2-Carbaldoximes of Pyridine-4- and 5-carboxylic Acids [1]

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A series of pyridine-2-carbaldoximes, all of which are substituted at the 4- or 5-position with derivatives of the corresponding carboxylic acids, have been prepared *via* the corresponding pyridine-2-carbaldehydes.

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Introduction.

Pyridine-2-carbaldoxime (**1**, [oxime geometry unspecified]) as its methochloride [5] and other aldoximes [6] remain useful weapons in the armamentarium of resources that may be deployed to aid in the regeneration of cholinesterase enzymes (*e.g.*, EC 3.1.1.7 and EC 3.1.1.8) poisoned by organophosphorus derivatization.

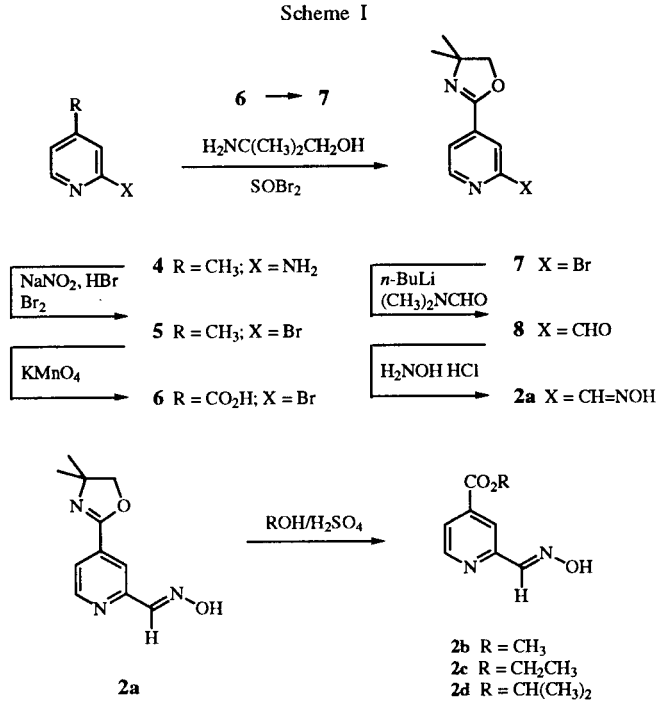
Although the details of amino acid sequence (526 residues) of the cholinesterase enzyme from *Torpedo Californica* [7], as well as the three-dimensional structure (to 2.8 angstrom resolution) [8] have become available, it is still *assumed* that active-site serine phosphorylation is responsible for loss of activity. Thus, (a) the ability of pyridine-2-carbaldehyde oxime methochloride and similar compounds to effect enzyme regeneration remains obscure and (b) the belief that hydrolysis of the (serine) oxygen-to-phosphorus bond is promoted by the pyridinecarbaldoxime derivative which, it is argued, must therefore also be in the active site or nearly so, remains current [9].

As we argued before with regard to the 3-substitued pyridine-2-carbaldoximes [1] (and in the absence of evidence to the contrary), it is possible that hydrolysis of the enzyme serine oxygen-to-phosphorus bond might be made more facile if coordination of the pyridine-2-carbaldoxime within the active site were improved. To that end, we have undertaken the synthesis of the hitherto unknown pyridine-2-carbaldoximes bearing esteratic substituents at positions 4- and 5- on the pyridine ring. While the testing of these materials is ongoing [10], the syntheses of the 2-carbaldoxime isonicotinic acid derivatives **2a-d** and the corresponding 5-alkoxycarbonylpyridine-2-carbaldehyde oximes **3a-c** are reported here.

Results and Discussion.

Scheme I provides an overview of the generalized synthetic protocol for the preparation of **2a** and, from **2a** to **2b-d** inclusive. Thus, as shown, commercially available 2-amino-4-picoline (**4**) [11] was diazotized in the presence of bromine [12] to yield the corresponding 2-bromo-4-methylpyridine (**5**) which was oxidized by permanganate to the known [13] 2-bromoisonicotinic acid (**6**).

