Reaction of 4-Methylpyrano[3,4-*b*]indol-3-one with (Dimethyltriazen-1-yl)pyridinecarboxylic Acids, Precursors of 3,4-Pyridynes

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In connection with another problem, the need arose for a supply of olivacine.[1] A slight modification of Moody's synthesis[2] of ellipticine (8) appeared to be most attractive because of its brevity and the availability of starting materials. Pyranoindolone 6[3] should react with triazene 4 to give olivacine (9), perhaps accompanied by its regioisomer.

Ethyl 3-acetyl-2-methylisonicotinate (1) (Scheme I) was obtained by refluxing ethyl 3-(ethoxymethylene)-2,4-dioxovalerate[4] and 2-imino-4-pentanone[5] in toluene.[6] A Schmidt reaction in concentrated H_2SO_4 gave ester 2, which was saponified to acid 3. Diazotization of 3 followed by coupling with dimethylamine gave 4 in 48% overall yield from 1. When pyranoindolone 6 was refluxed in dry acetonitrile for 6–40 h with either 4 or Moody's triazene 5,[2] *N*,*N*-dimethyl(2-acetyl-3-indolyl)acetamide (7) was obtained in about 40% yield. Refluxing pyranoindolone 6 with the more hindered triazene precursor 9 in acetonitrile resulted in recovery of the starting material 6. Addition of trifluoroacetic acid followed by reflux furnished an intractable mixture containing none of the desired product. Longer reaction times and elevated temperatures did not afford any of the desired 6*H*-pyrido[4,3-*b*]carbazoles. Amide 7 was also obtained by treating pyranoindolone 6 with methanolic dimethylamine.[3]

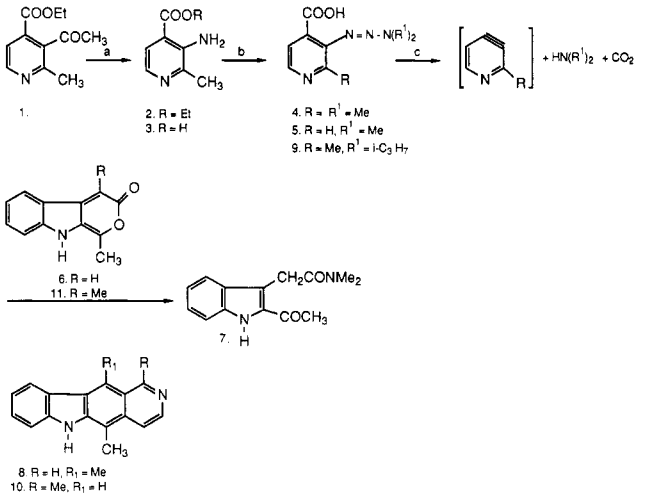
Since it was shown that pyranoindolone 6 did react with *N*-phenylmaleimide and maleic anhydride to furnish the expected Diels–Alder adducts,[3] it appears that in the Moody synthesis the presence of a methyl group at C-1 in 11 provided enough steric hindrance to prevent the dimethylamine generated during the thermolysis of 5 from attacking the carbonyl group in 11.

Moody[2] had shown that the pyridyne derived from 5 reacts with tetracyclone to give 5,6,7,8-tetraphenylisoquinoline in 45–52% yield. We were able to duplicate this reaction. However, when triazene 4 was allowed to react with tetracyclone under identical conditions, none of the expected isoquinoline was formed; only a small amount (<10%) of the triazene was recovered. Since dimethylamine was generated in the reaction of 6 with triazene 4, it is assumed that the latter and 9 both generated 2-methyl-3,4-pyridyne, which appeared to be too sluggish a dienophile to react with 6 to furnish the desired olivacine or its regioisomer.

Experimental Section

Commercially available compounds were used as received without further purification. Melting points were determined on a Mel-Temp open capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian XL-200 MHz spectrophotometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as the internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 298 spectrophotometer. Column chromatography was performed on silica gel (60–230 mesh) with ethyl acetate and hexane as eluants. Mass spectra were obtained on Hewlett-Packard HP 5987A GC/MS spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Scheme I[a]



[a] (a) (i) Concentrated H_2SO_4, NaN_3; (ii) NaOH–H_2O, reflux; (b) $NaNO_2$, concentrated HCl, amines; (c) CH_3CN, reflux.

