Oxidation of 3a with $Ca(ClO)_2$. A suspension of $Ca(ClO)_2$ (61 mg, 0.26 mmol) in benzene (2 mL)–H_2O (1 mL) was added to a solution of **3a** (100 mg, 0.51 mmol) dissolved in benzene (4 mL)–H_2O (2 mL). After vigorous stirring at 65 °C for 1 h, $Ca(ClO)_2$ (183 mg, 0.77 mmol) suspended in benzene (2 mL)–H_2O (1 mL) was added again and the mixture was stirred for additional 2 h. After adding AcOEt and centrifuging a precipitate, the organic substances were extracted with AcOEt and the usual workup provided **1** (75 mg, 98%).

1-[2-Chloro-4,5-(methylenedioxy)phenyl]propane-1,2-diol (6). A suspension of $Ca(ClO)_2$ (60% purity, 92 mg, 0.39 mmol) in AcOH (0.12 mL)–H_2O (1.2 mL) was added dropwise to a solution of **3a** (50 mg, 0.26 mmol) dissolved in MeCN (2 mL)–CH_2Cl_2 (1 mL). The reaction mixture was stirred at room temperature for 1 h. Ether extraction followed by usual workup and chromatography provided **6** (50 mg, 85%) as colorless crystals: mp 85–86 °C; IR ($CHCl_3$) 3560 (OH), 3380 (OH), 1475, 1220, 1120, 1035, 935, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.96 (s, 1 H, Ar H), 6.80 (s, 1 H, Ar H), 5.97 (s, 2 H, CH_2), 4.86 (d, J = 7 Hz, 1 H, CH), 3.84 (quint, J = 7 Hz, 1 H, CH), 3.04 (br s, 1 H, OH), 2.64 (br s, 1 H, OH), 1.14 (d, J = 7 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 147.6 (s), 147.1 (s), 132.4 (s), 124.5 (s), 109.6 (d), 107.7 (d), 101.8 (t), 74.4 (d), 71.8 (d), 18.8 (q). Anal. Calcd for $C_{10}H_{11}O_4Cl$: C, 52.07; H, 4.81. Found: C, 52.26; H, 4.99.

1-[3,4-(Methylenedioxy)phenyl]-2-propanone (5). A solution of **3a** (100 mg, 0.5 mmol) and *p*-TsOH (200 mg) dissolved in a distilled benzene (20 mL) was refluxed for 20 min. The usual workup gave **5** (75 mg, 84%).[8,9]

Registry No. **1**, 120-57-0; **2**, 120-58-1; **3a**, 62512-79-2; **3b**, 57961-85-0; **5**, 4676-39-5; **6**, 89321-20-0; CAN, 16774-21-3; $NaIO_4$, 7790-28-5; $Ca(ClO)_2$, 7778-54-3.

Reaction of the Anion of Meldrum's Acid with an *N*-Alkylpyridinium Salt

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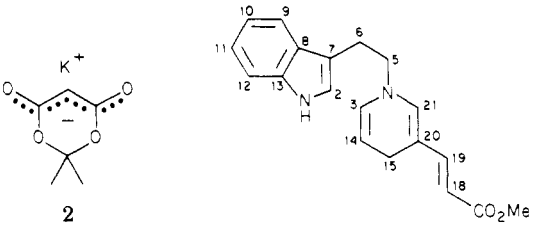
A two-step reaction scheme emanating from 1-[β-(β-indolyl)ethyl]-3-acylpyridinium salts or their vinylogues (carbon nucleophile addition, followed by acid-induced cyclization) has formed the basis for some time for synthesis of a variety of indole alkaloids.[1] Thus the reactions in Scheme I constituted early steps in the synthesis of the yohimbines.[2,3] An attempt to modify the first of these reactions by the replacement of the dimethyl malonate anion by the salt of Meldrum's acid led to a dramatic change in the reaction outcome—the subject of the present report.

