Functionalization of Substituted 2-(1*H*)Pyridones. II. Synthetic Pathways to C-6 Modified 3-Cyano- and 3-Carboxy-2-(1*H*)Pyridones From a Common Precursor (1)

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Starting from readily available 1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile, **1**, viable synthetic pathways to a number of C-6 functionalized 1,2-dihydro-2-oxo-3-pyridinecarbonitriles and corresponding acids are presented. Through the utilization of dianion chemistry, the C-6 methyl substituent is selectively functionalized to three different oxidation levels.

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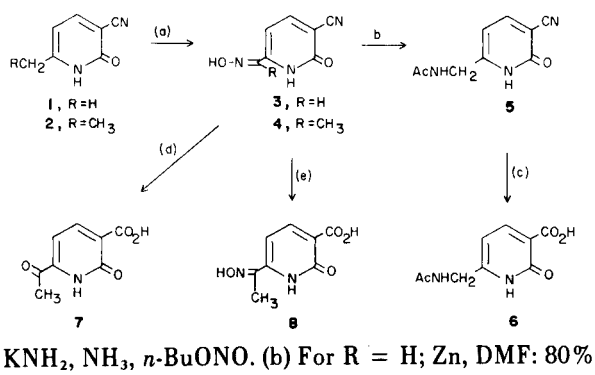
As part of a continuing program to utilize modified 1,2-dihydro-2-oxo-3-pyridinecarboxylic acids as side chains for various penicillin and cephalosporin nuclei (2), we required synthetic methodology which would allow us ready access into C-6 functionalized systems. Reported herein are three routes, utilizing readily available 1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile, **1**, (3) as starting material, in which the C-6 methyl substituent is derivatized to three different oxidation states. Of particular interest in this regard was the synthesis of acetamide **6**, methyl ketone **7**, nitrile ester **13**, and enamine **18**, all of which would serve as convenient substrates for further modification.

Scheme I

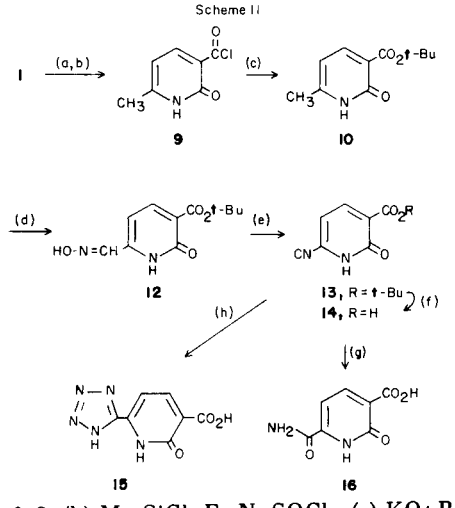


(a) KNH_2, NH_3, *n*-BuONO. (b) For R = H; Zn, DMF: 80% aq HOAc; Ac_2O. (c) 50% aq KOH; Ac_2O. (d) For R = CH_3; conc. HCl. (e) For R = CH_3; 10% aq KOH.

The synthesis of **6** and **7** is revealed in Scheme I. Generation of the dianion of nitrile **1** at -33° with potassium amide in liquid ammonia (4), after the method of Hauser (5), followed by quenching with *n*-butyl nitrite afforded aldoxime **3** in 80% yield as a mixture of stereoisomers. In an analogous fashion, oximation of homologous nitrile **2** (5a) gave keto oxime **4** in 86% yield as a single stereoisomer. After examining a variety of conditions, including numerous metal-solvent combinations, it was found that the reduction of oxime **3** could be effected most efficiently with powdered zinc in *N,N*-dimethylformamide: 80% aqueous acetic acid (3:1) at 50°. Acetylation of the intermediate amino nitrile followed by nonaqueous workup gave in 63% yield the partially water-soluble acetamide **5**. Conversion to target acetamide **6** proceeded routinely in 41% yield (6) *via* aqueous potassium hydroxide hydrolysis followed by acetylation.

