, $J_{4,5}$ = 7.8 Hz), 7.10 (1H, dd, $J_{5,6}$ = 4.8 Hz, $J_{5,4}$ = 7.8 Hz), 5.18 (1H, h, J = 6.3 Hz), 2.80 (3H, s), 1.35 (6H, d, J = 6.3 Hz); cmr: 166.1, 159.5, 151.5, 138.2, 126.1, 120.8, 68.8, 24.8, 21.8.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.80; H, 7.21; N, 8.14.

t-Butyl 2-Methylnicotinates (**6d**).

Prepared as above (Method B, 42%) from *t*-butyl aminocrotonate has bp 85-90° (1 torr); ir (neat): 1735 cm^{-1} (C=O); pmr: 8.80, (1H, dd, $J_{6,4}$ = 2.0 Hz, $J_{6,5}$ = 4.8 Hz), 8.40 (1H, dd, $J_{4,6}$ = 2.0 Hz, $J_{4,5}$ = 8 Hz), 7.10 (1H, dd, $J_{5,6}$ = 4.8 Hz, $J_{5,4}$ = 8 Hz), 2.70 (3H, s), 1.50 (9H, s); cmr: 158.7, 150.7, 137.4, 120.1, 81.3, 27.8, 24.2.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.20; H, 7.72; N, 7.11.

Ethyl 2-(Bisacetoxy)methylnicotinate (**7b**) [16].

To a stirred solution of the product of the reaction between ethyl 2-methylnicotinate and 3-chloroperoxybenzoic acid, followed by rearrangement through heating with acetic anhydride [12] (1.25 g, 5.6 mmoles) in dichloromethane (100 ml) at 0° was slowly added a solution of 3-chloroperoxybenzoic acid (2.36 g, 13.67 mmoles) in dichloromethane (100 ml) [11]. The resulting yellow solution was stirred at room temperature for 2 hours, transferred to a separatory funnel, washed with 5% sodium carbonate (2 x 100 ml), and dried over anhydrous sodium sulfate. After filtration and removal of solvent, the residue was chromatographed on silica gel (50 g, 9:1 chloroform:methanol) and the product, the presumed corresponding *N*-oxide [16] (1.15 g, 4.76 mmoles, 85% of theory) without further purification was dissolved in acetic anhydride (10 ml) and added, dropwise, to refluxing acetic anhydride (30 ml). The reaction mixture was heated at reflux for 30 minutes after the addition was complete and, subsequently, with gentle heating, the solvent was removed at reduced pressure. Water (50 ml) was added to the residue, the resulting solution brought to neutrality with saturated aqueous sodium carbonate, and the latter extracted with chloroform (2 x 50 ml). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated to yield a yellow oil. Chromatography (silica gel, 100 g) gave in the 1:1 chloroform:ethyl acetate eluent **7b**, mp 99-101° (lit [16] 100-103°) 780 mg, 2.8 mmoles, 50%; ir (potassium bromide): 1718 cm^{-1} (C=O); pmr: 8.75 (1H, dd, $J_{6,4}$ = 2.5 Hz, $J_{6,5}$ = 3 Hz), 8.30 (1H, s), 8.25 (1H, dd, $J_{4,6}$ = 2.5 Hz, $J_{4,5}$ = 8 Hz), 7.42 (1H, dd, $J_{5,6}$ = 3 Hz, $J_{5,4}$ = 8 Hz), 4.40 (2H, q, J = 7 Hz), 2.16 (6H, s), 1.39 (3H, t, J = 7 Hz); cmr: 138.4, 123.5, 118.9, 87.6, 61.8, 20.3, 20.2, 13.9; ms 78, 106, 123, 134(100), 150, 180, 196, 208, 281.

Anal. Calcd. for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.45; H, 5.39; N, 4.96.

Methyl 2-(Bisacetoxy)methylnicotinate (**7a**).

Prepared as above from methyl 2-methylnicotinate (**6a**) in 47% yield, mp 86.5°; ir (potassium bromide): 1745 cm^{-1} (C=O); pmr: 8.80 (1H, dd, $J_{6,4}$ = 1.8 Hz, $J_{6,5}$ = 5 Hz), 8.31 (1H, dd, $J_{4,6}$ = 1.8 Hz, $J_{4,5}$ = 11 Hz), 8.29 (1H, s), 7.45 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 11 Hz), 3.94 (3H, s), 2.16 (6H, s); cmr: 168.9, 152.2, 139.0, 124.0, 87.5, 52.9, 20.7.

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.88; H, 4.98; N, 5.11.

Isopropyl 2-(Bisacetoxy)methylnicotinate (**7c**).

Prepared as above from isopropyl 2-methylnicotinate (**6c**) in 50% yield, mp 91-92°; ir (potassium bromide): 1745 cm^{-1} (C=O); pmr: 8.80 (1H, dd, $J_{6,4}$ = 1.8 Hz, $J_{6,5}$ = 4.8 Hz), 8.33 (1H, s), 8.30 (1H, dd, $J_{4,6}$ = 1.8 Hz, $J_{4,5}$ = 7.8 Hz), 7.41 (1H, dd, $J_{5,6}$ = 4.8 Hz, $J_{5,4}$ = 7.8 Hz), 5.30 (1H, h, J = 6.3 Hz), 2.16 (6H, s), 1.39 (6H, d, J = 6.3 Hz); cmr: 168.9, 164.6, 153.3, 152.0, 138.9, 124.0, 87.5, 70.1, 21.7, 20.7.

Anal. Calcd. for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 57.27; H, 5.89; N, 4.81.

t-Butyl 2-(Bisacetoxy)methylnicotinate (**7d**).

Prepared as above from *t*-butyl 2-methylnicotinate (**6d**) in 41% yield; ir (neat): 1730 cm^{-1} (C=O); pmr: 8.73 (1H, dd, $J_{6,4}$ = 2.5 Hz, $J_{6,5}$ = 5 Hz, 8.30 (1H, s), 8.17 (1H, dd, $J_{4,6}$ = 2.5 Hz, $J_{4,5}$ = 7.5 Hz), 7.5 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 7.5 Hz), 2.11 (6H, s), 1.67 (9H, s); cmr: 168.2, 164.0, 152.6, 151.0, 138.2, 127.6, 123.4, 82.9, 20.2, 17.7.

Anal. Calcd. for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 57.98; H, 6.14; N, 4.72.

Ethyl 2-(Carbaldoxime)nicotinate (**2b**).

