Functionalization of Substituted 2-(1*H*)pyridones. I. A Novel Synthesis of α-Arylgyloxylates and Related Systems

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A novel synthetic strategy is presented in which the heteroaryl[(trimethylsilyl)oxy]acetonitrile intermediate **3** is utilized either as a homologation or reverse-polarity synthon for convenient entry into its corresponding α-hydroxy- and α-ketoarylalkanoate **4** and **6**, respectively. Further functionalization, including a stereoselective oximation procedure, is described.

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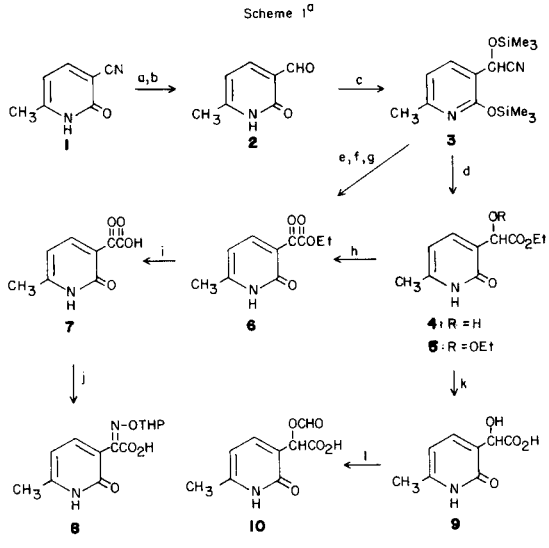
The literature contains numerous recent entries of novel and therapeutically significant antibiotics in which the β-lactam nucleus is appended either to an α-alkoxyimino-, α-hydroxyimino-, or α-hydroxy-α-arylacetamido side chain (1). In conjunction with an ongoing program concerning the synthesis of 2-(1*H*)pyridones in our laboratories, we required an efficient route to the functionally equivalent 2-(1*H*)pyridone side chains **8** and **10** (Scheme I). Reported herein is a novel route to such systems in which heteroaryl-[(trimethylsilyl)oxy]acetonitrile **3** is utilized either as a homologation or reverse-polarity synthon.

Our initial target was the synthesis of α-keto ester **6**, a compact, highly functionalized molecule with reactivity at C-5 and the C-6 methyl for further elaboration. A major consideration in our approach was to selectively carry out all transformations without the necessity of singular protection/deprotection of the pyridone lactam moiety.

Initial attempts to gain a quick entry to acid **7** *via* selenium dioxide/pyridine oxidation (2) of 3-acetyl-6-methyl-2-(1*H*)pyridone (3) or cuprous cyanide homologation (4) of the acid chloride of 3-carboxy-6-methyl-2-(1*H*)-pyridone met with failure. Friedel-Crafts acylation of 6-methyl-2-(1*H*)pyridone with oxalyl chloride or ethyl oxalyl chloride was deemed to be nonregiospecific (5), and thus was not pursued.

The successful route to our targeted system is revealed in Scheme I. Prior silylation of 3-cyano-6-methyl-2-(1*H*)-pyridone (6) with hexamethyldisilazane (HMDS) rendered **1** sufficiently organic soluble for reduction by diisobutylaluminum hydride (DIBAL-H) in toluene to afford in 80% yield the partially water-soluble vinylogous formamide **2**. Subsequent conversion to the trimethylsilyl cyanohydrin ether **3** proceeded smoothly in 99% yield by the Evans procedure (7), with concurrent masking of the lactam function as its silylated lactim ether. Room temperature treatment of **3** with acidic 95% ethanol resulted in simultaneous desilylation along with nitrile ethanolysis to provide the carbinol ester **4** in 73% yield (8). Heating of **3** at reflux under similar conditions resulted in considerable formation of oily ether **5**, whose generation is a consequence of the acid-catalyzed solvolysis of initially formed **4** (9). Elaboration of **4** into the α-hydroxy acid **9**, and thence the formate ester **10**, proceeded in routine fashion by first alkaline hydrolysis of **4** to water-soluble **9** in 73% yield followed by formylation with acetic-formic anhydride (10) to give water-soluble **10** in 75% yield.