Scheme I



The carboxylic acid **6** was converted to the recently reported [14] oxazoline derivative **7** by reaction with 2-amino-2-methylpropanol. Either (a) a rapid and strongly exothermic reaction with thionyl bromide, or (b) a slower, less vigorous and somewhat lower yield thermal process directly from **6** and 2-amino-2-methylpropanol could be used to generate **7**.

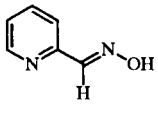
Lithiation of the 2-bromo-4-(4,4'-dimethyloxazolin-2-yl)pyridine (**7**) by low temperature reaction with *n*-butyllithium and carefully controlled reaction of the presumed 2-pyridyllithium intermediate with dimethylformamide in tetrahydrofuran yielded the corresponding pyridine-2-carboxaldehyde derivative **8** directly. Purification of the aldehyde could be effected by column chromatography (silica gel) and while we presume the aldehyde might be stored at low temperature in an inert atmosphere, its relative ease of oxidation prompted us to use it immediately. Interestingly, as described in the Experimental, simple dissolution of

the aldehyde in ethanol containing hydroxylamine hydrochloride and sodium acetate rapidly led to the corresponding oxime **2a**.

Our initial attempts to simultaneously convert the oxazoline function to ester and aldehyde to acetal by treatment of the aldehyde **8** with, *e.g.*, methanolic sulfuric acid, followed by purification of the ester-acetal, and direct conversion as earlier [1] to oxime (*e.g.*, **2b**) while successful, suffered from poor yields. Thus, we were pleasantly surprised to find that when the oxime **2a** itself was simply treated with the appropriate alcohol-sulfuric acid mixtures, good yields of the corresponding esters **2b-d** were obtained.

The preparation of pyridine-2-carbaldoxime-5-carboxylic acid derivatives was somewhat more straightforward as both 6-methylnicotinic acid (**9a**) and the corresponding ester methyl 6-methylnicotinate (**9b**) are commercially available [11]. Methyl 6-methylnicotinate **9b** was converted to the corresponding *N*-oxide with *meta*-chloroperbenzoic acid and, without isolation, following the procedure of Boekelheide and Linn [15], the rearrangement of the *N*-oxide to methyl 6-acetoxymethylnicotinate (**9c**) was affected. Repetition of the protocol beginning with formation of the *N*-oxide of **9c** led to the diacetate **9d** and, with hydroxylamine hydrochloride in methanol, the later produced the oxime **3a** directly.

Simple acid catalyzed ester interchange with ethanol or 2-propanol, respectively, produced **3b** and **3c**.



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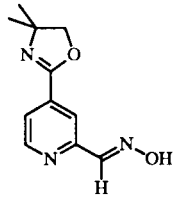
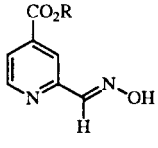
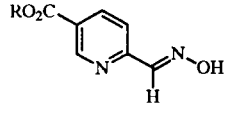


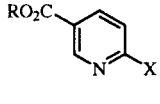
2a



2b R = CH_3
2c R = CH_2CH_3
2d R = $CH(CH_3)_2$



3a R = CH_3
3b R = CH_2CH_3
3c R = $CH(CH_3)_2$



9a R = H; X = CH_3
9b R = X = CH_3
9c R = CH_3; X = $CH_2O_2CCH_3$
9d R = CH_3; X = $CH(O_2CCH_3)_2$

EXPERIMENTAL

General.

All moisture and air-sensitive reactions were performed in oven dried glassware under a positive pressure of argon. Sensitive liquids and solutions (*e.g.*, butyllithium) were transferred by syringe or cannula and introduced into the reaction vessels through rubber septa. All commercial solvents and reagents were used without further purification unless otherwise indicated. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl under argon.

Analtech silica gel GF 0.25 mm plates (with indicator) were used for analytical tlc and flash chromatography was performed with Merck silica gel (230-400).