The synthesis of methyl ketone **7** had been previously reported (7), but our attempts to scale-up this process led to poor yields. We were particularly interested in a viable route to **7**, as it readily lends itself to further derivatization. It was easily obtained in 75% yield upon heating nitrile **4** in refluxing concentrated hydrochloric acid. Alternatively, heating of **4** in refluxing 10% aqueous potassium hydroxide afforded oximino acid **8** in 85% yield.

Scheme II



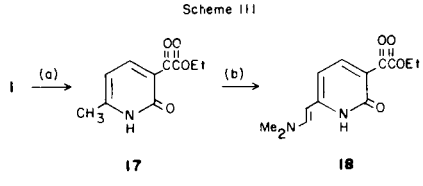
(a) Ref. 8. (b) Me_3SiCl, Et_3N; $SOCl_2$. (c) KO*t*-Bu, *t*-BuOH. (d) KNH_2, NH_3, *n*-BuONO. (e) *N,N'*-carbonyldiimidazole. (f) For R = *t*-Bu; TFA, dimethoxybenzene. (g) For R = *t*-Bu; conc. H_2SO_4. (h) For R = H; NaN_3, NH_4Cl, DMF.

The generation of target nitrile ester **13** (Scheme II) was best approached by prior conversion of nitrile **1** to *t*-butyl

ester **10** such that ready discrimination between equivalent oxidation states at C-3 and C-6 could be maintained (8). Nitrile **1** was hydrolyzed to 1,2-dihyro-2-oxo-3-pyridinecarboxylic acid by a literature procedure (9) and thence to acid chloride **9** in 50% yield by first silylation followed by treatment with thionyl chloride (10). Reaction of **9** with potassium *t*-butoxide in *t*-butyl alcohol provided ester **10** in 65% yield. A suspected dimer **11** was formed in this reaction in varying amounts, and indeed in high yields when acid chloride **9** was treated with base in an ethereal solvent. Other conventional methods for preparing *t*-butyl esters (11), utilizing the above acid, failed due to its insolubility and bifunctional nature.

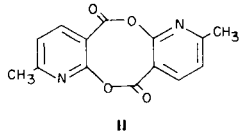
Attempts to selectively derivatize the C-6 methyl group of ester **10** *via* oxidation with potassium permanganate (12), selenium dioxide (13), or the dianion of **10** with oxygen (14) failed because of substrate overoxidation. However, the dianion of **10** was readily nitrosated to a stereoisomeric mixture of aldoxime **12** in 67% yield as previously described for nitrile **3**. Further oxidation of **12** to pivotal nitrile ester **13** (68%) was effected by reaction with *N,N*-carbonyldiimidazole. Treatment of **13** with trifluoroacetic acid afforded acid **14** (83%) which was converted to tetrazole **15** (82%) with sodium azide under standard conditions. Sulfuric acid hydrolysis of **13** gave primary carboxamide **16** in 95% yield.

Scheme III



17 18

(a) Ref. 1 (b) DMF-diethylacetal.



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During the course of some work directed toward the synthesis of α-keto ester **17** and other α-oxoarylacetates (1), we were interested in methods for ready homologation of the C-6 methyl moiety. Based on reports by Baldwin, *et al.*, on the utilization of amide acetals for similar purposes (15), we treated **17** with *N,N*-dimethylformamide diethyl acetal in *N,N*-dimethylformamide and obtained the conjugated enamine **18** in 73% yield (Scheme III).

An extension of the chemistry and the synthesis of several biologically active species using the intermediates outlined herein will be the subject of future reports.

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 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-[(hydroxyimino)methyl]-2-oxo-3-pyridinecarbonitrile; *syn: anti* Mixture (**3**).