Scheme I[a]



(a) HMDS, toluene, 110°. (b) DIBAL-H, toluene, -42°; H_3O^+. (c) Me_3SiCN, ZnI_2, 25°. (d) HCl, 95% EtOH, 25°. (e) $LiN(SiMe_3)_2$, THF, -78°. (f) $ClCO_2Et$, -78° → 10°. (g) Et_3N-HF, THF, 5°; 1% aq. $NaHCO_3$, (h) Ac_2O-DMSO, 25°. (i) 6*N* aq. NaOH, *p*-dioxane, EtOH, 25°; Dowex 50W-X4(H^+). (j) NH_2OTHP, pyridine, -5°; Dowex 50W-X4(H^+). (k) For R = H; 2*N* aq. NaOH, EtOH, 25°; Dowex 50W-X4(H^+). (l) AcOCHO, pyridine, CH_2Cl_2, 0°; Dowex 50W-X4(H^+).

Conversion of the carbinol ester **4** to the α-keto ester **6** was examined by several methods including Collin's reagent (11), pyridinium chloroformate (12), Fetizon's reagent (13), and several variations of the Pfitzner-Moffatt process (14), one of which (acetic anhydride-dimethyl sulfoxide) provided **6** in 66% yield (15). An operationally easier route to **6** was effected *via* deprotonation of **3** with

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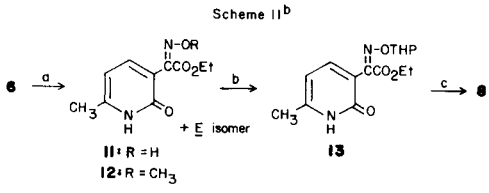
lithium bis(trimethylsilyl)amide followed by acylation of the lithiated anion with ethyl chloroformate to afford an α-cyano-α-[(trimethylsilyl)oxy]heteroarylacetate intermediate whose treatment with triethylamine-hydrogen fluoride (16) followed by mild aqueous base afforded **6** in 73% overall yield (17). While in principle various organosilicon reagents could have provided carbanion-stabilizing adducts equivalent to **3** (18), we chose to employ the trimethylsilyl cyanohydrin ether as its application to the nucleophilic acylation of alkyl halides, dialkyl sulfates, and alkyl tosylates had previously been examined by Hunig (16). Furthermore, the intermediate adduct (*vide supra*) is rendered susceptible to mild hydrolysis to an α-keto ester, a necessary requirement due to the sensitivity of this class of molecules to mild alkaline hydrolysis.

Scheme II[b]



(a) $NH_2OR \cdot HCl$, pyridine, 25°. (b) For R = H; DHP, *p*-TsOH, $ClCH_2CH_2Cl$, 4A sieves, 25°. (c) 2*N* aq. NaOH, EtOH, 45°, H_3O^+.

Completion of the sequence to α-alkoximino acid **8** proceeded smoothly by first alkaline hydrolysis of the ester **6** to the water-soluble α-keto acid **7** in 95% yield, followed by alkoximation with *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (19) in pyridine at -5° to give stereospecifically the water-soluble *Z* isomer of **8** in 75% yield (20). The assignment of stereochemistry rests on corroborative structural and spectral data of **8** with compounds **11** and **12** whose synthesis and subsequent transformations are depicted in Scheme II. Furthermore, it is well documented that alkaline hydrolysis of the *E* isomer of α-aryl-α-alkoxyimino alkanoate esters occurs much faster than the corresponding *Z* isomer (21) and such is observed for **12**.

The utilization of acids **7-10** in the synthesis of several biologically active species will be reported in due course.

EXPERIMENTAL

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Digilab FTS-14 or Beckman IR9 prism grating dispersion instrument. Ultraviolet (uv) spectra were taken on a Cary Model 118c recording spectrophotometer. Proton magnetic resonance (pmr) spectra were recorded on a Varian EM-390 or Bruker WH-90 instrument. The Bruker WH-90 was modified with a Nicolet Technology Corporation B-NC12 data acquisition system. Chemical shifts are reported as δ values in ppm from internal tetramethylsilane. Combustion analyses were performed on a Perkin-Elmer 240 elemental analyzer.