Melting points were determined on a Thomas-Hoover MelTemp apparatus and are uncorrected. Boiling points were obtained during distillation are uncorrected. CW infrared spectra were measured on a Perkin Elmer 137 grating spectrometer and FT-IR's on a Mattson 4020 as neat liquids between salt plates or solids ground with potassium bromide and then pressed into transparent discs in a Wilks die. Absorbances are reported in wavenumbers (cm^{-1}). The pmr and cmr spectra were obtained on a GE QE 300 spectrometer operating at 300 MHz for the former and 75.48 MHz for the latter in deuteriochloroform ($CDCl_3$) or perdeuteriodimethyl sulfoxide (d_6-DMSO) solvents (as noted) and are reported as δ (ppm) relative to TMS = 0.00. Usually a peak due to a trace of undeuterated solvent was used as reference.

Routine mass spectra were obtained on an HP 5995 GC/MS and elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, or by Micro-Analysis Inc., Wilmington, DE.

2-Bromo-4-methylpyridine (**5**).

2-Amino-4-methylpyridine (50 g, 0.46 mole) was added over 10 minutes to cold (-5°) aqueous hydrobromic acid (292 ml, 2.59 moles). With stirring and external cooling, bromine (70 ml, 1.37 moles) was added slowly enough to allow the temperature to remain below 0°. When the addition was complete, the dark red precipitate was treated with a solution of sodium nitrite (87.5 g, 1.27 moles) in water (125 ml) that was added at such a rate as to keep the temperature of the reaction mixture below 5°. After stirring for one hour while the temperature gradually rose to about 20°, a solution of sodium hydroxide (187.7 g, 4.7 moles) in water (248 ml) was added dropwise, with external cooling, at a rate such that the temperature of the reaction mixture did not rise above 25°. When the addition was complete, the reaction mixture was extracted with ether (3 x 100 ml), the combined ether extracts washed with brine (2 x 50 ml), dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. Two distillations yielded the bromopicoline **5**, bp 226-228° (760 torr) (lit [12] 223-224°); pmr (deuteriochloroform): 8.1 (1H, d, $J_{6,5}$ = 4.8 Hz), 7.2 (1H, d, $J_{4,5}$ = 0.6 Hz), 7.0 (1H, dd, $J_{5,6}$ = 4.8, $J_{5,4}$ = 0.6 Hz), 2.3 (3H, s); cmr: 150.2, 149.6, 142.0, 128.4, 123.6, 20.6.

2-Bromoisonicotinic Acid (**6**).

2-Bromo-4-methylpyridine (**5**) (50.0 g, 0.29 mole) was suspended in water (1.0 l) and potassium permanganate (114.0 g, 0.72 mole) was added in one portion. The purple solution was

heated to reflux for 6 hours and then an additional portion of potassium permanganate (10 g, 60 mmoles) was added and refluxing continued for one more hour. The hot solution was filtered with suction and the residue washed with boiling water (50 ml). The cooled aqueous solution was extracted with ether (2 x 25 ml) and concentrated *in vacuo* to a volume of about 500 ml and the cool solution was acidified with hydrochloric acid (6 *N*) while the acid precipitated. Recrystallization of the precipitate from hot water yielded 2-bromoisonicotinic acid, (35%) mp 180° (lit [13] mp 185°); pmr (d_6-DMSO): 8.5 (1H, d, $J_{6,5}$ = 4.8 Hz), 7.9 (1H, d, $J_{5,3}$ = 0.3 Hz), 7.8 (1H, dd, $J_{5,6}$ = 4.8 Hz, $J_{3,5}$ = 0.3 Hz); cmr: 164.6, 151.5, 141.8, 141.2, 127.0, 122.4.

2-Bromo-4-(4,4'-dimethyloxazolin-2-yl)pyridine (**7**).

Method A.