Ethyl 3-Acetyl-2-methylisonicotinate (1). A mixture of ethyl 3-(ethoxymethylene)-2,4-dioxovalerate[4] (5.1 g, 29.6 mM) and 2-imino-4-pentanone[5] (2.94 g, 29.7 mM) in 20 mL of toluene was refluxed under argon for 4 h. The resulting dark-brown solution was cooled, and the solvent was removed under reduced pressure to give an oil. Column chromatography of the oil gave 2.33 g (38%) of 1. Recrystallization from ether provided an analytically pure sample: mp 74–76 °C; NMR ($CDCl_3$) δ 8.05 (2 H, s, H_5, H_6), 4.50 (2 H, q, CH_2CH_3), 2.82 (3 H, s, $COCH_3$), 2.63 (3 H, s, CH_3), 1.45 (3 H, t, CH_2CH_3); IR (KBr) 1720, 1670, 1550, 1275, 1160, 1095, 930, 790 cm^{-1}; MS (CI, *i*-C_4H_{10}), *m*/*e* 208 (M + 1). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.77; H, 6.28; N, 6.76. Found: C, 63.87; H, 6.34; N, 6.73.

Ethyl 3-Amino-2-methylisonicotinate (2). A suspension of 1 (3.53 g, 17 mM) in 4 mL of dry $CHCl_3$ and 7 mL of concentrated H_2SO_4 was cooled to 0 °C (ice bath). Sodium azide (1.7 g, 25.6 mM) was added carefully to the reaction flask over 10 min. After being stirred at room temperature for 18 h, the mixture was diluted with 10 mL of water and then refluxed for 1.5 h. The dark solution was cooled to 0 °C and basified (pH ≈ 8.0) with NH_4OH. After extraction with chloroform, the organic layer was dried over anhydrous Na_2SO_4. Filtration followed by concentration gave 2.9 g (94%) of a white solid, which was recrystallized from ether: mp 115–116 °C; NMR ($CDCl_3$) δ 7.86 (1 H, d, J = 8.4, H_6), 6.94 (1 H, d, J = 8.4, H_5), 4.38 (2 H, q, CH_2CH_3), 4.11 (2 H, br, s, NH_2), 2.47 (3 H, s, CH_3), 1.41 (3 H, t, CH_2CH_3); IR (KBr) 3435, 3345, 3240, 1700, 1630, 1570, 1275, 1130 cm^{-1}; MS (CI, *i*-C_4H_{10}), *m*/*e* 180 (M + 1). Anal. Calcd for $C_7H_8N_2O_2$: C, 60.00; H, 6.67; N, 15.56. Found: C, 60.09; H, 6.76; N, 15.48.

3-Amino-2-methylisonicotinic Acid (3). To a solution of 1.1 g of NaOH in 60 mL of an ethanol–water (1:1) mixture at 25 °C was added 2.9 g (5.25 mM) of 2. The reaction mixture was refluxed for 1 h, cooled to 0 °C, and adjusted to pH 4–5 by the addition of glacial acetic acid. The resulting suspension was refrigerated overnight and filtered. The solids, washed with a minimum amount of water and methanol, were dried, yielding 1.98 g (81%) of 3. Recrystallization from 95% ethanol provided the analytical sample: mp 211–214 °C; NMR (DMSO-d_6) δ 7.66 (1 H, d, J = 8.4, H_6), 6.93 (1 H, d, J = 8.4, H_5), 5.86 (2 H, br, s, NH_2), 2.31 (3 H, s, CH_3); IR (KBr) 3200, 2930, 1600–1500, 1350, 1320, 1150, 1040, 990, 940, 815, 795, 705 cm^{-1}; MS (CI, *i*-C_4H_{10}), *m*/*e* 153 (M + 1). Anal. Calcd for $C_7H_8N_2O_2 \cdot 0.4H_2O$: C, 52.73; H, 5.52; N, 17.58. Found: C, 52.70; H, 5.34; N, 17.30.

3-(3,3-Dimethyltriazen-1-yl)-2-methylpyridine-4-carboxylic Acid (4). To a suspension of 3 (700 mg, 4.6 mM)

(1) For a review of olivacine syntheses, see: Kansal, V. K.; Potier, P. *Tetrahedron* **1986**, *42*, 2389.
(2) May, C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 247.
(3) Plieninger, H.; Muller, W.; Weinerth, K. *Chem. Ber.* **1964**, *97*, 667.
(4) Jones, R. G. *J. Am. Chem. Soc.* **1951**, *73*, 3684.
(5) Wee, A. G. H.; Shu, A. Y. L.; Bunnenberg, E.; Djerassi, C. *J. Org. Chem.* **1984**, *49*, 3327.
(6) Kurihara, T.; Uno, T. *Heterocycles* **1977**, *6*, 547.