Thin-layer chromatography (tlc) was performed on E. Merck 5 x 10 cm glass plates coated with silica gel 60F-254, 0.25 mm. "Alumina" refers to the grade I neutral variety manufactured by M. Woelm, Eschwege, Germany. Silica gel was E. Merck "Silica Gel 60", 70-230 mesh ASTM.

When necessary, solvents and reagents were dried prior to use. Charcoal refers to activated "Darco" G-60. *In vacuo* refers to 1.0-1.5 mm. All other solvents were concentrated on a rotary evaporator at 30-40° and at pressures of 15-20 mm unless noted otherwise.

1,2-Dihydro-6-methyl-2-oxo-3-pyridinecarboxaldehyde (**2**).

A suspension of 20 g. (149 mmoles) of 3-cyano-6-methyl-2-(1*H*)pyridone **1**, and 31 ml. of hexamethyldisilazane in 50 ml. of toluene was heated at reflux for 3 hours. The solution was cooled and concentrated to an oil which was dissolved in 250 ml. of toluene. The mixture was cooled to -42° under nitrogen and a solution of 130 ml. of diisobutylaluminum hydride (25% in toluene) was added dropwise over 1 hour. The resultant solution was stirred at -42° for 6 hours. Cooling was removed and 500 ml. of 3*N* aqueous hydrochloric acid was added carefully to the deep orange solution. The mixture was continuously extracted with methylene chloride for 2.5 days. The organic extract was diluted with acetonitrile and the solution was briefly heated to solubilize all solids, treated with solid sodium bicarbonate, filtered, then decolorized with charcoal while hot. Concentration left 16.8 g. of solid residue whose trituration from diethyl ether yielded 16.4 g. (80%) of light yellow needles; m.p. 213-216°. An analytical sample, m.p. 214-217°, was obtained from acetonitrile crystallization with 90% recovery; uv (methanol): 358 nm (ε 9,270), 248 (5,540); ir (potassium bromide): 1700-1660 (br), 1620, 1565, 825 cm^{-1}; pmr (DMSO-d_6): δ 2.30 (s, 3H), 6.23 (d, 1H, J = 7 Hz), 7.90 (d, 1H, J = 7 Hz), 10.08 (s, 1H), 12.38 (br s, 1H); ms: m/e (relative %) 137 (M+, 54), 136 (19), 109 (100), 108 (45), 80 (57), 53 (31).

Anal. Calcd. for $C_7H_7NO_2$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.30; H, 5.27; N, 10.26.

(±)-6-Methyl-α,2-bis[(trimethylsilyl)oxy]-3-pyridineacetonitrile (**3**).

A suspension of 6.86 g. (50 mmoles) of aldehyde **2**, 4 mg. of anhydrous zinc iodide, and 12.7 ml. (109 mmoles) of trimethylsilylcyanide was stirred at 25° for 3.5 hours (caution: exothermicity almost immediately after admixture of reagents). Excess reagent was evaporated and the residual viscous oil was pumped *in vacuo*/25° overnight. Kugelrohr distillation at 70-80°/0.09 mm afforded 15.33 g. (99%) of a clear oil. An analytical sample was obtained by short-path distillation, b.p. 75-76°/0.07 mm; uv (acetonitrile): 276 nm (ε 8,670), 220 (12,340); ir (neat): 1590, 1470, 1255, 850 cm^{-1}; pmr (deuteriochloroform): δ 0.18 (s, 9H), 0.35 (s, 9H), 2.32 (s, 3H), 5.55 (s, 1H), 6.68 (d, 1H, J = 7 Hz), 7.60 (d, 1H, J = 7 Hz); ms: m/e (relative %) 308 (M+, 8) 293 (8), 221 (7), 194 (100), 166 (16).

Anal. Calcd. for $C_{14}H_{24}N_2O_2Si_2$: C, 54.50; H, 7.84; N, 9.08. Found: C, 54.46; H, 8.13; N, 9.04.

(±)-1,2-Dihydro-α-hydroxy-6-methyl-2-oxo-3-pyridineacetic Acid Ethyl Ester (**4**).