A mixture of ethyl 2-bromoisonicotinate (10 g, 43 mmoles) and 2-amino-2-methyl-1-propanol (5 g, 56 mmoles) was brought to reflux. After 2 hours the excess 2-amino-2-methylpropanol was removed by distillation at reduced pressure (57-63° at 3 torr) and the remaining thick oil triturated with ethanol (4 ml). The precipitate, *ca.* 9 g (assumed to be the amide), was removed by filtration and dissolved, at room temperature, in thionyl bromide (15 ml) over about 0.5 hour. With cooling in an ice-bath, ammonium hydroxide (*ca.* 60 ml) was added dropwise (**CAUTION**). The resulting aqueous solution was extracted with chloroform (4 x 25 ml), the organic layers combined, washed with brine (1 x 25 ml), dried over anhydrous potassium carbonate, and the solvent removed at reduced pressure. Distillation at 2 torr (105-110°, lit [16] 101° at 2 torr) yielded the title compound (9.0 g, 0.04 mmole, 81%) which spontaneously crystallized (mp 49.5°).

Method B.

A mixture of ethyl 2-bromoisonicotinate (10 g, 43 mmoles) and 2-amino-2-methyl-1-propanol (7.7 g, 87 mmoles) was refluxed for 48 hours and allowed to cool to room temperature. The title compound (5.6 g, 21.9 mmoles, 50%, bp 105-110°, lit [16] 101° at 2 torr), which spontaneously crystallized (mp 49.5°), was obtained as the second fraction of a fractional distillation; ir (potassium bromide): 1589 cm^{-1} (C=N); pmr (deuteriochloroform): 8.8 (1H, d, $J_{6,5}$ = 5.1 Hz), 8.4 (1H, s), 8.1 (1H, d, $J_{5,6}$ = 5.1 Hz), 4.6 (2H, s), 1.8 (6H, s); cmr 158.6, 149.9, 142.0, 137.5, 126.0, 120.5, 79.0, 67.7, 27.7.

Anal. Calcd. for $C_{10}H_{11}N_2OBr$: C, 47.08; H, 4.35; N, 10.98. Found: C, 46.78; H, 4.43; H, 10.81.

4-(4',4'-dimethyloxazolin-2-yl)pyridine-2-carbaldehyde Oxime (**2a**).

To a stirred solution of 2-bromo-4-(4',4'-dimethyloxazolin-2-yl)pyridine (**7**) (1.0 g, 3.9 mmoles) in THF (60 ml) at -78° under an atmosphere of argon there was added *n*-butyllithium (4.3 mmoles). After 1 hour, a solution of dimethylformamide (0.70 ml, 9.0 mmoles) in tetrahydrofuran (10 ml) was added as one portion and the solution was allowed to stir for 2 hours at -78° before being poured into a vigorously stirred brine solution (30 ml) at room temperature. After stirring for an additional 10 minutes, the aqueous solution was extracted with ether (3 x 25 ml) and the combined material was washed with water, brine, and dried over anhydrous sodium sulfate. The mixture was filtered, concentrated at reduced pressure, and chromatographed on silica gel (ether) to give a yellowish oil (640 mg) which was presumed to be the corresponding aldehyde. The oil, without further purification, was dissolved in 50% aqueous ethanol (10 ml) and combined, with stirring, with a solution containing hydroxylamine hydrochloride (0.7 g, 9.42 mmoles) and sodium acetate (1.6 g, 12.0 mmoles) in 50% aqueous ethanol (40 ml). The title compound (550 mg, 2.5 mmoles, 80%) precipitated after about 10 minutes and was removed by suction filtration, mp 178°; ir (potassium bromide): 3178 cm^{-1}, 2796 cm^{-1} (CH=N-OH), 1589 cm^{-1} (C=N); pmr (deuteriochloroform): 10.9 (1H, s), 8.7 (1H, dd, $J_{6,5}$ = 5.1 Hz, $J_{6,3}$ = 0.9 Hz), 8.5 (1H, dd, $J_{3,5}$ = 1.2 Hz, $J_{3,6}$ = 0.9 Hz), 8.3 (1H, s), 7.7 (1H, dd, $J_{5,6}$ = 5.1 Hz, $J_{5,3}$ = 1.2 Hz), 4.2 (2H, s), 1.4 (6H, s); cmr: 152.7, 149.4, 149.3, 135.1, 121.3, 118.3, 79.2, 67.5, 27.6.