To a solution of diacetate **7b** (500 mg, 1.78 mmoles) in 95% ethanol (4 ml) was added hydroxylamine hydrochloride (363 mg, 5.22 mmoles) and aqueous hydrochloric acid (3%, 8.7 mmoles). The reaction mixture was stirred at room temperature for 72 hours, neutralized with aqueous sodium carbonate, and extracted with chloroform (3 x 10 ml). The combined chloroform extracts were dried over anhydrous sodium sulfatre, filtered, and concentrated at reduced pressure to yield the title ester as a light-brown, crystalline solid, mp 140° (from absolute ethanol) (213 mg, 1.10 mmoles, 62%); ir (potassium bromide): 3600-3000 cm^{-1} (OH), 1740 cm^{-1} (C=O); pmr: 11.73 (1H, s), 8.71 (1H, dd, $J_{6,4}$ = 3 Hz, $J_{6,5}$ = 4.5 Hz), 8.38 (1H, s), 8.06 (1H, dd, $J_{4,6}$ = 3 Hz, $J_{4,5}$ = 8.5), 7.49 (1H, dd, $J_{5,6}$ = 4.5 Hz, $J_{5,4}$ = 8.5 Hz), 7.27 (2H, q, J = 6 Hz), 1.27 (3H, t, J = 6 Hz); cmr: 150.1, 147.6, 138.6, 135.1, 128.4, 128.1, 123.6, 100.0, 65.4.

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.52; H, 5.22; N, 14.08.

Methyl 2-(Carbaldoxime)nicotinate (**2a**) [17].

Prepared, as above, from the corresponding diacetate **7a** in 62% yield, mp 128°; ir (potassium bromide): 3200-2700 cm^{-1} (OH), 1700 cm^{-1} (C=O); pmr: 11.85 (1H, s), 8.69 (1H, dd, $J_{6,4}$ = 1.8 Hz, $J_{6,5}$ = 4.8 Hz), 8.38 (1H, s), 8.06 (1H, dd, $J_{4,6}$ = 1.8 Hz, $J_{4,5}$ = 8.0), 7.47 (1H, dd, $J_{5,6}$ = 4.8 Hz, $J_{5,4}$ = 8.0 Hz), 3.81 (1H, s); cmr: 167.4, 152.0, 150.2, 147.6, 137.6, 126.8, 123.9, 53.0.

Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.39; H, 4.51; N, 15.25.

Isopropyl 2-(Carbaldoxime)nicotinate (**2c**).

Prepared, as above, from the corresponding diacetate **7c** in 60% yield, mp 125.5°; ir (potassium bromide): 3400-3000 cm^{-1} (OH), 1710 cm^{-1} (C=O); pmr: 11.7 (1H, s), 8.70 (1H, dd, $J_{6,4}$ = 1.6 Hz, $J_{6,5}$ = 4.6 Hz), 8.38 (1H, s), 8.03 (1H, dd, $J_{4,6}$ = 1.6 Hz, $J_{4,5}$ = 7.8 Hz), 7.46 (1H, dd, $J_{5,6}$ = 4.6 Hz, $J_{5,4}$ = 7.8 Hz), 5.10 (1H, h, J = 6.3 Hz), 1.26 (6H, d, J = 6.3 Hz); cmr: 166.5, 151.8, 150.1, 147.6, 137.4, 127.4, 123.9, 69.5, 21.9.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 58.04; H, 5.94; N, 13.50.

t-Butyl 2-(Carbaldoxime)nicotinate (**2d**).

Prepared, as above, from the corresponding diacetate **7d** in 60% yield, mp 141-142°; ir (potassium bromide): 3600-3000 cm^{-1} (OH), 1730 cm^{-1} (C=O); pmr: 8.9 (1H, s), 8.78 (1H, dd, $J_{6,4}$ = 2 Hz, $J_{6,5}$ = 5 Hz), 8.15 (1H, dd, $J_{4,6}$ = 2 Hz, $J_{4,5}$ = 8 Hz), 7.36 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 8 Hz), 1.69 (9H, s); cmr: 164.9, 151.7, 150.4, 148.1, 138.1, 127.9, 123.2, 83.9, 28.1; ms 78, 92, 131, 135, 150, 166(100), 222.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.45; H, 6.40; N, 12.44.

An ORTEP representation of the X-ray crystal structure for **2d** is given Figure 1 [18].

t-Butyl 1-methyl-2-(carbaldoxime)nicotinate Methosulfate.

This compound was prepared from the corresponding oxime **2d** by adding dimethyl sulfate (0.22 ml, 294 mg, 2.33 mmoles) in one portion to a solution of the oxime (250 mg, 1.13 mmoles) in anhydrous tetrahydrofuran (5 ml). The reaction mixture was stirred at 50° under an atmosphere of nitrogen for 20 hours during which time a white precipitate formed. Recrystallization from methanol/tetrahydrofuran yielded the title salt as white crystals (mp 138-140°, 270 mg, 0.78 mmole, 69%); ir (potassium bromide): 3600-3000 cm^{-1} (-OH), 1730 cm^{-1} (C=O); pmr (DMSO-d_6): 9.20 (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 8 Hz), 8.82 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 10 Hz), 8.22 (1H, dd, $J_{5,4}$ = 10 Hz, $J_{5,6}$ = 8 Hz), 8.6 (1H, s), 3.4 (3H, s), 1.5 (9H, s); cmr (DMSO-d_6): 163.1, 149.4, 146.4, 145.4, 141.6, 133.5, 137.7, 53.2, 47.6, 28.0.

Anal. Calcd. for $C_{13}H_{20}N_2O_7S$: C, 44.82; H, 5.79. Found: C, 45.03; H, 6.08.

Ethyl Pyridine-2-(carbaldoxime)-3-acetate (**2e**).

Flash chromatographically purified ethyl 2-(acetoxymethyl)-pyridine-3-acetate [11,12,19,20] [bp 171-173° at 7 torr] (5.2 g) contaminated with about 5% of ethyl 5-acetoxy-2-methylpyridine-3-acetate in cold (10°) dichloromethane (75 ml) was, without further purification, treated with 3-chloroperoxybenzoic acid (7.6 g, 43.9 mmoles) in dichloromethane (75 ml). Stirring was continued after the addition was complete while the solution warmed to room temperature and for an additional 4 hours. The reaction mixture was diluted with an additional portion of dichloromethane (75 ml) and shaken with aqueous saturated sodium carbonate solution (100 ml). The dichloromethane phase was separated, dried by gravity filtration, the solvent evaporated and the presumed crude *N*-oxide residue, dissolved in acetic anhydride (20 ml) and added dropwise into boiling acetic anhydride (10 ml). The reaction mixture was then heated at reflux for 20 minutes and the excess acetic anhydride removed *in vacuo*. Water (10 ml) was added to the residue which was then neutralized with solid sodium carbonate and extracted with chloroform (4 x 40 ml). The combined chloroform extracts were dried over sodium sulfate, filtered, and the solvent removed at reduce pressure to give an oil which was chromatographed (200 g silica gel, ethyl acetate/chloroform 1:1; v:v) to give (second fraction) ethyl 2-(bisacetoxy)methylpyridine-3-acetate (**7e**) (3.71 g, 12.6 mmoles); ir (neat): 1740 cm^{-1} (C=O); pmr: 8.60 (1H, dd, $J_{6,4}$ = 1.5 Hz, $J_{6,5}$ = 5 Hz), 7.80 (1H, s), 7.60 (1H, dd, $J_{4,6}$ = 1.5 Hz, $J_{4,5}$ = 8 Hz), 7.30 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 8 Hz), 4.20 (2H, q, J = 7 Hz), 3.90 (2H, s), 2.12 (6H, s), 1.35 (3H, t, J = 7 Hz).