To an ice-cooled solution of 27 ml. of ethanol was bubbled hydrogen chloride for 0.5 hour, followed by the addition of 29 ml. of 95% ethanol. To the solution was added 17.0 g. (55 mmoles) of nitrile **3** in 25 ml. of 95% ethanol. The mixture was stirred at 5° for 0.5 hour, then at 25° for 49.5 hours. The mixture was slowly poured into a cold solution of saturated aqueous sodium bicarbonate. The aqueous mixture was continuously extracted with methylene chloride for 40 hours. The organic extract was dried (magnesium sulfate) and concentrated to a solid residue whose trituration from acetone left 9.99 g. (86%) of powdery ester: m.p. 139-140°; uv (methanol): 309 nm (ε 8,450), 232 (6,500); ir (potassium bromide): 3430, 1720, 1655, 1580 cm^{-1}; pmr (DMSO-d_6): δ 1.13 (t, 3H, J = 7 Hz), 2.18 (s, 3H), 4.05 (q, 2H, J = 7 Hz), 5.00 (poorly resolved d, 1H, collapses to s with deuterium oxide), 5.80 (poorly resolved d, 1H, exchanges deuterium oxide), 6.00 (d, 1H, J = 7 Hz), 7.35 (d, 1H, J = 7 Hz), 11.70 (br s, 1H); ms: m/e (relative %) 211 (M+, 3), 138 (100), 136 (18).

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.79; H, 6.17; N, 6.49.

(±)-α-Ethoxy-1,2-dihydro-6-methyl-2-oxo-3-pyridineacetic Acid Ethyl Ester (**5**).

A solution of 2.0 g. (6.5 mmoles) of nitrile **3** in 3 ml. of 95% ethanol and 1.4 ml. of concentrated sulfuric acid was heated at reflux for 6 hours.

The mixture was cooled, diluted with water, and extracted with methylene chloride (4 x 30 ml.). The combined extracts were washed with saturated aqueous sodium bicarbonate, dried (magnesium sulfate), and concentrated to a viscous oil whose tlc showed a mixture of esters **4** and **5**. Chromatography on alumina (Act II) with gradient elution using methanol/chloroform, afforded 548 mg. (35%) of an oil whose Kugelrohr distillation at 160°/0.04 mm gave an analytical sample; uv (methanol): 311 nm (ε 8,160), 232 (5,960); ir (neat): 1740, 1645, 1625, 1570 cm^{-1}; pmr (deuteriochloroform): δ 1.30 (overlapping t, 6H), 2.33 (s, 3H), 3.65 (d of q, 2H), 4.20 (q, 2H), 5.18 (s, 1H), 6.08 (d, 1H, J = 7 Hz), 7.52 (d, 1H, J = 7 Hz), 13.15 (br s, 1H); ms: m/e (relative %) 195 (5), 166 (63), 138 (100).

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.21; H, 7.30; N, 6.04.

1,2-Dihydro-6-methyl-α,2-dioxo-3-pyridineacetic Acid Ethyl Ester (**6**).

Run A. By Oxidation of Carbinol **4**.

To a solution of 4.22 g. (20 mmoles) of carbinol **4** in 40 ml. of dimethyl sulfoxide at 25°, was added 12 ml. (128 mmoles) of acetic anhydride. After stirring for 19 hours, excess acetic anhydride was evaporated at 30°/10 mm and the residual mixture was lyophilized at 0.01 mm. The residue was dissolved in chloroform and the mixture was washed with brine (2 x 100 ml.), dried (magnesium sulfate), and clarified with charcoal. Concentration gave an orange solid whose crystallization from ethanol left 2.0 g. of analytically pure yellow needles: m.p. 204-207°. A second crop (0.74 g., m.p. 150-152°) was obtained by concentration of the mother liquor. Total yield = 2.74 g. (66%): uv (methanol): 365 nm (ε 11,700), 249 (4,400); ir (potassium bromide): 1745, 1660, 1610, 1555 cm^{-1}; pmr (deuteriochloroform): δ 1.38 (t, 3H, J = 7 Hz), 2.44 (s, 3H), 4.36 (q, 2H, J = 7 Hz), 6.30 (d, 1H, J = 7 Hz), 8.20 (d, 1H, J = 7 Hz); ms: m/e (relative %) 209 (M+, 5), 181 (3), 137 (10), 136 (100), 108 (6), 80 (5).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.42; H, 5.30; N, 6.70. Found: C, 57.45; H, 5.26; N, 6.66.