To a solution of 166 mmoles of potassium amide in 300 ml anhydrous liquid ammonia at -33° was added portionwise over 10 minutes 6.71 g (50 mmoles) of powdered nitrile **1**. After stirring for 1 hour, 7.0 g (68 mmoles) of *n*-butyl nitrite in 30 ml anhydrous ethyl ether was added dropwise over 15 minutes to the reddish-green dianion. After stirring for 1 hour, 20 ml of water was added, cooling was removed, and the solution was let stand overnight. The residue was dissolved in water and the solution was washed with ethyl ether, than adjusted to *p*H 4.0 with concentrated hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, then redissolved in 2*N* aqueous sodium hydroxide. Acidification and collection of precipitate as before followed by drying over phosphorus pentoxide to constant weight afforded 6.55 g (80%) of a tan powder, mp 225-231° dec shown by pmr to be a 57:43 mixture of stereoisomers; uv (methanol): 365 nm (ε = 12,700), 248 (10,300), 218 (16,600); ir (potassium bromide): 2230, 1655 (br), 1600, 1555 cm^{-1}; pmr (DMSO-d_6): major isomer, δ 7.23 (d, 1H, J = 8 Hz), 7.40 (s, 1H), 8.19 (d, 1H, J = 8 Hz); minor isomer, δ 6.65 (d, 1H, J = 8 Hz), 7.99 (s, 1H), 8.10 (d, 1H, J = 8 Hz), 12.6 (br s, 2H).

Anal. Calcd. for $C_7H_5N_3O_2$: C, 51.54; H, 3.09; N, 25.76. Found: C, 51.32; H, 3.33; N, 25.58.

Reaction of the mixture with 3*N* aqueous sodium hydroxide at 25° for several hours results in conversion of the major to minor isomer.

1,2-Dihydro-6-[1-(hydroxyimino)ethyl]-2-oxo-pyridinecarbonitrile (**4**).

Reaction of 29.2 g (200 moles) of nitrile **2** with 650 mmoles of potassium amide in 800 ml of liquid ammonia at -40° followed by nitrosation with 22.7 g (220 mmoles) of *n*-butyl nitrite at -78°, was carried out essentially in the same manner as described for nitrile **1** to afford 30.3 g (86%) of product, mp 295-296°. Recrystallization from ethanol afforded an analytical sample, mp. 295-296°; ir (potassium bromide): 3320, 2245, 1660 cm^{-1}; pmr (DMSO-d_6): δ 2.13 (s, 3H), 6.73 (d, 1H, J = 8 Hz), 8.17 (d, 1H, J = 8 Hz), 12.2 (br s, 2H).

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.02; H, 4.06; N, 23.80.

N-[(5-Cyano-1,6-dihydro-6-oxo-2-pyridinyl)methyl]acetamide (**5**).

A 50° suspension of 326 mg (2 mmoles) of oxime **3** and 4 ml of *N,N*-dimethylformamide: 80% aqueous acetic acid (3:1) under nitrogen was treated portionwise with 130 mg of zinc dust. The mixture was kept at 50° for 1.5 hours, treated with 260 mg additional zinc, then maintained at 65° for 4.5 hours. The mixture was filtered through celite and the filtrate was concentrated *in vacuo* to an oil which was diluted with 3 ml each of glacial acetic acid and acetic anhydride. After stirring overnight at 25°, the solution was concentrated *in vacuo* to a solid residue which was dissolved in a minimum of methanol and filtered through a column of neutral alumina. Product eluates were combined, clarified with charcoal, and concentrated to a solid whose crystallization from methanol afforded 240 mg (63%) of a pale yellow soild, mp 212-213°. An analytical

sample, mp 215-216°, was obtained by recrystallization from methanol; uv (methanol): 335 nm (ε = 11,000), 235 (6,480); ir (potassium bromide): 3345, 2240, 1670 (br), 1625, 1570 cm^{-1}; pmr (DMSO-d_6): δ 1.90 (s, 3H), 4.14 (d, 2H, J = 6 Hz, collapses to s with deuterium oxide), 6.15 (d, 1H, J = 8 Hz), 8.05 (d, 1H, J = 8 Hz), 8.39 (poorly resolved t, 1H, J = 6 Hz, exchanges deuterium oxide), 12.5 (br s, 1H).

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.26; H, 4.91; N, 22.38.

6-[(Acetylamino)methyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**6**).