Anal. Calcd. for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.87; H, 5.77; N, 4.80.

In one portion, hydrochloric acid (6*N*, 13 ml) cooled to 0° was added to an ethanol solution (10 ml) of **7e** (0.7 g, 2.4 mmoles) also cooled to 0°. The reaction mixture was stirred at 0° for 20 hours. After neutralization with solid sodium bicarbonate, the aqueous solution was extracted with ether (3 x 25 ml) and the combined ether extracts were dried over sodium sulfate, filtered, and concentrated at reduced pressure to give a brown, viscous, lachrymatory oil (290 mg, 1.49 mmoles, 62%); ir (neat): 1730 cm^{-1} (C=O, ester), 1700 cm^{-1} (C=O, aldehyde); pmr: 10.20 (1H, s), 8.71 (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 5 Hz), 7.68 ($J_{4,6}$ = 1 Hz, $J_{4,5}$ = 9 Hz), 7.42 (1H, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 9 Hz), 4.18 (2H, q, J = 8 Hz), 4.13 (2H, s), 1.13 (3H, t, J = 8 Hz); cmr: 194.4, 169.6, 150.0, 148.2, 139.6, 130.9, 126.2, 60.5, 37.0, 13.7. This material, the presumed aldehyde derived from hydrolysis of the diacetate moiety in **7e**, was dissolved (220 mg) in 95% ethanol (1.5 ml) and the resulting solution was treated with a solution of hydroxylamine hydrochloride (174 mg, 2.5 mmoles) in pyridine (0.25 ml, 3.0 mmoles). The reaction mixture was heated at reflux for 16 hours, the solvent removed, and the solid residue triturated with hot chloroform (5 x 2 ml).

The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to yield a tan solid. Passage of a solution of this material in ether through a plug of silica gel yielded a pale oil which solidified on standing. Recrystallization from 1:1 (v:v) benzene:cyclohexane yielded **2e**, mp 127-128°; ir (potassium bromide): 3600-2600 cm^{-1} (-OH), 1730 cm^{-1} (C=O); pmr: 8.61 (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 5 Hz), 8.40 (1H, s), 7.64 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 9 Hz), 7.15 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 9 Hz), 4.05 (1H, q, J = 7 Hz), 3.90 (2H, s), 1.10 (3H, t, J = 7 Hz); cmr: 170.4, 150.3, 149.8, 139.2, 129.0, 122.78, 60.6, 38.9, 13.6.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.47; H, 5.84; N, 13.20.

Ethyl pyridine-2-(carbaldoxime)-3-acetate Methiodide.

This compound was prepared by methylation of the oxime **2e** as follows: To a solution of the oxime **2e** (0.40 g, 1.92 mmoles) in acetone (10 ml) there was added excess methyl iodide (2.0 ml) and the mixture was heated gently on the steam bath for 5 hours, during which time a pale yellow crystalline solid separated. The solid (mp 170-199° dec) was filtered off and the filtrate examined by tlc (ether eluent). A significant amount of unreacted starting material remained. The solvent and unreacted methyl iodide were removed at reduced pressure and the residue dissolved in fresh acetone (5 ml) and treated with an additional portion of methyl iodide (2.0 ml). Heating the reaction mixture at reflux for an additional 2 hours yielded a second crop of crystals - identical to the first. As additional starting material remained in the filtrate, the entire process was repeated, successively, until tlc no longer showed starting oxime in the filtrate. The several crops of crystals collected in this fashion were combined and recrystallized from anhydrous methanol to give the title salt (0.61 g, 1.74 mmoles, 91%); ir (potassium bromide): 3600 cm^{-1} (-OH), 1730 cm^{-1} (C=O); pmr: 9.19 (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 7 Hz), 8.70 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 9 Hz), 8.63 (1H, s), 8.10 (1H, dd, $J_{5,4}$ = 9 Hz, $J_{5,6}$ = 7 Hz), 4.45 (3H, s), 4.11 (2H, s), 4.02 (2H, q, J = 9 Hz), 1.27 (3H, t, J = 9 Hz).

Anal. Calcd. for $C_{11}H_{15}N_2O_3I$: C, 37.73; H, 4.32. Found: C, 37.62; H, 4.42.

2-Methylpyridine-3-carbaldehyde (**10**) [15].

2-Methyl-3-(hydroxymethyl)pyridine (**9**) [Aldrich Chemical Co., Milwaukee, WI] (100 mg, 0.813 mmoles) and manganese dioxide (200 mg, 23 mmoles) were suspended in dry dichloromethane (30 ml) and heated at reflux for 24 hours. The solid residue was removed by filtration and the solvent removed at reduced pressure. The residue was chromatographed on preparative tlc plates to yield the title aldehyde (893.3 mg, 0.76 mmole, 95%); ir (neat): 1720 cm^{-1} (C=O); pmr: 10.3 (1H, s), 8.65 (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 7 Hz), 8.05 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 9 Hz), 7.30 (1H, dd, $J_{5,6}$ = 7 Hz, $J_{5,4}$ = 9 Hz), 2.85 (3H, s); cmr: 191.9, 153.8, 150.9, 139.9, 130.4, 122.4, 23.0.

Methyl (*E*)-3-(2-Methyl-3-pyridyl)propenoate (**11**).

A mixture of 2-methylpyridine-3-carbaldehyde (**10**) [21] (100 mg, 0.83 mmole) and methyl triphenylphosphoranylidineacetate (553 mg, 1.65 mmoles) in benzene (30 ml) was heated under reflux for 2 hours. The solvent was removed at reduced pressure and the residue chromatographed on preparative tlc plates with ether as eluent to yield the title compound (110 mg, 0.63 mmole, 76%); ir (neat): 1720 cm^{-1} (C=O); pmr: 8.49 (1H, d, $J_{6,5}$ = 4.5 Hz), 7.90 (1H, d, J = 16 Hz), 7.79 (1H, d, $J_{4,5}$ = 8 Hz), 7.16 (1H, dd, $J_{5,6}$ = 4.5 Hz, $J_{5,4}$ = 8 Hz), 6.36 (1H, d, J = 16 Hz), 3.81 (3H, s), 2.66 (3H, s); cmr: 166.7, 157.3, 150.1, 140.8, 133.7, 128.9, 121.5, 120.9, 51.7, 22.7.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.51; H, 6.30; N, 7.87.

Methyl (*E*)/(*Z*)-3-(2-Methyl-3-pyridyl)propenoate (*E*/*Z*-**11**).