Run B. By Ethyl Chloroformate Acylation of Nitrile **3**.

To a mixture of 24.1 ml. (116 mmoles) of hexamethyldisilazane and 25 ml. tetrahydrofuran at 5°, was added dropwise 55 ml. of *n*-butyl lithium (2.15*M* solution in *n*-hexane). The solution was stirred at 15-20° for 20 minutes, the *n*-hexane was removed by evaporation, and the resultant suspension was diluted with 20 ml. tetrahydrofuran. The vigorously stirred suspension was cooled to -78° under nitrogen and 35.6 g. (115 mmoles) of nitrile **3** in 80 ml. tetrahydrofuran was added all at once. After stirring for 1 hour at -78°, 12.2 ml. (127 mmoles) of ethyl chloroformate was added in one portion to the deep orange solution. The solution was stirred vigorously at -78° for 1 hour, allowed to warm to -40° over 1.5 hours and kept here for 2 hours, then let warm to 10° over 0.5 hour. The mixture was diluted with methylene chloride and poured into an ice-cold solution of saturated aqueous ammonium chloride. The layers were separated and the aqueous layer was extracted twice with methylene chloride. The combined organic extracts were dried (sodium sulfate) and concentrated to leave a solid cake which was dissolved in 550 ml. tetrahydrofuran. The solution was ice-cooled, treated with 32.3 g. (266 mmoles) triethylamine-hydrogen fluoride, and stirred at 5° for 4.5 hours. Concentration left a residue which was partitioned between 1% aqueous hydrochloric acid and methylene chloride. The methylene chloride layer was washed with 1% aqueous hydrochloric acid, stirred vigorously with 1% aqueous sodium bicarbonate for 5 minutes, decolorized with charcoal, and dried (magnesium sulfate). Concentration left a solid residue whose crystallization from ethanol afforded 13.76 g. of analytically pure product, m.p. 207-208°. Purification of the mother liquor by alumina chromatography (Act III), with chloroform elution, gave additional material whose crystallization left 3.87 g. of product, m.p. 205-207°, total yield 17.63 g. (73%).

1,2-Dihydro-6-methyl-α,2-dioxo-3-pyridineacetic Acid (**7**).

To a 5° solution of 1.8 g. (8.6 mmoles) of the α-keto ester **6** in 34.5 ml. of ethanol and 10.5 ml. of *p*-dioxane, was added slowly a solution of 2.87 ml. (17.2 mmoles) of 6*N* aqueous sodium hydroxide. The viscous suspension was stirred for 10 minutes, then concentrated to leave a solid that was dissolved in a minimum volume of water. The solution was acidified by aqueous elution over a column of Dowex 50W-X4 (H^+). Combined product eluates were lyophilized to leave a fluffy residue which was stirred overnight in *p*-dioxane. The residue was filtered and dried *in vacuo*/60° for 3 days to leave 1.3 g. of analytically pure white powder, m.p. 215-227° dec. Processing of the filtrate gave an additional 180 mg. of product, m.p. 210-218° dec., total yield 1.48 g. (95%); p*Ka'* (water): 2.1; uv (water): 348 nm (ε 11,800), 249 (5,150); ir (potassium bromide): 3400-2500, 1730, 1660, 1610, 1560 cm^{-1}; pmr (DMSO-d_6): δ 2.35 (s, 3H), 6.32 (d, 1H, J = 7 Hz), 8.10 (d, 1H, J = 7 Hz), 13.0 (br s, 1H); ms: m/e (relative %) 181 (M+, 6), 136 (100), 109 (11), 108 (12), 80 (10).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 53.05; H, 3.90; N, 7.73. Found: C, 53.15; H, 3.97; N, 7.63.

(*Z*)-1,2-Dihydro-6-methyl-2-oxo-α-[[(tetrahydro-2*H*-pyran-2-yl)oxy]imino]-3-pyridineacetic Acid (**8**).