A solution of 450 mg (2.3 mmoles) of nitrile **5** and 6 ml of 50% aqueous potassium hydroxide was heated at reflux under argon for 22 hours. The solution was cooled, adjusted to *p*H 9.0 with concentrated hydrochloric acid, then stirred at 25° for 3 hours with excess acetic anhydride. Acetic anhydride was evaporated and the aqueous solution was acidified to *p*H 2.0 then desalted over HP-20 resin, eluting first with water to remove salts followed by 25% methanol:water to remove the product. Product fractions were concentrated to a solid residue whose crystallization from 95% ethanol left 170 mg of analytically pure light orange powder, mp 241-242° dec. Concentration of the mother liquor followed by trituration from ethanol afforded 35 mg of additional product, mp 234-236° dec. Total yield is 205 mg (41%); uv (methanol): 330 nm (ε = 9,330), 223 (6,220); ir (potassium bromide): 3280, 1735, 1640 (br), 1620, 1555 cm^{-1}; pmr (DMSO-d_6): δ 1.90 (s, 3H), 4.22 (d, 2H, J = 6 Hz, collapses to s with deuterium oxide), 6.43 (d, 1H, J = 8 Hz), 8.23 (d, 1H, J = 8 Hz), 8.35 (poorly resolved t, 1H, J = 6 Hz, exchanges with deuterium oxide), 13.1 (br s, 1H), 14.4 (br s, 1H).

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.23; H, 4.80; N, 13.20.

6-Acetyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**7**).

A suspension of 23.0 g (130 mmoles) of oxime **4** in 250 ml of concentrated hydrochloric acid was refluxed for 4 hours. Following initial solution, a thick precipitate formed. The mixture was concentrated to 125 ml and the precipitate was filtered, then dissolved in 1.5 l of 95% ethanol. Following clarification with charcoal, crystallization left 13.0 g (55%) of analytically pure product, mp 280-282°. Concentration of the mother liquor to 500 ml afforded 4.7 g (20%) of additional material, mp 280-282°; lit (7) mp 271°; uv (*p*H 7 buffer): 330 nm (ε = 8,550); ir (potassium bromide): 1755, 1705, 1645 cm^{-1}; pmr (DMSO-d_6): δ 2.60 (s, 3H), 7.38 (d, 1H, J = 8 Hz), 8.46 (d, 1H, J = 8 Hz).

Anal. Calcd. for $C_8H_7NO_4$: C, 53.04; H, 3.90; N, 7.73. Found: C, 52.86; H, 3.96; N, 7.75.

1,2-Dihydro-6-[1-(hydroxyimino)ethyl]-2-oxo-3-pyridinecarboxylic Acid (**8**).

A solution of 4.8 g (27 mmole) of oxime **4** in 70 ml of 10% aqueous potassium hydroxide was refluxed for 18 hours. The solution was ice-cooled and acidified to *p*H 1.5 with 6*N* aqueous hydrochloric acid. The precipitate was filtered, washed with cold water, then dissolved in 200 ml of 50% ethanol. Following clarification with charcoal, crystallization afforded 2.63 g (60%) of analytically pure product, mp 246-248°. Concentration of the mother liquor to 100 ml afforded 1.1 g (25%) of additional material, mp 246-248°; uv (*p*H 7 buffer): 402 nm (ε = 7,870), 329 (9,370); ir (potassium bromide): 1750, 1715, 1640 cm^{-1}; pmr (DMSO-d_6): δ 2.18 (s, 3H), 2.8-5.3 (br s, 2H), 6.95 (d, 1H, J = 8 Hz), 8.38 (d, 1H, J = 8 Hz), 12.8 (br s, 1H).

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.83; H, 3.97; N, 14.42.

1,2-Dihydro-6-methyl-2-oxo-3-pyridinecarbonyl Chloride (**9**).

To 30.6 g (200 mmoles) of 1,2-dihydro-2-oxo-3-pyridinecarboxylic acid in 1.5 l of methylene chloride was added 27.8 ml of triethylamine and after 10 minutes 25.3 ml of chlorotrimethylsilane. After 1 hour, 29.2 ml of thionyl chloride was added and stirring was continued for 2 hours. The slurry was concentrated to *ca.* 750 ml, then the solids were filtered and dried *in vacuo* to give 17.5 g (50%) of the acid chloride which was used without purification; ir (chloroform): 1770, 1645, 1600, 1510 cm^{-1}.