A mixture of 2-methylpyridine-3-carbaldehyde (**10**) [21] (100 mg, 0.83 mmole) and trimethylphosphonoacetate (165 g, 0.91 mmole) in aqueous potassium carbonate (3*M*, 20 ml) was stirred at room temperature for 4 hours. The solution was extracted with chloroform (2 x 25 ml) and the combined chloroform solutions dried over sodium sulfate, filtered and the solvent removed at reduced pressure to yield (100%) the title compounds (*ca.* 1:3 (*Z*):(*E*)). The spectroscopic data for the (*E*)-isomer is given above and the presumed (*Z*)-isomer had pmr: 8.45 (1H, d, $J_{6,5}$ = 4 Hz), 7.66 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 7.5 Hz), 7.09 (1H, dd, $J_{5,6}$ = 4 Hz, $J_{5,4}$ = 7.5 Hz), 7.08 (1H, d, J = 12 Hz), 6.11 (1H, d, J = 12 Hz), 3.64 (3H, s), 2.51 (3H, s); cmr: 165.7, 155.6, 148.8, 141.2, 136.7, 130.1, 121.9, 120.4, 51.4, 22.9.

Methyl 3-(2-Methyl-3-pyridyl)propionoate (**13**) [21].

A solution of alkene **11**, [either the single isomer, methyl (*E*)-3-(2-methyl-3-pyridyl)propenoate or the mixture of corresponding *E*/*Z* isomers] (100 mg, 0.56 mmole) in ethyl acetate (20 ml) was hydrogenated at room temperature and 50 pounds/in^2 hydrogen with 5% platinum on carbon (10 mg) in a Parr shaker. Hydrogen uptake was complete in 8 hours and removal of the solvent at reduced pressure yielded the title ester (93 mg, 0.52 mmole, 95%); ir (neat): 1760 cm^{-1} (C=O); pmr: 8.36 (1H, dd, $J_{6,4}$ = 2 Hz, $J_{6,5}$ = 6 Hz), 7.44 (1H, dd, $J_{4,6}$ = 2 Hz, $J_{4,5}$ = 9 Hz), 7.08 (1H, dd, $J_{5,6}$ = 6 Hz, $J_{5,4}$ = 9 Hz), 3.67 (3H, s), 2.95 (2H, t, J = 7.5 Hz), 2.60 (2H, t, J = 7.5 Hz), 2.55 (3H, s); cmr: 172.7, 156.6, 147.0, 134.1, 133.6, 121.3, 51.7, 27.7, 22.1].

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31. Found: C, 67.12; H, 7.27.

Methyl 3-[2-(Carbaldoxime)-3-pyridyl]propionate (**2f**).

The title oxime was prepared from methyl 3-(2-methyl-3-pyridyl)propionoate (**13**) (500 mg, 2.79 mmoles) by conversion of **13** to the *N*-oxide (435 mg, 2.23 mmoles, 80%) and thence to the presumed monoacetate (344 mg, 1.45 mmoles, 65%) as indicated above for its homologue **2e**; ir (neat): 1760 cm^{-1} (C=O); pmr: 8.49 (1H, dd, $J_{6,4}$ = 2 Hz, $J_{6,5}$ = 6 Hz), 7.55 (1H, dd, $J_{4,6}$ = 2 Hz, $J_{4,5}$ = 9 Hz), 7.22 (1H, dd, $J_{5,6}$ = 6 Hz, $J_{5,4}$ = 9 Hz), 5.27 (2H, s), 3.68 (3H, s), 3.02 (2H, t, J = 7.5 Hz), 2.46 (2H, t, J = 7.5 Hz), 1.92 (3H, s); cmr: 172.6, 170.6, 153.0, 147.6, 137.3, 134.9, 123.5, 65.5, 51.9, 34.7, 26.7, 20.9. This (presumed) monoacetate (500 mg, 2.2 mmoles), again as outlined above for **2e**, was converted to the corresponding *N*-oxide (439 mg, 1.73 mmoles) which, without purification, led to the corresponding (presumed) diacetate as a yellow oil (420 mg, 1.42 mmoles 82%); ir (neat): 1740 cm^{-1} (C=O); pmr: 8.52 (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 6 Hz), 7.90 (1H, s), 7.60 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 8 Hz), 7.21 (1H, dd, $J_{5,6}$ = 6 Hz, $J_{5,4}$ = 8 Hz), 3.62 (3H, s), 3.15 (2H, t, J = 7 Hz), 2.65 (2H, t, J = 7 Hz), 2.10 (6H, s); cmr: 173.0, 169.1, 152.1, 148.4, 138.6, 135.3, 124.9, 89.0, 35.4, 16.8, 11.2. To this oil (420 mg, 1.42 mmoles) in 95% **methanol** (4 ml) was added hydroxylamine hydrochloride (363 mg, 5.22 mmoles) and hydrochloric acid (3%, 8.7 ml, 8.7 mmoles). The reaction mixture was stirred at room temperature for 72 hours and then brought to neutrality with aqueous sodium bicar-

bonate, extracted with chloroform (3 x 30 ml), and the combined organic extracts dried over anhydrous sodium sulfate, filtered, and concentrated to give the title compound methyl 3-[2-(carbaldoxime)-3-pyridyl]propionate (**2f**) as white crystals, mp 107° (216 mg, 1.04 mmoles, 73%); ir (potassium bromide): 1740 cm^{-1} (C=O); pmr: 8.55 (1H, dd, $J_{6,4}$ = 3 Hz, $J_{6,5}$ = 6 Hz), 8.47 (1H, s), 7.61 (1H, dd, $J_{4,6}$ = 3 Hz, $J_{4,5}$ = 9 Hz), 7.22 (1H, dd, $J_{5,6}$ = 6 Hz, $J_{5,4}$ = 9 Hz), 3.62 (3H, s), 3.22 (2H, t, J = 7.5 Hz), 2.65 (2H, t, J = 7.5 Hz); cmr: 173.2, 149.8, 149.2, 147.5, 138.9, 135.5, 123.5, 51.7, 34.4, 28.1.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.66; H, 5.81; N, 13.45. Found: C, 57.47; H, 5.48; N, 13.20.

Methyl 3-[2-(carbaldoxime)-3-pyridyl]propionate Methosulfate.

This compound was prepared from **2f** by taking a solution of that oxime (75 mg, 0.35 mmole) in anhydrous tetrahydrofuran (4 ml) and adding dimethyl sulfate (0.033 ml, 0.35 mmole) to it. The reaction mixture was heated on a water bath at 40-50° under an atmosphere of nitrogen for 18 hours, during which time an oil separated. The solution was decanted from the oil and the latter was triturated with anhydrous tetrahydrofuran. Crystallization could not be effected; ir (neat): 3600-2600 cm^{-1} (OH), 1740 cm^{-1} (C=O); pmr (DMSO-d_6): 9.00 (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 4 Hz), 8.71 (1H, s), 8.62 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 8 Hz), 8.22 (1H, dd, $J_{5,6}$ = 4 Hz, $J_{5,4}$ = 8 Hz), 4.39 (3H, s), 3.70 (3H, s), 3.40 (3H, s), 3.20 (2H, t, J = 7.5 Hz), 2.80 (2H, t, J = 7.5 Hz).