To a -10° mixture of 906 mg. (5 mmoles) of the α-keto acid **7**, 6 ml. pyridine, and activated 4A sieves, was added 703 mg. (6 mmoles) of *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine. The solution was stirred at -10° to -5° for 1 hour, then the pyridine was removed *in vacuo* to leave a residual oil that was diluted with water. The solution was adjusted to *p*H 8, washed with ethyl acetate, adjusted to *p*H 2 by batchwise addition of Dowex 50W - X4 (H^+), then lyophilized to leave a white solid whose trituration from ethyl acetate/diethyl ether afforded 1.06 g. (75%) of white powdery acid, m.p. 149-150°; p*Ka'* (67% aqueous*N,N*-dimethylformamide): 5.1; uv (methanol): 340 nm (*e* 10,900), 250 (7,450); ir (potassium bromide): 3700-2400, 1755, 1655, 1625 cm^{-1}; pmr (DMSO-d_6): δ 1.33-1.75 (m, 6H), 2.20 (s, 3H), 3.30-3.95 (m, 2H), 5.19-5.30 (br s, 1H), 6.09 (d, 1H, J = 7 Hz), 7.70 (d, 1H, J = 7 Hz); ms: m/e (relative %) 152 (37), 135 (17), 134 (18), 105 (30), 85 (100).

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 10.00. Found: C, 55.64; H, 6.02; N, 9.85.

(±)-1,2-Dihydro-α-hydroxy-6-methyl-2-oxo-3-pyridineacetic Acid (**9**).

A solution of 422 mg. (2.0 mmoles) of the ester **4** and 5 ml. each of 2*N* aqueous sodium hydroxide and ethanol was stirred at 25° under nitrogen for 6.5 hours. The solution was concentrated and the aqueous phase was worked up as described for acid **7** to leave a powder which was stirred in diethyl ether. Filtration of the residue followed by drying left 266 mg. (73%) of a white powder, m.p. 183-184°; p*Ka'* (50% aqueous methanol): 4.3; uv (methanol): 307 nm (ε 8,370), 231 (5,910); ir (potassium bromide): 3440, 3260-2800, 1705, 1635, 1460 cm^{-1}; pmr (DMSO-d_6): δ 2.22 (s, 3H), 5.03 (s, 1H), 6.18 (d, 1H, J = 7 Hz), 7.51 (d, 1H, J = 7 Hz); ms: m/e (relative %) 139 (79), 138 (100), 136 (34).

Anal. Calcd. for $C_9H_9NO_4$: C, 52.47; H, 4.95; N, 7.65. Found: C, 52.33; H, 5.15; N, 7.57.

α-(Formyloxy)-1,2-dihydro-6-methyl-2-oxo-3-pyridineacetic Acid (**10**).

To a 0° suspension of 1.28 g. (7 mmoles) of the acid **9**, 1.75 ml. of pyridine, and 21 ml. of methylene chloride was added 1.75 ml. of acetic-formic anhydride. The solution was stirred for 25 minutes then treated with excess ethanol. The mixture was stirred for 20 minutes then concentrated to a residue that was worked up as described for the acid **8**. Trituration from diethyl ether left 1.1 g. (75%) of white powdery acid, m.p. 99-102° dec.; p*Ka'* (50% aqueous methanol): 4.0; uv (methanol): 312 nm (ε 8,470), 232 (6,930); ir (potassium bromide): 3400-2600, 1725, 1640, 1615, 1160 cm^{-1}; pmr (DMSO-d_6): δ 2.20 (s, 3H), 6.10 (s overlapping d, 3H), 7.47 (d, 1H, J = 7 Hz), 8.40 (s, 1H), 12.30 (br s, 1H).

Anal. Calcd. for $C_9H_9NO_5$: C, 51.20; H, 4.30; N, 6.63. Found: C, 50.88; H, 4.37; N, 6.96.

(*Z*)-1,2-Dihydro-α-(hydroxyimino)-6-methyl-2-oxo-3-pyridineacetic Acid Ethyl Ester (**11**).