Exposure of the pyridinium salt 1 to the potassium salt 2 of 2,2-dimethyl-4,6-dioxo-1,3-dioxane (Meldrum's acid) in refluxing tetrahydrofuran for 3 days and treatment of the reaction mixture with methanolic hydrochloric acid for 3 days led to two isolable products. The minor constituent could be recognized to be tetracycle 4, i.e., the product of the acid-induced ring closure of the product 3 of 1,4-reduction of the pyridinium salt 1. The structurally more complex major constituent could be assumed to be a product of oxidation of the adduct of the two salts by



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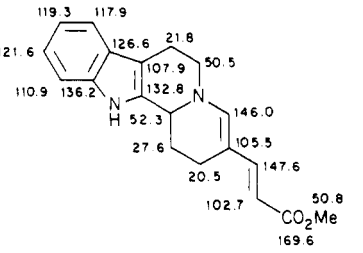
3



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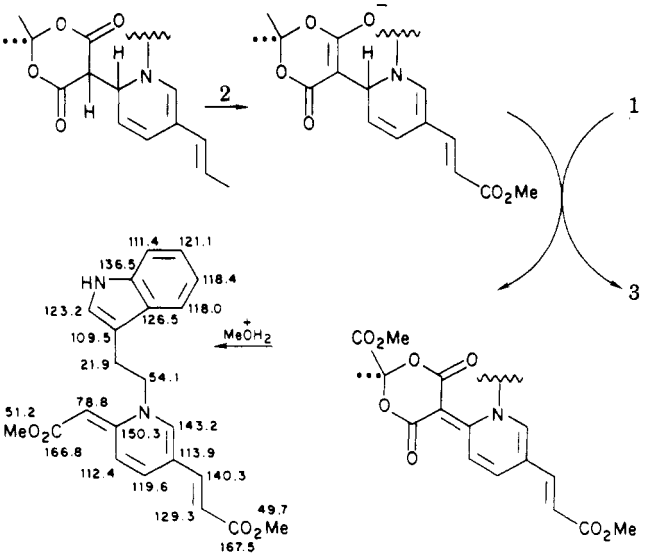
analogy with the unusual chemistry experienced recently in the reaction of methyl sodioacetoacetate with 1-[β-(β-indolyl)ethyl]-3-formylpyridinium bromide.[4]

The molecular formula of $C_{22}H_{22}O_4N_2$ of the major product appeared to justify the aforementioned surmise. Its yellow color and ultraviolet spectra [λ_{max}^{EtOH} 221 nm (log ϵ 4.57), 253 (4.10), 275 (4.04), 290 (3.88), 3.92 (4.57); $\lambda_{max}^{EtOH/HCl}$ 220 nm (log ϵ 4.62), 270 (4.27), 290 (4.10)] showed the presence of an extended chromophore and hence a complex system of conjugated multiple bonds. Its infrared spectrum [ν_{max}^{KBr} NH 3250 (m), C=O, C=C 1700 (s), 1660 (s), 1610 (s), 1570 (s) cm^{-1}] exhibited indole N–H, ester carbonyl, and vinylogous amide carbonyl absorption bands. Its low-resolution mass spectrum revealed intense m/e 144 and 143 fragments, characteristic of the β-ethylindole cation, indicating that the β-indolylethyl unit of the starting compound had remained unmodified in the product. In the face of these spectral data, the ^1H and ^{13}C NMR spectra, and the following mechanism for the formation of the substance as well as dihydropyridine 3 the new substance could be assigned structure 5.



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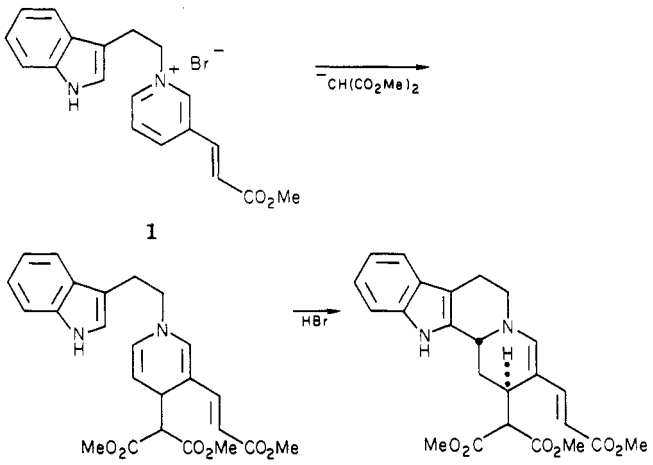
Structure 5 could be confirmed by ^1H and ^{13}C NMR spectral analyses of the compound's protic salt 6 and by