Silica gel tlc of a small amount of the acid chloride treated with methanol showed a single spot corresponding to the methyl ester.

1,2-Dihydro-6-methyl-2-oxo-3-pyridinecarboxylic Acid, *t*-Butyl Ester (**10**).

To a rapidly stiring solution of 56.5 g (500 mmoles) of potassium *t*-butoxide in 2.5 l of dry *t*-butyl alcohol on a water bath was added 85.5 g (500 mmoles) of acid chloride **9**. After 30 minutes, the mixture was concentrated to a residue that was diluted with water and methylene chloride. With stirring the aqueous layer was adjusted to *p*H 6.0 with dilute aqueous hydrochloric acid, then the organic layer was separated, dried (magnesium sulfate), and concentrated to a waxy solid which was purified by silica gel column chromatography, eluting with chloroform: ethanol (9:1), to yield 68 g (65%) of a white solid, mp 121-122°; ir (chloroform): 1720, 1640, 1618 cm^{-1}; pmr (deuteriochloroform): δ 1.60 (s, 9H), 2.50 (s, 3H), 6.20 (d, 1H, J = 8 Hz), 8.05 (d, 1H, J = 8 Hz), 13.3 (br s, 1H).

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.06; H, 7.18; N, 6.66. Found: C, 62.79; H, 7.19; N, 6.27.

1,2-Dihydro-6-[hydroxyiminomethyl]-2-oxo-3-pyridinecarboxylic Acid, *t*-Butyl Ester; Syn:Anti Mixture (**12**).

A solution of 10 g (48 mmoles) of *t*-butyl ester **10** in 80 ml tetrahydrofuran was added dropwise to 132 mmoles of potassium amide in 600 ml of liquid ammonia. After stirring for 3 hours at -33°, 7.5 ml (60 mmoles) of *n*-butyl nitrite was added and the solution was stirred for 1 hour, then cooling was removed. Workup as described before for nitrile **3** with acidification to *p*H 5.0 with 6*N* aqueous hydrochloric acid afforded 7.65 g (67%) of a tan solid, mp 105-108°, shown by hplc and tlc to be a 61:39 mixture of stereoisomers; ir (potassium bromide): 3130, 1725, 1645, 1625, 1560 cm^{-1}; pmr (DMSO-d_6): δ 1.50 (s, 9H), 6.57 (d, 0.39 H, J = 8 Hz), 7.08 (d, 0.61 H, J = 8 Hz), 7.30 (s, 0.66H), 7.8-8.0 (m, 1.44H), 12.1 (br s, 2H).

The mixture was used without further purification.

6-Cyano-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid, *t*-Butyl Ester (**13**).

To 4.00 g (17 mmoles) of oximino ester **12** in 75 ml of methylene chloride was added 2.72 g (17 mmoles) of *N,N'*-carbonyldiimidazole. The mixture was gently refluxed for 2 hours, then washed with water. The organic layer was dried (magnesium sulfate) and concentrated to a solid residue which was purified by silica gel column chromatography, eluting with chloroform: hexane: 2-propanol (6:3:1), to give 2.5 g (68%) of a white solid; ir (potassium bromide): 3440, 2360, 1710, 1690 cm^{-1}; pmr (deuteriochloroform): δ 1.60 (s, 9H), 7.25 (d, 1H, J = 8 Hz), 8.20 (d, 1H, J = 8 Hz).

The solid was used without further purification.

6-Cyano-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**14**).