A mixture of 418 mg. (2.0 mmoles) of the α-keto ester **6**, 153 mg. (2.2 mmoles) of hydroxylamine hydrochloride, and 2 ml. of pyridine was stirred at 25° for 5 hours. Pyridine was removed *in vacuo* to leave a syrup that was coevaporated twice with ethanol. Crystallization from 95%

ethanol left 272 mg. of white plates, m.p. 208-211°. Another crystallization from ethanol gave pure *Z* isomer. The mother liquor was purified by thick-layer chromatography to leave a residue whose trituration from 50% ethyl acetate/2-propanol left 136 mg. of a white powder showing a 30:70 *Z:E* isomeric ratio (pmr integration), total yield 408 mg. (91%); *Z* isomer, m.p. 226-227°; uv (methanol): 338 nm (ε 10,300), 248 (7,050); ir (potassium bromide): 1725, 1660, 1620, 1045 cm^{-1}; pmr (DMSO-d_6): δ 1.20 (t, 3H, J = 7 Hz), 2.20 (s, 3H), 4.15 (q, 2H, J = 7 Hz), 6.04 (d, 1H, J = 7 Hz), 7.70 (d, 1H, J = 7 Hz), 11.60 (s, 1H, exchanges deuterium oxide), 11.90 (br s, 1H); ms: m/e (relative %) 224 (M+, 30), 178 (44), 151 (19), 148 (71), 135 (100), 134 (64), 120 (26); *E* isomer; pmr: 4.10 (q), 7.48 (d).

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.40; N, 12.49. Found: C, 53.35; H, 5.22; N, 12.83.

(*Z*)-1,2-Dihydro-α-(methoxyimino)-6-methyl-2-oxo-3-pyridineacetic Acid Ethyl Ester (**12**).

Reaction of ester **6** with methoxylamine hydrochloride, as described for **11**, afforded 392 mg. (82%) of a 92:8 *Z:E* isomeric mixture; *Z* isomer, m.p. 208-209°; uv (methanol): 342 nm (ε 10,970), 252 (7,260); ir (potassium bromide): 1745, 1640, 1620, 1230 cm^{-1}; pmr (DMSO-d_6): δ 1.25 (t, 3H, J = 7 Hz), 2.28 (s, 3H), 3.90 (s, 3H), 4.25 (q, 2H, J = 7 Hz), 6.18 (d, 1H, J = 7 Hz), 7.82 (d, 1H, J = 7 Hz), 12.17 (br s, 1H); ms: m/e (relative %) 238 (M+, 42), 192 (26), 165 (11), 150 (16), 135 (100); *E* isomer; pmr: 3.95 (s), 4.22 (q), 7.55 (d).

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.20; H, 5.87; N, 11.65.

(*Z*)-1,2-Dihydro-6-methyl-2-oxo-α-[[(tetrahydro-2*H*-pyran-2-yl(oxy]imino]-3-pyridineacetic Acid Ethyl Ester (**13**).

A suspension of 487 mg. (2.2 mmoles) of the oxime **11**, 0.99 ml. (11 mmoles) of dihydropyran, 31.7 mg. of *p*-toluenesulfonic acid monohydrate, 4.5 ml. of 1,2-dichloroethane, and activated 4A sieves was stirred at 5° for 2 hours. Potassium carbonate was added, the solution was stirred for 30 minutes, filtered, then concentrated to an oil which was coevaporated thrice with toluene. Trituration with diethyl ether afforded 572 mg. (86%) of a white powder, m.p. 164-166°. Crystallization from toluene:hexanes gave analytical material, m.p. 175-176°, with 75% recovery; uv (methanol): 343 nm (ε 10,700), 250 (7,300); ir (potassium bromide): 1742, 1654 cm^{-1}; pmr (DMSO-d_6): δ 1.27 (t, 3H, J = 7 Hz), 1.39-1.80 (m, 6H), 2.22 (s, 3H), 3.30-3.90 (m, 2H), 4.20 (q, 2H, J = 7 Hz), 5.25 (s, 1H), 6.05 (d, 1H, J = 7 Hz), 7.68 (d, 1H, J = 7 Hz), 11.90 (br s, 1H); ms: m/e (relative %) 224 (75), 178 (28), 148 (15), 85 (100).

Anal. Calcd. for $C_{15}H_{20}N_2O_5$: C, 58.44; H, 6.54; N, 9.09. Found: C, 58.23; H, 6.48; N, 8.89.

Hydrolysis of **13** to Acid **8**.