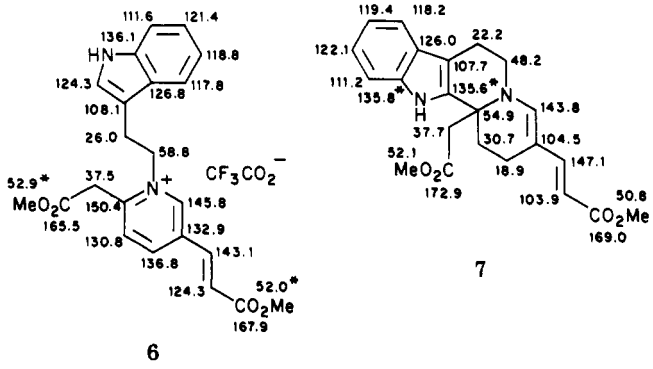
(1) Wenkert, E. *Heterocycles*, in press.
(2) Wenkert, E.; Halls, T. D. J.; Kunesch, G.; Orito, K.; Stephens, R. L.; Temple, W. A.; Yadav, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 5370; **1982**, *104*, 6166.
(3) In a recent review of the chemistry of dihydropyridines (Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223), the wrong starting compound and intermediates were shown to have been transformed into yohimbine.
(4) Wenkert, E.; Pyrek, J. St.; Uesato, S.; Vankar, Y. D. *J. Am. Chem. Soc.* **1982**, *104*, 2244.

0022-3263/84/1949-1832$01.50/0

Scheme I



spectral analysis of the product 7 of dithionite reduction of the salt and subsequent acid-catalyzed ring closure.[5]



The production of compounds 4 and 5 from the two-step reaction sequence starting with pyridinium salt 1 is of interest not only as a second example of an oxidation–reduction interference in the desired synthesis path[4] but also because it constitutes the first case of the trapping of an enolate at the pyridine α-carbon site in the initial step of the usual indole alkaloid synthesis scheme. Since the addition of nucleophiles to *N*-alkylpyridinium salts is considered to proceed at the α- and γ-carbon centers under kinetic control and at the γ-carbon center under thermodynamic control,[6] the present observation illustrates an example of the interference in the thermodynamic process by a fast oxidation of the kinetic product.[7]

Experimental Section

Melting points were taken on a Reichert micro hotstage and are uncorrected. Infrared spectra on KBr pellets of solids were measured on a Beckman IR 4230 spectrophotometer and ultraviolet spectra of ethanol solutions on a Cary 17 spectrophotometer. ^{1}H NMR spectra of Me_2SO-d_6 solutions with Me_4Si as internal standard (δ = 0 ppm) were recorded on a Varian EM-390 spectrometer and on a 360-MHz instrument with a highly modified Varian HR220 console, an Oxford magnet, and a Nicolet 1180-E computer system. The ^{13}C NMR spectra of compounds 4–6 in Me_2SO-d_6 solutions and of tetracycle 7 in $CDCl_3$ solution were taken on a Varian XL-100-15 spectrometer. Mass spectra were observed on a CEC 21-110B spectrometer.

The carbon shifts on the formulas are in ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm $= \delta(CDCl_3) + 76.9$ ppm. Asterisked numbers may be interchanged.

Esters 4 and 5. Salt 1, 5.81 g (15 mmol), was added to a mixture of 4.76 g (33 mmol) of Meldrum's acid and 4.00 g (35 mmol) of KO-*t*-Bu in 125 mL of anhydrous THF and the suspension refluxed under argon for 72 h. Upon being cooled the mixture was treated with 200 mL of 1 N methanolic hydrogen chloride and then stirred under argon at room temperature for 72 h. The mixture was neutralized with solid $NaHCO_3$ and filtered. The precipitate was washed with methanol and the combined washings and filtrate were evaporated. The residue was extracted with CH_2Cl_2 and the extract evaporated. Chromatography of the residual oil, 9.2 g, on 500 g of silica gel and elution with CH_2Cl_2 yielded 305 mg (7%) of solid, whose crystallization from MeOH gave ester 4:[8] mp 239 °C; UV λ_{max} 225 nm (log ϵ 4.50), 273 (3.87), 290 (3.78), 358 (4.68); IR NH 3350 (s), C=O, C=C 1680 (s), 1585 (br s) cm^{-1}; ^{1}H NMR δ 1.7–1.9 (m, 1, H-14), 2.2-2.4 (m, 2, H-6), 2.6–2.8 (m, 1, H-14), 2.8–3.0 (m, 2, H_2-5), 3.5–3.6 (m, 1, H-15), 3.66 (s, 3, OMe), 3.8–3.9 (m, 1, H-15), 4.63 (d, 1, J = 14 Hz, H-3), 5.29 (d, 1, J = 15 Hz, H-18), 7.07 (t, 1, J = 8 Hz, H-10), 7.16 (t, 1, J = 8 Hz, H-11), 7.18 (s, 1, H-21), 7.36 (d, 1, J = 15 Hz, H-19), 7.42 (d, 1, J = 8 Hz, H-12), 7.50 (d, 1, J = 8 Hz, H-9); MS, *m/e* (relative intensity) 308 (M^+, base), 293 (22), 277 (25), 249 (25), 247 (15), 170 (40), 169 (30), 168 (25), 156 (80), 154 (25), 139 (30); exact mass *m/e* 308.1528 (calcd for $C_{19}H_{20}O_2N_2$, 308.1525).