Anal. Calcd. for $C_{12}H_{18}N_2O_7S + H_2O$: C, 40.90; H, 5.72; N, 7.95. Found: C, 40.54; H, 5.52; N, 7.70.

Diethyl 2-(2-Methylpridyl)ethylene-1,1-dicarboxylate (**12**).

A mixture of 2-methylpyridine-3-carbaldehyde (**10**) [21] (100 mg, 0.83 mmole) and diethyl malonate (145 mg, 0.91 mmole) in benzene (30 ml) containing a catalytic amount of piperidine was heated under reflux for 48 hours, cooled, and poured into a separatory funnel containing ether (100 ml). The etherial solution was washed, successively, with 5% aqueous hydrochloric acid (100 ml) and 5% aqueous sodium bicarbonate (50 ml). The ether solution was dried over sodium sulfate, filtered, and the solvent removed to yield the title diester (206 mg, 0.785 mmole, 95%); (neat): 1720 cm^{-1} (C=O); pmr: 8.50, (1H, dd, $J_{6,4}$ = 3 Hz, $J_{6,5}$ = 6 Hz), 7.62 (1H, dd, $J_{4,6}$ = 3 Hz, $J_{4,5}$ = 9 Hz), 7.11 (1H, dd, $J_{5,4}$ = 9 Hz, $J_{5,6}$ = 6 Hz), 7.89 (1H, s), 4.30 (4H, m, overlapping q, J = 6.0 Hz), 2.60 (3H, s), 1.35 (3H, t, J = 6.0 Hz), 1.23 (3H, t, J = 6.0 Hz); cmr: 165.8, 164.0, 157.7, 150.6, 140.0, 135.8, 129.0, 121.6, 62.3, 23.5, 14.7.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.51; H, 6.33; N, 5.30.

3-(Diethyl Methylpropanedioate)pyridine-2-carbaldoxime (**2g**).

A solution of diethyl 2-(2-methylpyridyl)ethylene-1,1-dicarboxylate (**12**) (100 mg, 0.38 mmole) in ethanol (20 ml) was hydrogenated at room temperature and 50 pounds/in^2 of hydrogen with 10% palladium on carbon (10 mg) in a Paar shaker. Hydrogen uptake was complete in 8 hours, the catalyst was removed by filtration, and the solvent removed at reduced pressure to yield chromatographically pure material, presumed to be **14**; ir (neat): 1720 cm^{-1} (C=O); pmr: 8.35 (1H, dd, $J_{6,4}$ = 2 Hz, $J_{6,5}$ = 6 Hz), 7.50 (1H, dd, $J_{4,6}$ = 2 Hz, $J_{4,5}$ = 9 Hz), 7.05 (1H, dd, $J_{5,4}$ = 9 Hz, $J_{5,6}$ = 6 Hz), 4.25 (4H, q, J = 8 Hz), 3.55 (1H, t, J = 7 Hz), 3.25 (2H, d, J = 7.0 Hz), 2.50 (3H, s), 1.20 (6H, t, J = 8 Hz) and which, without further purification, was dissolved (100 mg, 0.38 mmole) in dichloromethane (30 ml) at 0° and treated with a solution of 3-chloroperoxybenzoic acid (131 mg, 0.76 mmole) in dichloromethane (20 ml). The same work up as previously used generated the presumed corresponding *N*-oxide (102 mg, 034 mmole, 80%) and this material, without further purification, was converted by treatment with refluxing acetic anhydride, as before, to the presumed corresponding monoacetate (77 mg, 0.24 mmole, 65%); ir (neat): 1730 cm^{-1} (C=O) and thence, by the same sequence of reactions to the corresponding diacetate (60 mg, 0.16 mmole, 60%); ir (neat): 1735 cm^{-1} (C=O); pmr: 8.60 (1H, dd, $J_{6,4}$ = 1.5 Hz, $J_{6,5}$ = 5 Hz), 7.95 (1H, s), 7.70 (1H, dd, $J_{4,6}$ = 1.5 Hz, $J_{4,5}$ = 9 Hz), 7.30 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 9 Hz), 4.20 (4H, q, J = 8 Hz), 3.81 (1H, t, J = 7 Hz), 3.46 (2H, d, J = 7 Hz), 2.18 (6H, s), 1.20 (6H, t, J = 8 Hz).

Anal. Calcd. for $C_{18}H_{23}NO_8$: C, 56.69; H, 6.08; N, 3.67. Found: C, 56.55; H, 5.98; N, 3.44.

To a solution of the presumed diacetate (500 mg, 1.33 mmoles) in ethanol (95%, 4 ml) was added hydroxylamine hydrochloride (273 mg, 3.94 mmoles) and hydrochloric acid (3%, 6.56 ml, 6.56 mmoles). The reaction mixture was stirred at room temperature for 72 hours and dilute aqueous sodium carbonate was added to neutrality. Work up as previously described and chromatography on preparative tlc plates with chloroform as eluent, yielded the title compound **2g** as white crystals, mp 96-98° (216 mg, 0.73 mmole, 56%); ir (potassium bromide): 3200-2800 cm^{-1} (OH), 2740 cm^{-1} (C=O); pmr: 8.55 (1H, dd, $J_{6,4}$ = 3 Hz, $J_{6,5}$ = 6 Hz), 8.45 (1H, s), 7.62 (1H, dd, $J_{4,6}$ = 3 Hz, $J_{4,5}$ = 9 Hz), 7.30 (1H, dd, $J_{5,6}$ = 6 Hz, $J_{5,4}$ = 9 Hz), 4.11 (4H, m, J = 4 Hz), 3.84 (1H, t, J = 9 Hz), 3.48 (2H, d, J = 9 Hz), 1.17 (6H, m, J = 3 Hz); cmr: 168.8, 150.3, 149.4, 147.9, 139.8, 132.9, 123.2, 61.5, 51.9, 31.9, 13.9.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16; N, 9.52. Found: C, 56.94; H, 6.22; N, 9.78.

3-(Diethyl methylpropanedioate)pyridine-2-carbaldoxime Methosulfate.