A mixture of 154 mg. (0.5 mmole) of the ester **13**, 6.5 ml. of ethanol, and 3.3 ml. of 2*N* aqueous sodium hydroxide was stirred under argon at 45° for 2.5 hours. The solution was diluted with water, ice-cooled, acidified to *p*H 2, washed with diethyl ether, saturated with sodium chloride, and exhaustively extracted with methylene chloride. The combined extracts were dried (magnesium sulfate) and concentrated to a residue whose trituration from diethyl ether-ethyl acetate gave 71 mg. (51%) of a white powder, m.p. 149-150°, identical in all respects to the acid **8** obtained by the aforementioned procedure.

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REFERENCES AND NOTES

(1a) G. V. Kaiser, M. Gorman and J. A. Webber, *J. Infect. Dis.*, **137**, S10 (1978); (b) P. C. Cherry, M. C. Cook, M. W. Foxton, M. Gregson, G. I. Gregory and G. B. Webb, *Spec. Publ. Chem. Soc.*, **28**, 145 (1977); (c) R. Bucourt, R. Heymes, A. Lutz, L. Penasse and J. Perronnet, *Tetrahedron*, **34**, 2233 (1978); (d) L. D. Cama and B. G. Christensen, in "Annual Reports in Medicinal Chemistry", Vol. 13, F. H. Clark, Ed., Academic Press, New York, N. Y., 1978, Chapter 16.

(2) M. Hatanaka and T. Ishimaru, *J. Med. Chem.*, **16**, 978 (1973).

(3) H. Yanagisawa, H. Nakao and A. Ando, *Chem. Pharm. Bull.*, **21**, 1080 (1973).

(4) J. F. Normant and C. Piechucki, *Bull. Soc. Chim. France*, 2402 (1972).

(5) H. Tieckelmann, in "Pyridine and its Derivatives", Suppl., Part. III, R. A. Abramovitch, Ed., Wiley-Interscience, New York, N. Y., 1974, Chapter 12.

(6) R. P. Mariella, *Org. Synth., Coll. Vol. IV*, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 210.

(7) D. A. Evans, L. K. Truesdale and G. L. Carroll, *J. Chem. Soc., Chem. Commun.*, 55 (1973).

(8) For a similar acid-catalyzed procedure to cyanohydrins, see P. G. Gassman and J. J. Talley, *Tetrahedron Letters*, 3773 (1978).

(9) For a similar ether formation in the total synthesis of (±)-flavipucine, see J. A. Findlay, J. W. H. Tam and J. Krepinsky, *Synth. Commun.*, 7, 149 (1977).

(10) W. Stevens and A. Van Es, *Rec. Trav. Chim.*, **83**, 1287 (1964).

(11) J. C. Collins, W. W. Hess and F. J. Frank, *Tetrahedron Letters*, 3363 (1968).

(12) E. J. Corey and J. W. Suggs, *ibid.*, 2647 (1977).

(13) M. Fetizon and M. Golfier, *C. R. Acad. Sci., Ser. C.*, **267**, 900 (1968).

(14) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963).

(15) For a similar oxidation in the synthesis of vitamin C, see T. C. Crawford and R. Breitenbach, *J. Chem. Soc., Chem. Commun.*, 388 (1979).

(16) K. Deuchert, U. Hertenstein, S. Hunig and G. Wehner, *Chem. Ber.*, **112**, 2045 (1979) and references therein.

(17) Current work on the generality of this novel homologation procedure to α-keto esters is in progress in our laboratories. Further details will be provided in a separate communication.

(18a) D. A. Evans, K. M. Hurst and J. M. Takacs, *J. Am. Chem. Soc.*, **100**, 3467 (1978) and references therein; (b) D. A. Evans, J. M. Takacs and K. M. Hurst, *ibid.*, **101**, 371 (1979) and references therein.

(19) T. Oguri, T. Shioiri and S.-I. Yamada, *Chem. Pharm. Bull.*, **23**, 167 (1975).

(20) Stereoselective alkoximation and oximation of glyoxylates to the *Z* adduct utilizing this methodology appears to be a general process; P. W. K. Woo, unpublished results.

(21) J. Bradshaw and G. B. Webb, U. S. Patent 3,903,113 (1975).