Nitrile ester **13**, 2.50 g (11 mmoles), was added to a 0° solution of 25 ml of trifluoroacetic acid and 5 ml of dimethoxybenzene. After 1.5 hours at 0°, the mixture was warmed to 25° and then concentrated to a residue which was dissolved in mild alkali (*p*H 8.5). The aqueous solution was washed with ethyl ether, acidified to *p*H 2.0, and exhaustively extracted with ethyl acetate. The organic layer was dried (magnesium sulfate) and concentrated to yield 1.56 g (83%) of a pale yellow powder, mp 210-213°; ir (potassium bromide): 3350, 2240, 1740, 1650, 1600 cm^{-1}; pmr (DMSO-d_6; pmr (DMSO-d_6): δ 7.45 (d, 1H, J = 8 Hz), 8.25 (d, 1H, J = 8 Hz), 12.6 (br s, 2H).

Anal. Calcd. for $C_7H_4N_2O_3$: C, 51.22; H, 2.44; N, 17.07. Found: C, 51.04; H, 2.60; N, 17.15.

1,2-Dihydro-2-oxo-6-(1*H*-tetrazol-5-yl)-3-pyridinecarboxylic Acid (**15**).

A mixture of 5.00 g (22 mmoles) of nitrile acid **14**, 4.31 g (66 mmoles) of sodium azide, 3.55 g (66 mmoles) of aluminum chloride, and 100 ml of *N,N*-dimethylformamide was heated overnight at 98°. The solids were filtered and the filtrate was concentrated *in vacuo* to a residue which was dissolved in water. Following acidification to *p*H 1.5 with 6*N* aqueous hydrochloric acid, the precipitated solid was filtered to leave 3.75 g (82%) of a tan powder, mp > 300°; ir (potassium bromide): 3200-2400,

1710, 1625 cm^{-1}; pmr (DMSO-d_6): δ 7.50 (d, 1H, J = 8 Hz), 8.45 (d, 1H, J = 8 Hz), 13.5 (br s, 3H).

Anal. Calcd. for $C_7H_5N_5O_3$: C, 40.58; H, 2.42; N, 33.83. Found: C, 40.82; H, 2.57; N, 33.60.

6-(Aminocarbonyl)-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**16**).

A mixture of 700 mg (3.2 mmoles) of nitrile ester **13** and 10 ml of concentrated sulfuric acid was stirred at 25°. The solution was poured onto ice and the precipitated product was collected to give 550 mg (95%) of a white powder, mp > 300°; ir (potassium bromide): 3460, 3320, 3280, 1730, 1690, 1630, 1590 cm^{-1}; pmr (DMSO-d_6): δ 7.20 (d, 1H, J = 8 Hz), 8.0-8.5 (m, 3H), 12.8 (br s, 2H).

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.15; H, 3.30; N, 15.38. Found: C, 46.39; H, 3.00; N, 15.09.

(*E*)-Ethyl 6-[2-(dimethylamino)ethenyl]-1,2-dihydro-α,2-dioxo-3-pyridineacetate (**18**).

To a 25° solution of 418 mg (2 mmoles) of α-keto ester **17** in 3 ml *N,N*-dimethylformamide was added 0.5 ml of *N,N*-dimethylformamide diethyl acetal. After stirring for 1.5 hours, 0.1 ml more acetal was added followed by stirring for 1 hour. The suspension was diluted with 3 ml ethyl ether and the precipitate was collected by filtration, washed well with ethyl ether, and dried to afford 383 mg (73%) of a bright orange powder, mp 237-238°; uv (methanol): 452 nm (ε = 68,160), 312 (6,830), 275 (4,820), 218 (14,490); ir (chloroform): 1740, 1660, 1620, 1575, 1540, 1290, 1100 cm^{-1}; pmr (DMSO-d_6): δ 1.22 (t, 3H, J = 7 Hz), 2.7-3.5 (poorly resolved d, 6H), 4.20 (q, 2H, J = 7 Hz), 5.12 (d, 1H, J = 13 Hz), 6.38 (d, 1H, J = 9 Hz), 7.76 (d, 1H, J = 9 Hz), 8.05 (d, 1H, J = 13 Hz), 11.5 (br s, 1H).

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.09; H, 6.10; N, 10.60. Found: C, 58.91; H, 6.25; N, 10.55.

Acknowledgment.

We thank Dr. F. A. MacKellar and his staff for the acquisition of spectral data.

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