This compound was prepared from the oxime **2g** (100 mg, 0.34 mmole) in anhydrous ether (2 ml) to which was added dimethyl sulfate (0.033 ml, 0.35 mmole). The reaction mixture was allowed to reflux gently under a nitrogen atmosphere for 3 hours, during which time a white precipitate formed. Another portion of dimethyl sulfate (0.016 ml, 0.17 mmole) was added and refluxing continued for an additional 24 hours. The white precipitate was removed by filtration, washed with anhydrous ether and dried in a vacuum oven for 10 hours at 1 torr. Recrystallization from methanol/ether yielded the methosulfate of **2g**, mp 112-115° (44%); ir (potassium bromide): 3600-2600 cm^{-1} (OH), 1740 cm^{-1} (C=O); pmr (DMSO-d_6): 9.10 (1H, d, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 5 Hz), 8.67 (1H, s), 8.65 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 8 Hz), 8.09 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 8 Hz), 4.26 (3H, s), 4.10 (4H, q, J = 7 Hz), 4.00-3.29 (3H, m), 3.41 (3H, s), 1.10 (6H, t, J = 7 Hz).

Anal. Calcd. for $C_{16}H_{24}N_2O_9S$: C, 45.71; H, 5.75. Found: C, 45.53; H, 5.72.

3-Acetoxypyridine-2-carbaldeoxime (**2i**).

Sodium hydroxide (3 ml of a stock solution prepared by dissolving solid sodium hydroxide (154 mg) in water (10 ml), 1.16 mmoles by titration) was added to (*E*)-3-hydroxypyridine-2-carboxaldoxime (**2h**) mp 175-176° (lit [21] 175-176°) (100 mg, 0.725 mmole) and the suspension stirred until dissolution was complete. Dichloromethane (5 ml) was added and the two-phase mix-

ture vigorously stirred while a solution of acetyl chloride (0.58 ml, 0.86 mmoles) in dichloromethane (8 ml) was added dropwise over 1.5 hours at 0-5° [22]. When the addition was complete, the biphasic reaction mixture was stirred for an additional 30 minutes, the phases separated, and the aqueous layer extracted once with dichloromethane (20 ml). The combined organic phases were washed with saturated sodium bicarbonate (1 x 10 ml), dried over sodium sulfate, filtered and concentrated at reduced pressure to yield the title compound as a pale yellow solid (99 mg, 0.44 mmole, 76%) mp 103-107°; ir (potassium bromide): 3600-3200 cm^{-1} (OH), 1780 cm^{-1} (C=O); pmr: 9.55 (1H, broad s), 8.30 (1H, s), 8.00 (2H, m), 7.10 (2H, m), 1.95 (3H, s). Although recrystallization could be effected from cyclohexane, there was no improvement in mp.

Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.18; H, 4.28; N, 15.33.

(*E*)-3-Acetoxy-*N*-methylpyridinium-2-carbaldoxime Tetrafluoroborate.

To a stirred suspension of trimethyloxonium tetrafluoroborate (1.42 g, 9.59 mmoles) in dry dichloromethane (200 ml) under nitrogen, was added solid 3-acetoxypyridine-2-carbaldoxime (**2i**) (1.73 g, 9.61 mmoles). Stirring was continued under nitrogen for 6 hours and the suspended solid was filtered with suction and washed with dry dichloromethane (3 x 75 ml) to give the title salt, mp 109-111° (1.93 g, 71%). Recrystallization without deacetylation could not be effected; ir (potassium bromide): 3600-2400 cm^{-1} (OH), 1780 cm^{-1} (C=O); pmr (DMSO-d_6): 8.80 (1H, s), 8.58 (1H, m), 8.00 (2H, m), 4.43 (3H, s), 2.33 (3H, s).

Anal. Calcd. for $C_9H_{11}N_2O_3BF_4(H_2O)_{0.5}$: C, 37.15; H, 4.16; N, 9.63. Found: C, 37.07; H, 4.31; N, 10.01.

3-(Acetoxymethyl)pyridine-2-carbaldoxime (**2j**).

To acetic anhydride (32.5 g, 318 mmoles, 30 ml) containing a few drops of acetyl chloride there was added commercially obtained 2-methyl-3-(hydroxymethyl)pyridine (**2**) (9.64 g, 78.4 mmoles) and the resulting mixture was heated at reflux for 12 hours. On cooling to room temperature, the mixture was concentrated at reduced pressure to a dark residue which was dissolved in a minimum amount of water. The aqueous solution was continuously extracted with chloroform for 24 hours, the organic solution dried over sodium sulfate, filtered, and concentrated at reduced pressure to the presumed corresponding primary acetate; ir (neat): 1715 cm^{-1} (C=O); pmr: 8.40 (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 5 Hz), 7.61 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 8 Hz), 7.10 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 8 Hz), 5.11 (2H, s), 2.60 (3H, s), 2.13 (3H, s); cmr: 167.9, 154.8, 146.4, 134.1, 127.2, 118.8, 61.2, 19.5, 18.3.

This material (9.90 g, 60 mmoles) was converted to the presumed corresponding *N*-oxide and thence, by the methods indicated above, to the presumed 2,3-diacetate; ir (neat): 1720 cm^{-1} (broad, C=O); pmr: 8.59 (1H, dd, $J_{6,4}$ = 2 Hz, $J_{6,5}$ = 6 Hz), 7.75 (1H, dd, $J_{4,6}$ = 2 Hz, $J_{4,5}$ = 6 Hz), 7.28 (1H, dd, $J_{5,6}$ = 6 Hz, $J_{5,4}$ = 6 Hz), 5.29 (2H, s), 5.21 (2H, s), 2.13 (3H, s), 2.10 (3H, s); cmr: 170.6, 153.7, 149.2, 148.6, 130.4, 123.4, 65.0, 62.6, 20.8.

Again, by the methods above and without further purification, this presumed diacetate (2.23 g, 10 mmoles) was converted, *via* the *N*-oxide, to the presumed corresponding 2,2,3-triacetate (1.30 g, 4.6 mmoles); ir (neat): 1760 cm^{-1} (C=O); pmr: 8.55 (1H, dd, $J_{6,4}$ = 2 Hz, $J_{6,5}$ = 5 Hz), 7.80 (1H, s), 7.72 (1H, dd, $J_{4,6}$ = 2 Hz, $J_{4,5}$ = 9 Hz), 7.25 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 9 Hz), 5.30 (2H, s), 2.15 (6H, s), 2.10 (3H, s). The 2,2,3-triacetate, in turn, was converted directly to the title oxime **2j** as follows: hydroxylamine hydrochloride (124 mg, 1.78 mmoles) followed by ice cold aqueous hydrochloric acid (1*N*, 3.2 ml) was added to a cold (−10°) solution of the triacetate (250 mg, 0.89 mmole) in ethanol (95%, 2 ml). The reaction mixture was stirred at −10° for 1 hour and then allowed to stand at −20° for 48 hours, after which it was made basic with dilute aqueous sodium bicarbonate (15 ml) and extracted with ether (3 x 25 ml). The combined ether extracts were dried over sodium sulfate, filtered, and the solvent removed at reduced pressure **without heating** to give a pale yellow solid which was dissolved in ether and chromatographed on a silica gel column. Elution from silica gel with ether yielded the title oxime **2j** (125 mg, 0.64 mmole, 72%, mp 173-175°); ir (potassium bromide): 3600-2400 cm^{-1} (OH), 1735 cm^{-1} (C=O); pmr: 8.65 (1H, d, J = 5 Hz), 8.50 (1H, s), 7.81 (1H, d, J = 9 Hz), 7.30 (1H, dd, $J_{5,4}$ = 5 Hz, $J_{5,6}$ = 9 Hz), 5.40 (2H, s), 2.11 (3H, s); cmr: 170.6, 150.4, 148.9, 148.5, 136.2, 131.2, 123.3, 63.3, 20.7.