Anal. Calcd. for $C_{11}H_{13}O_2N_3$: C, 60.27; H, 5.94; N, 18.94. Found: C, 60.31; H, 6.02; N, 19.18.

4-Methoxycarbonylpyridine-2-carbaldehyde Oxime (**2b**).

Method A.

To a stirred solution of 2-bromo-4-(4',4'-dimethyloxazolin-2-yl)pyridine (**7**) (1.0 g, 3.9 mmoles) in THF (60 ml) at -78° under an atmosphere of argon was added *n*-butyllithium (4.3 mmoles). After 1 hour, a solution of dimethylformamide (0.70 ml, 9.0 mmoles) in tetrahydrofuran (10 ml) was added as one portion and the reaction mixture was allowed to stir for 2 hours at -78° before being poured into a vigorously stirred brine solution (30 ml) at room temperature. After stirring for an additional 10 minutes, the aqueous solution was extracted with ether (3 x 25 ml) and the combined organic material was washed with water, brine, and dried over anhydrous sodium sulfate. The mixture was filtered, concentrated at reduced pressure, and chromatographed on silica gel (ether) to give a yellowish oil (640 mg) which was presumed to be the corresponding aldehyde. The oil, without further purification, was immediately dissolved in methanolic sulfuric acid (100 ml of a solution prepared by mixing 50 ml of methanol, 4 ml of concentrated sulfuric acid and 5 ml of water and bringing the volume to 100 ml by addition of methanol) and the resulting solution brought to reflux. After heating at reflux for 18 hours, the volume of the cooled solution was brought to about 50 ml at reduced pressure, neutralized with 10% aqueous sodium bicarbonate and extracted with chloroform (4 x 25 ml). The combined organic extracts were washed with brine (2 x 15 ml) and dried over anhydrous sodium sulfate. Filtration and removal of the solvent at reduced pressure gave a dark oil which, qualitatively, by pmr appeared to be a mixture of about 4:1 acetal:aldehyde esters. Without further purification, the crude mixture was taken up in methanol (25 ml) and that solution was treated with hydroxylamine hydrochloride (700 mg, 10 mmoles) and hydrochloric acid (3%, 10 ml). After 72 hours, the mixture was neutralized with aqueous sodium bicarbonate and extracted with chloroform (4 x 15 ml). The combined chloroform extracts were dried over anhydrous sodium sulfate, filtered, and the solvent removed at reduced pressure to yield a yellowish solid, mp 168-173° (235 mg, 1.3 mmoles, 33%), subsequently identified as the title oxime (*vide infra*).

Method B.

A methanolic sulfuric acid solution was prepared by mixing methanol (50 ml) with concentrated sulfuric acid (4 ml) and water (5 ml) and bringing the total volume to 100 ml with additional methanol. To this solution was added 4-(4',4'-dimethyloxazolin-2-yl)pyridine-2-carbaldehyde oxime (**2a**) (500 mg, 2.3

mmoles) in one portion and the resulting red solution was heated at reflux for 18 hours. After cooling, the volume was brought to about 50 ml by removal of the solvent at reduced pressure, neutralized by addition of 10% aqueous sodium carbonate solution and extracted with chloroform (4 x 25 ml). The combined chloroform extracts were washed with brine, dried over sodium sulfate, filtered and the solvent removed at reduced pressure to yield the title oxime methyl ester, mp 178° (from methanol) (316 mg, 1.6 mmoles, 71%); ir: 3200-2850 cm^{-1} (CH=N-OH), 1728 cm^{-1} (C=N); pmr (d_6-DMSO): 11.8 (1H, s), 8.7 (1H, d, $J_{6,5}$ = 5.1 Hz), 8.1 (2H, s), 7.7 (1H, dd, $J_{5,6}$ = 5.1 Hz, $J_{5,3}$ = 1.5 Hz), 3.9 (3H, s); cmr: 165.2, 153.7, 151.2, 148.2, 137.9, 122.2, 118.3, 52.81.

Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.33; H, 4.44; N, 15.56. Found: C, 53.49; H, 4.37; N, 15.86.

4-Ethoxycarbonylpyridine-2-carbaldehyde Oxime (**2c**).

If ethanol is used in place of methanol as in the preparation of **2b** above the ethyl ester **2c**, mp 149° (346 mg, 1.78 mmoles, 78% from ethanol), is isolated instead of the methyl ester **2b**; ir (potassium bromide): 3172-2783 cm^{-1} (CH=N-OH), 1726 cm^{-1} (C=N); pmr (d_6-DMSO): 11.8 (1H, s), 8.7 (1H, d, $J_{6,5}$ = 5.1 Hz), 8.1 (2H, s), 7.7 (1H, d, $J_{5,6}$ = 5.1 Hz), 4.3 (2H, q, J = 7.2 Hz), 1.3 (3H, t, J = 7.2 Hz); cmr: 164.2, 153.2, 150.6, 148.2, 137.6, 122.2, 118.3, 61.6, 13.9.

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.15; N, 14.93. Found: C, 55.62; H, 5.16; N, 14.55.

4-Isopropoxycarbonylpyridine-2-carbaldehyde Oxime (**2d**).

If 2-propanol is used in place of methanol as in the preparation of **2b** above the isopropyl ester **2d**, mp 124° (380 mg, 1.83 mmoles, 80% from 2-propanol), is isolated instead of the methyl ester **2b**; ir (potassium bromide): 3500-2500 cm^{-1} (CH=N-OH),1703 cm^{-1} (C=N); pmr (d_6-DMSO): 11.9 (1H, s), 8.7 (1H, d, $J_{6,5}$ = 5.1 Hz), 8.1 (2H, 1s, d, $J_{3,5}$ = 1.2 Hz), 7.7 (1H, dd, $J_{5,3}$ = 1.2 Hz, $J_{5,6}$= 5.1 Hz), 5.1 (1H, h, J = 6.3 Hz), 1.3 (6H, d, J = 6.3 Hz); cmr: 163.7, 153.2, 150.5, 148.1, 137.9, 122.2, 118.1, 69.4, 21.4.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.77; N, 13.46. Found: C, 57.91; H, 5.61; N, 13.20.

Methyl 6-Acetoxymethylnicotinate (**9c**).

To a stirred solution of methyl 6-methylnicotinate (**9b**) (15.0 g, 99.3 mmoles) in dry dichloromethane (50 ml) at 0° was added, dropwise, a solution of *meta*-chloroperbenzoic acid (20.6 g, 0.12 mole) in dichloromethane (30 ml) [17]. After 10 hours at room temperature, the reaction mixture was diluted with an additional portion of dichloromethane (125 ml), washed with 10% sodium carbonate solution (2 x 75 ml) and brine and then dried over anhydrous sodium sulfate. Filtration and removal of the solvent at reduced pressure yielded an oil, presumed to be the *N*-oxide (14.1 g, 84.4 mmoles, 85%) which was, without further purification, immediately dissolved in acetic anhydride (25 ml). The resulting acetic anhydride solution was added dropwise to gently refluxing acetic anhydride (35 ml) and after an additional 30 minutes at reflux, the reaction mixture was allowed to cool to room temperature and concentrated by distillation of the solvent at reduced pressure. Water (30 ml) and aqueous 10% sodium carbonate (until neutrality) was added to the residue which was then extracted with chloroform (3 x 50 ml). The combined organic extracts were washed with water and then with brine and then dried over sodium sulfate. After filtration and removal of the solvent, a dark residue remained which was distilled under vacuum to afford the title compound as an oil (10.1 g, 48.5 mmoles, 60%) that solidified during distillation (bp 117-120° at 3 torr, mp 88°); ir (potassium bromide): 1750 cm^{-1}, 1695 cm^{-1} (C=O); pmr: 9.1 (1H, d, $J_{6,4}$ = 2.1 Hz), 8.3 (1H, dd, $J_{4,6}$ = 2.1 Hz, $J_{4,3}$ = 8.1 Hz), 7.4 (1H, d, $J_{3,4}$ = 8.1 Hz), 5.3 (2H, s), 3.9 (3H, s), 2.2 (3H, s); cmr: 170.4, 165.4, 160.1, 150.9, 138.1, 125.1, 120.9, 66.3, 52.2, 20.8.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.42; H, 5.26; N, 6.70. Found: C, 57.41; H, 5.04; N, 6.47.