0022-3263/89/1954-5189$01.50/0

in 12 mL of absolute ethanol was added 2.1 mL of concentrated HCl. The mixture was cooled to 0–5 °C and then treated with a cold solution of sodium nitrite (0.8 g, 11.6 mM) in water (11 mL), over a 5-min period, with the reaction temperature maintained at 0–5 °C. The resulting mixture was stirred for a further 20 min. The cold diazotized solution was then added dropwise to a cold mixture of Na_2CO_3 (1.5 g, 14.2 mM) and dimethylamine (30% aqueous solution, 3 mL) in 12 mL of H_2O. The resulting solution was stirred for 30 min and then acidified with concentrated HCl to pH 4.5–5.0. After 20 min, a light colored solid separated from the solution and was collected by filtration to give 250 mg (26%) of **4**. The filtrate was thoroughly extracted with chloroform. The chloroform layer was dried ($MgSO_4$) and concentrated to give 450 mg (47%) of **4** in a total yield of 73%. All attempts to recrystallize **4** failed; however, it appeared to be pure enough to use in the next step: mp 169–171 °C;[7] NMR (DMSO-d_6) δ 7.63 (1 H, d, J = 8.4, H_6), 7.52 (1 H, d, J = 8.4, H_5), 3.58 (3 H, s, NCH_3), 3.25 (3 H, s, NCH_3), 2.59 (3 H, s, CH_3); IR (KBr) 3480–3360, 2980, 1950, 1685, 1620, 1580, 1520, 1480, 1340, 1180, 1145, 1080, 900, 800, 780, 745, 660, cm^{-1}; MS (CI, i-C_4H_{10}), m/e 209 (M + 1).

3-(3,3-Diisopropyltriazen-1-yl)-2-methylpyridine-4-carboxylic Acid (9). Compound **9** was prepared by the same method as **4** in 51% yield. It was obtained as an oil:[7] NMR ($CDCl_3$) δ 7.98 (1 H, d, J = 8.2, H_6), 7.78 (1 H, d, J = 8.4, H_5), 5.22 (1 H, m), 4.11 (1 H, m) 2.65 (3 H, s, CH_3), 1.40 (6 H, d, J = 6.8), 1.30 (6 H, d, J = 6.8); IR (neat) 3470–3365, 2980, 1950, 1690, 1620, 1570, 1180, 1080, 780 cm^{-1}; MS (CI, i-C_4H_{10}), m/e 265 (M + 1).

(7) Satisfactory elemental analyses were not obtained, presumably owing to the rapid thermal decomposition of the triazene.

***N,N*-Dimethyl(2-acetyl-3-indolyl)acetamide (7).** (A) A suspension of **5** (320 mg, 1.56 mM) and 4-methylpyrano[3,4-*b*]-indol-3-one (**6**)[3] (111 mg, 0.56 mM) in 22 mL of dry acetonitrile was refluxed for 40 h. The solvent was removed in vacuo, and the residue was chromatographed ($CHCl_3$–MeOH) to give 53 mg (36%) of **7**. Recrystallization from ethanol gave colorless crystals: mp 224–227 °C; NMR ($CDCl_3$) δ 9.86 (1 H, br, s, NH), 7.57 (1 H, d, J = 8.2, H_6), 7.26–7.08 (3 H, m), 4.15 (2 H, s, CH_2CO), 3.28 (3 H, s, NCH_3), 3.14 (3 H, s, NCH_3), 1.88 (3 H, s, $COCH_3$); IR (KBr) 3180, 1662, 1540, 1400, 1260, 1145, 745 cm^{-1}; MS (CI, i-C_4H_{10}), m/e 245 (M + 1). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.85; H, 6.56; N, 11.48. Found: C, 68.78; H, 6.64; N, 11.39.

(B) A mixture of **4** (280 mg, 1.35 mM) and pyranoindolone **6** (180 mg, 0.90 mM) in 20 mL of dry acetonitrile was refluxed for 50 h. Solvents were evaporated, and the dark residue was chromatographed to give 35 mg (35%) of **7**, mp 223–226 °C, which was identical in all respects with the sample described above.

(C) A mixture of **6** (655 mg, 3.29 mM) in 100 mL of dry methanol, saturated with dimethylamine, was refluxed for 2 h and then allowed to cool to room temperature overnight. Methanol was removed in vacuo, and the residue was chromatographed ($CHCl_3$–MeOH) to give 353 mg (44%) of the desired dimethyl amide, **7**, mp 224–227 °C, which was identical in all respects with the sample described above.