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.52; H, 5.11; N, 14.33.

N-Methyl-3-(acetoxymethyl)pyridinium-2-carbaldoxime Methosulfate.

This salt of the oxime, 3-(acetoxymethyl)pyridine-2-carbaldoxime (**2j**) was prepared from the oxime (500 mg, 2.58 mmoles) by dissolving **2j** in freshly distilled anhydrous tetrahydrofuran (13 ml), under nitrogen, with heating and then, after cooling, treating the cooled solution with dimethyl sulfate (325 mg, 0.244 ml, 2.58 mmoles) added *via* a syringe. The contents of the septum-sealed-flask were then stirred at room temperature until precipitation appeared complete (3 days) at which time, the entire contents of the reaction flask were transferred to a centrifuge tube, the centrifugate washed with anhydrous tetrahydrofuran, and the supernatent treated with additional dimethyl sulfate. A total of 510 mg (1.59 mmoles, 62%) of off-white powder, mp 55-59° which decomposed upon attempted recrystallization was obtained in this way; ir (potassium bromide): 3600-2650 cm^{-1} (OH), 1740 cm^{-1} (C=O); pmr (DMSO-d_6): 12.80 (1H, s), 9.05 (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 5 Hz), 8.65 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 9 Hz), 8.62 (1H, s), 8.15 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 9 Hz), 5.29 (2H, s), 4.31 (3H, s), 3.33 (3H, s), 2.10 (3H, s).

Anal. Calcd. for $C_{11}H_{16}N_2O_7S(H_2O)$: C, 39.05; H, 5.36. Found: C, 39.12; H, 4.99.

2-[3-(2-Methylpyridyl)]ethanol (**15**).

A solution of ethyl 2-methylpyridyl-3-acetate (**8**) [12] (22.0 g, 122.9 mmoles) in anhydrous ether (75 ml) was added dropwise to a mechanically stirred suspension of lithium aluminum hydride (7.1 g, 186.6 mmoles) in anhydrous ether (200 ml) immersed in an ice-water bath. After the addition was complete, the cold bath was removed and the reduction continued at room temperature for 14 hours. Excess hydride was destroyed with water and the contents of the flask filtered through a celite mat. The residue on the celite pad was transferred to a breaker and washed with warm ether (2 x 300 ml) and once with absolute ethanol (100 ml). The combined organics were dried over sodium sulfate, filtered, and concentrated to a brown oil which, after chromatography on silica gel (elution from ether to ethyl acetate) yielded the title compound (15.5 g, 113.1 mmoles, 92%) mp 53-55°; ir (neat): 3200-3600 cm^{-1} (OH); pmr: 8.20 (1H, dd, $J_{6,4}$ = 2 Hz, $J_{6,5}$ = 5 Hz), 7.50 (1H, dd, $J_{4,6}$ = 2 Hz, $J_{4,5}$ = 9 Hz), 7.09 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 9 Hz), 4.50 (1H, broad s), 3.80 (2H, t, J = 6 Hz), 2.83 (2H, t,

J = 6 Hz), 2.50 (3H, s); cmr: 157.4, 147.2, 138.0, 133.3, 121.9, 62.2, 36.6, 22.5.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.95; H, 8.13; N, 10.20.

3-(2-Acetoxy)ethylpyridine-2-carbaldoxime (**2k**).

Acetic anhydride (54.3 g, 530 mmoles, 50 ml) containing several drops of acetyl chloride and 2-[3-(2-methylpyridyl)]ethanol (**15**) (15.5 g, 113.1 mmoles) was heated at reflux for 12 hours. Work up as above for the analogue with one fewer carbon yielded the presumed 2-methyl-3-[(2-acetoxy)ethyl]pyridine (20.0 g, 111.7 mmoles, 99%); ir (neat): 1740 cm^{-1} (C=O); pmr: 8.42 (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 5 Hz), 7.50 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 9 Hz), 7.10 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 9 Hz), 4.30 (2H, t, J = 7 Hz), 2.96 (2H, t, J = 7 Hz), 2.60 (3H, s), 2.02 (3H, s).

Without further purification, this presumed ester (20.0 g, 111.7 mmoles) was converted as previously indicated for its homologue *via* the corresponding *N*-oxide to the 2,3-substituted diacetate (18.4 g, 77.7 mmoles, 75%); ir (neat): 1755 cm^{-1} and 1740 cm^{-1} (C=O); pmr: 8.45, (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 4 Hz), 7.52 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 8 Hz), 7.25 (1H, dd, $J_{5,6}$ = 4 Hz, $J_{5,4}$ = 8 Hz), 5.25 (2H, s), 4.22 (2H, t, J = 7 Hz), 2.95 (2H, t, J = 7 Hz), 2.10 (3H, s), 1.94 (3H, s) and this presumed diacetate (5.9 g, 25 mmoles), again *via* the corresponding *N*-oxide and without purification of the intermediates (as described above), was converted to presumed 2,2,3-triacetate (4.8 g, 16.3 mmoles, 65%); ir (neat): 1765-1740 cm^{-1} (C=O); pmr: 8.62 (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 4 Hz), 7.96 (1H, s), 7.70 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 8 Hz), 7.35 (1H, dd, $J_{5,6}$ = 4 Hz, $J_{5,4}$ = 8 Hz), 4.36 (2H, t, J = 7 Hz), 3.20 (2H, t, J = 7 Hz), 2.15 (6H, s), 2.02 (3H, s). Finally, hydroxylamine hydrochloride (110 mg, 1.70 mmoles) followed by cold aqueous hydrochloric acid (1*N*, 2.0 ml) was added to a cold (−10°) solution of this presumed triacetate, *i.e.* 2-(bisacetoxy)-methyl-3-[(2-acetoxy)-ethyl]-pyridine (250 mg, 0.89 mmole) in ethanol (1.5 ml, 95%).