Methyl 6-Nicotinaldehyde Diacetate (**9d**).

To a stirred solution of methyl 6-acetoxymethylnicotinate (**9c**) (7.5 g, 36 mmoles) in dry dichloromethane (20 ml) at 0° was added, dropwise, a solution of *meta*-chloroperbenzoic acid (7.4 g, 43.0 mmoles) in dichloromethane (20 ml) [17]. After 12 hours at room temperature, the reaction mixture was diluted with an additional portion of dichloromethane (100 ml), washed with 10% sodium carbonate solution (2 x 50 ml) and brine and then dried over anhydrous sodium sulfate. Filtration and removal of the solvent at reduced pressure yielded an oil, presumed to be the *N*-oxide (6.5 g, 28.7 mmoles, 80%) which was, without further purification, immediately dissolved in acetic anhydride (20 ml). The resulting acetic anhydride solution was added dropwise to gently refluxing acetic anhydride (30 ml) and after an additional 30 minutes at reflux, the reaction mixture was allowed to cool to room temperature and concentrated by distillation of the solvent at reduced pressure. Water (20 ml) and aqueous 10% sodium carbonate (until neutrality) was added to the residue which was then extracted with chloroform (3 x 50 ml). The combined organic extracts were washed with water and then with brine and then dried over sodium sulfate. After filtration and removal of the solvent, a dark residue remained which was purified by column chromatography (ether) afford the title compound as white crystalline solid (3.68 g, 14.43 mmoles, 58%) mp 120° from methanol); ir (potassium bromide): 1766 cm^{-1}, 1724 cm^{-1} (C=O); pmr: 9.2 (1H, d, $J_{6,4}$ = 2.1 Hz), 8.3 (1H, dd, $J_{4,6}$ = 2.1 Hz, $J_{4,3}$ = 8.1 Hz), 7.7 (1H, s), 7.6 (1H, d, $J_{3,4}$ = 8.1 Hz), 4.0 (3H, s), 2.2 (6H, s); cmr: 168.6, 165.1, 157.8, 150.6, 138.0, 126.6, 121.2, 88.8, 52.4, 20.8.

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.87; N, 5.24. Found: C, 53.47; H, 4.73; N, 5.13.

5-Methoxycarbonylpyridine-2-carbaldehyde Oxime (**3a**).

To a stirred solution of methyl 6-nicotinaldehyde diacetate (**9d**) (1.0 g, 3.9 mmoles) in methanol (10 ml) there was added hydroxylamine hydrochloride (8.2 mg, 11.8 mmoles) and hydrochloric acid (3%, 16 ml, 16 mmoles). The reaction mixture was stirred at room temperature for 72 hours, was then neutralized with 20% aqueous sodium carbonate, and extracted with dichloromethane (3 x 25 ml). The organic material was combined, dried over anhydrous sodium sulfate, filtered, and evaporated to yield the oxime **3a**, mp 182° (from methanol); ir (potassium bromide): 3525 cm^{-1} - 2737 cm^{-1} (CH=N-OH); 1726 cm^{-1} (C=O); pmr (d_6-DMSO): 12.0 (1H, s), 9.0 (1H, d, $J_{6,4}$ = 1.8 Hz), 8.2 (1H, dd, $J_{4,6}$ = 1.8 Hz, $J_{5,4}$ = 8.4 Hz), 8.1 (1H, s), 7.8 (1H, d, $J_{4,5}$ = 8.4 Hz), 3.85 (3H, s); cmr: 164.8, 155.6, 149.8, 148.2, 137.3, 125.0, 119.5, 52.3.

Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.33; H, 4.44; N, 15.55. Found: C, 53.17; H, 4.40; N, 15.30.

5-Ethoxycarbonylpyridine-2-carbaldehyde Oxime (**3b**).

5-Methoxycarbonylpyridine-2-carbaldehyde oxime (**3a**) (1.6 g, 8.9 mmoles) in a solution of ethanolic sulfuric acid (100 ml, prepared by mixing water [5 ml], absolute ethanol [50 ml] and sulfuric acid [4 ml, 98%] and bringing the total volume to 100 ml with additional absolute ethanol) was heated to reflux for 24 hours. After cooling, the solution was concentrated at reduced pressure to a total volume of *ca.* 30 ml and neutralized by addition of aqueous (10%) sodium carbonate. The aqueous solution was extracted with chloroform (4 x 25 ml) and the organic phases were combined and dried over anhydrous sodium sulfate. The desiccant was removed by filtration and the title oxime was obtained as a crystalline solid, mp 123° (from ethanol) on removal of the solvent; ir (potassium bromide): 3219 cm^{-1} - 2744 cm^{-1} (CH=N-OH), 1723 cm^{-1} (C=O); pmr (d_6-DMSO): 12.0 (1H, s), 9.0 (1H, d, $J_{6,4}$ = 2.1 Hz), 8.2 (1H, dd, $J_{4,6}$ = 2.1 Hz, $J_{4,5}$ = 8.4 Hz), 8.1 (1H, s), 7.8 (1H, d, $J_{5,4}$ = 8.4 Hz), 4.3 (2H, q, J = 7.2 Hz), 1.3 (3H, t, J = 7.2 Hz); cmr: 164.3, 155.6, 149.9, 148.2, 137.3, 125.2, 119.5, 61.1, 13.9.

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.15; N, 14.43. Found: C, 55.33; H, 4.93; N, 14.62.

5-Isopropoxycarbonylpyridine-2-carbaldehyde Oxime (**3c**).

2-Propanol was substituted for ethanol in the above procedure. With this alcohol, 5-methoxycarbonylpyridine-2-6-carbaldehyde oxime (**3a**) (1.5 g, 8.3 mmoles) yielded the title compound **3c**, mp 130° from 2-propanol (1.4 g, 6.7 mmoles, 80%); ir: 3421 cm^{-1} - 2741 cm^{-1} (CH=NH-OH), 1721 cm^{-1} (C=O); pmr (d_6-DMSO): 12.0 (1H, s), 9.0 (1H, d, $J_{6,4}$ = 1.8 Hz), 8.2 (1H, dd, $J_{4,6}$ = 1.8 Hz, $J_{5,4}$ = 8.4 Hz), 8.1 (1H, s), 7.9 (1H, d, $J_{4,5}$ = 8.4 Hz), 5.1 (1H, h, J = 6.3 Hz), 1.2 (6H, d, J = 6.4 Hz); cmr: 183.8, 155.6, 149.9, 148.2, 137.2, 125.5, 119.5, 68.8, 21.5.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.77; N, 13.46. Found: C, 57.02; H, 5.50; N, 12.75: C, 57.33; 5.49; 13.74.

REFERENCES AND NOTES

[1] For the previous paper in this series, please see *J. Heterocyclic Chem.*, **28**, 1315 (1991).

[2] Taken, in part, from the Ph. D. dissertation of Hector Manuel Reyes-Rivera, Temple University, 1994.

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[10] 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 materials 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 are not encouraging.

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[17] *m*-Chloroperbenzoic acid (40-50%) is commercially available [11] and it was purified by suspending the commercial material (100 g) in acetate *p*H 7.40 buffer solution (1 l), stirring for 24 hours, and filtering off the undissolved material. The purified acid was taken up in chloroform, dried over sodium sulfate, and the chloroform removed at reduced pressure to produce material suitable for preparation of the *N*-oxides.