(D) A mixture of **6** (90 mg, 0.45 mM) and **9** (250 mg, 0.95 mM) in 22 mL of dry acetonitrile was refluxed for 39 h. TLC indicated presence of the starting material only. Then 2–3 drops of trifluoroacetic acid were added, and reflux was continued for an additional 60 h. Workup as in the previous experiment (C) did not result in any identifiable product.

Acknowledgment. This work was supported by a grant (CA 19674) from the National Cancer Institute.

Additions and Corrections

Vol. 50, 1985

Bryan P. Murphy and Thomas M. Schultz*. Synthesis and Physical Properties of 5,6-Dihydroxyindole.

Page 2791, Table I. Assignments for H_2 and H_3 should be reversed to read

H_2 6.98 ppm
H_3 6.22 ppm

Vol. 53, 1988

Francesco Fringuelli,* Lucio Minuti, Lajos Radics, Aldo Taticchi,* and Ernest Wenkert*. Diels–Alder Reactions of Cycloalkenones. 13. Reactions of 2-Cycloalkenones with (*E*)-1-Methoxy-1,3-butadiene.

Page 4607. Formula **4** should depict a C(8)–C(9) double bond.

Page 4609 (left column). Line 13 should read $^3J_{6,7A} + {}^3J_{6,7B}$ = 16.0 Hz; lines 16 and 17 should read $^3J_{9A,10} + {}^3J_{9B,10}$ = 6.5 Hz.

Page 4609 (right column). Lines 19 and 20 should read 5.76 (H-8), 5.93 (H-9); lines 43 and 44 should read 5.55 (H-8), 5.71 (H-12), 5.74 (H-9), 5.88 (H-13); lines 54 and 55 should read 5.44 (H-8), 5.72 (H-12), 5.74 (H-9), 5.92 (H-13).

Page 4610 (left column). Lines 30 and 31 should read 5.80 (H-8), 5.87 (H-9).

Page 4610 (right column). Lines 5–12 should read ^{1}H NMR δ 1.15 (H-11B), 1.20 (H-5B), 1.22 (H-9B), 1.24 (H-12B), 1.29 (H-7B), 1.31 (H-8B), 1.36 (H-13B), 1.37 (H-9A), 1.38 (H-7A), 1.42 (H-8A), 1.56 (H-11A), 1.71 (H-4B, H-12A), 1.84 (H-13A), 1.90 (H-4A), 2.11 (H-10), 2.31 (H-6), 2.34 (H-3B), 2.47 (H-5A), 2.49 (H-3A), 2.80 (H-14), 3.15 (OMe); ^{13}C NMR δ 19.6 (C-4), 20.1 (C-8), 24.2 (C-12), 25.3 (C-13), 26.1 (C-5), 26.2 (C-11), 28.5 (C-9), 30.6 (C-7), 32.2 (C-6), 35.9 (C-10), 40.8 (C-3), 57.2 (C-1, OMe), 89.5 (C-14), 217.6 (C-2).

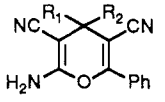
Vol. 54, 1989

Vera M. Kolb,* Joseph W. Stupar, Timothy E. Janota, and William L. Duax. Abnormally High IR Frequencies for the Carbonyl Group of Semicarbazones of the Benzaldehyde and Acetophenone Series.

Page 2345. Column 1, line 13, should read as follows: The literature search revealed that no X-ray structures of semicarbazones of this series were reported, except that of benzaldehyde semicarbazone (Naik, D. V.; Palenik, G. J. *Acta Crystallogr.* **1974**, *B30*, 2396–2401).

Diego Armesto,* William M. Horspool, Nazario Martin, Ana Ramos, and Carlos Seoane. Synthesis of Cyclobutenes by the Novel Photochemical Ring Contraction of 4-Substituted 2-Amino-3,5-dicyano-6-phenyl-4*H*-pyrans.

Page 3069, column 2. The structure for compound **9** had the cyano groups omitted. The correct structure is given below.



9a: R^1, R^2 = $(CH_2)_4$
b: R^1, R^2 = $(CH_2)_5$
c: R^1 = R^2 = CH_3
d: R^1 = $(CH_3)_2CH$, R^2 = H
e: R^1 = C_6H_5, R^2 = H
f: R^1 = *p*-CNC_6H_4, R^2 = H
g: R^1, R^2 = $(CH_2)_3$
h: R^1 = R^2 = CN