The reaction mixture was stirred at −10° for 1 hour and then allowed to stand in the refrigerator (−20°) for 48 hours, after which it was poured into a separatory funnel containing saturated sodium bicarbonate (10 ml) and the resulting aqueous solution extracted with ether (4 x 20 ml). The combined ether extracts were dried over anhydrous sodium sulfate and, after filtration, the solvent removed at reduced pressure to yield the title oxime, 3-(2-acetoxy)ethyl-pyridine-2-carbaldoxime (**2k**) (106 mg, 0.51 mmole, 60%) from ether, mp 46-50°; ir (potassium bromide): 3600-2600 cm^{-1} (OH), 1735 cm^{-1} (C=O); pmr: 8.60-8.50 (2H, broad s), 7.65 (1H, dd, $J_{4,6}$ = 0.5 Hz, $J_{4,5}$ = 4 Hz), 7.30 (1H, dd, $J_{5,6}$ = 2 Hz, $J_{5,4}$ = 4 Hz), 4.36 (2H, t, J = 7 Hz), 3.25 (2H, t, J = 7 Hz), 2.10 (3H, s); cmr: 149.9, 149.5, 147.8, 139.4, 133.0, 123.4, 63.9, 31.9, 20.8.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.57; H, 5.46; N, 13.13.

1-Methyl-3-(2-acetoxy)ethylpyridinium-2-carbaldoxime Methosulfate.

In anhydrous tetrahydrofuran (5 ml) and under a nitrogen atmosphere, there was dissolved 3-(2-acetoxy)ethylpyridine-2-carbaldoxime (**2k**) (100 mg, 0.48 mmole) and dimethyl sulfate (0.05 ml) was added. The reaction mixture was stirred under nitrogen for 48 hours at room temperature and the product, presumed to be the desired salt 1-methyl-3-(2-acetoxy)ethyl-pyridinium-2-carbaldoxime methosulfate, separated as an oil (100 mg, 0.28 mmole, 62%). Crystallization could not be effected; ir (neat): 3600-2800 cm^{-1} (OH), 1740 cm^{-1} (C=O); pmr (DMSO-d_6): 12.90 (1H, s), 9.00 (1H, dd, $J_{6,4}$ = 1 Hz, $J_{6,5}$ = 5 Hz), 8.60 (1H, dd, $J_{4,6}$ = 1 Hz, $J_{4,5}$ = 8 Hz), 8.58 (1H, s), 8.10 (1H, dd, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 8 Hz), 4.30 (3H, s), 4.20 (2H, t, J = 7 Hz), 3.40 (3H, s), 3.10 (2H, t, J = 7 Hz), 1.95 (3H, s); cmr (DMSO-d_6): 148.6, 147.9, 146.5, 142.0, 139.0, 126.9, 63.3, 53.2, 47.9, 31.6, 21.0.

Anal. Calcd. for $C_{12}H_{18}N_2O_7S$: C, 43.11; H, 5.43. Found: C, 42.94; H, 5.43.

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Supplementary Material Available.

Tables of atomic parameters for *t*-butyl 2-(carbaldoxime)-nicotinate (**2d**) as well as observed and calculated structure factors (21 pages) are available on request.

REFERENCES AND NOTES

[1] Presented, in part, at the 199th ACS National Meeting, Boston, MA, April 1990, ORGN 371.

[2] Taken, in part, from the Ph. D. dissertation of B.-C. Kao, Temple University, 1988. Present address: New England Nuclear Corporation, Boston, MA.

[3] Present address: Morton Chemical Company, Patterson, NJ.

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[5a] J. S. Smith, in The Chemistry of the Carbon-Nitrogen Double Bond, S. Patai, ed, Wiley-Interscience, Inc., New York, NY, 1970, p 235 ff; [b] S. R. Sandler and W. Karo, Organic Functional Group Preparation, Vol **6**, Academic Press, Inc., New York, NY. 1972, 365 ff and references therein.

[6a] D. M. Sanderson and E. F. Edson, *J. Pharm. Pharmacol.*, **11**, 721 (1959); [b] A. A. Kondritzer, R. I. Ellin and J. Edberg, *J. Pharm. Sci.*, **50**, 109 (1961) and references therein.

[7a] A. A. Kossiakoff and S. A. Spencer, *Nature*, **288**, 414 (1980); [b] L. A. P. de Jong, H. P. Benschop, G. R. van den Berg, G. Z. Wolring and D. C. de Korte, *Eur. J. Med. Chem.*, **17**, 257 (1981); [c] L. P. A. de Jong, G. A. Wolding and H. P. Benschop, *Arch. Toxicol.*, **49**, 175 (1982) and references therein.

[8] The details of *in vivo* action of the compounds whose preparation is reported here will be discussed elsewhere. However, preliminary results for some of the quaternary salts that were tested in the U. S. Army Medical Research Institute for Chemical Defense basic efficacy screen against Soman in the mouse are available. Survival data following a 2 x LD_{50} challenge for most are not encouraging.

[9] K. Tsuda, Y. Satch, N. Ikekawa and H. Mishima, *J. Org. Chem.*, **21**, 800 (1956).

[10] E. E. Ayling, *J. Chem. Soc.*, 1014 (1938).

[11] V. Boekelheide and W. J. Lin, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

[12] Y. Sato, T. Iwashige and T. Miyadera, *Chem. Pharm. Bull.*, **8**, 427 (1960).

[13] S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957).

[14] P. Baumgarten and A. Dornow, *Chem. Ber.*, **72**, 563 (1939).

[15] T. E. Catka and E. Leete, *J. Org. Chem.*, **43**, 2125 (1978).

[16] A. French, E. J. Blanz, Jr., J. R. DiAmaral and D. A. French, *J. Med. Chem.*, **13**, 1124 (1970).

[17] The corresponding aldehyde, prepared differently and from which the oxime could also, presumably, be made has been reported; [a] G. Queguiner and P. Pastour, *Bull. Soc. Chim. France*, 3678 (1969); [b] G. Queguiner and P. Pastour, *C. R. Acad. Sci. (Paris)*, **268**, 182 (1969).

[18] Crystals of **2d** suitable for analysis belong to the space group

$P2_12_12_1$ and a = 6.970(1)Å, b = 9.065(1)Å, c = 19.232(3)Å, volume = 1215Å^3, Z = 4. The data were collected on an Enraf-Nonius CAD4 Diffractometer using graphite-monochromatized Mo K_α radiation; 3913 reflections were collected; 3315 greater than 1 x $\sigma(F)$ were used in solution and refinement of the sturcture (1740 of these were independent). Crystal dimensions of the needle analyzed were 0.3 x 0.3 x 1.0 mm. The data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods and refined by full-matrix least squares techniques. The final R = 0.043 and the final weighted R, R_w = 0.055.

[19] C. R. Costin, C. J. Morrow and H. Rapoport, *J. Org. Chem.*, **41**, 535 (1976).

[20] The corresponding methyl ester progenitor, *i.e.* methyl 2-methylpyridyl-3-acetate, has also been reported. See G. S. S Murthi, S. K. Gangopadhyay and M. Murthi, *Indian J. Chem.*, **18B**, 274 (1979).

[21] The corresponding carboxylic acid has been reported, see P. Baumgarten, and A. Dornow, *Chem. Ber.*, **73**, 353 (1940).

[22] Low temperature and vigorous stirring are necessary for successful consummation of this reaction.