Further elution with 100:1 CH_2Cl_2–MeOH led to 921 mg (16%) of a solid, whose crystallization from MeOH afforded ester 5: mp 213–218 °C; ^{1}H NMR δ 3.09 (t, 2, J = 7 Hz, H-6), 3.55 (s, 3, OMe of acetic ester), 3.66 (s, 3, OMe of acrylic ester), 4.05 (t, 2, J = 7 Hz, H_2-5), 4.83 (s, 1, H-3′), 6.33 (d, 1, J = 16 Hz, H-18), 7.00 (t, 1, J = 8 Hz, H-10), 7.09 (t, 1, J = 8 Hz, H-11), 7.18 (d, 1, J = 16 Hz, H-19), 7.19 (s, 1, H-2), 7.35 (d, 1, J = 8 Hz, H-12), 7.48 (d, 1, J = 10 Hz, H-14), 7.73 (s, 1, H-21), 8.30 (d, 1, J = 10 Hz, H-15); MS, *m/e* (relative intensity) 378 (M^+, 1), 144 (80), 143 (base).

Anal. Calcd for $C_{22}H_{22}O_4N_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.68; H, 5.79; N, 7.30.

Diester 7. A suspension of 378 mg (1 mmol) of vinylogous amide 5 in 10 mL of dry benzene saturated with HBr gas was stirred for 10 min and then evaporated. The residue and 1.5 g of $NaHCO_3$ were taken up in 50 mL of methanol and 25 mL of water and 1.0 g of $Na_2S_2O_4$ added in small portions over a 1-h period to the stirring mixture under argon. After being stirred at room temperature for 20 h, the mixture was filtered and the filtrate evaporated. A solution of the residue in 100 mL of 2 N methanolic hydrochloric acid was stirred at room temperature for 48 h and then neutralized with solid $NaHCO_3$. The mixture was filtered and the precipitate washed with methanol. The combined washings and filtrate were evaporated, and the residue was extracted with CH_2Cl_2. The extract was evaporated and the residual oil chromatographed on silica gel. Elution with CH_2Cl_2 gave a solid whose preparative TLC (SiO_2) yielded 160 mg (42%) of amorphous ester 7; IR ($CHCl_3$) NH 3430 (w), C=O, C=C 1700 (s), 1680 (m), 1620 (m), 1610 (s) cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 1.7–1.9 (m, 1, H-14), 2.1–2.4, 2.8–3.1, 3.4–3.7 (m, 8, methylenes), 2.7–2.8 (m, 1, H-14), 3.73, 3.75 (s, 3 each, 2 OMe), 5.35 (d, 1, J = 13 Hz, H-18), 6.55 (s, 1, H-21), 7,12 (t, 1, J = 8 Hz, H-10), 7.20 (t, 1, J = 8 Hz, H-11), 7.35 (d, 1, J = 13 Hz, H-19), 7.38 (d, 1, J = 8 Hz, H-12), 7.52 (d, 1, J = 8 Hz, H-9); MS, *m/e* (relative intensity) 380 (M^+, 30), 308 (25), 307 (base); exact mass *m/e* 380.1752 (calcd for $C_{22}H_{24}O_4N_2$, 380.1735).

Acknowledgment. We are indebted to the U.S. Public Health Service for support of this work and to T. D. J. Halls and B. Porter for the ^{13}C NMR spectra.

Registry No. 1, 89486-66-8; 4, 89486-63-5; 5, 89486-64-6; 6, 89486-68-0; 7, 89486-65-7; Meldrum's acid, 2033-24-1.

(5) For the earliest examples of this two-step reaction sequence, see: (a) Supple, J. H.; Nelson, D. A.; Lyle, R. E. *Tetrahedron Lett.* **1963**, 1645. (b) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645; **1982**, *104*, 6166.

(6) Damji, S. W. H.; Fyfe, C. A. *J. Org. Chem.* **1979**, *44*, 1757. Damji, S. W. H.; Fyfe, C. A.; Smith, D.; Sharom, F. J. *J. Org. Chem.* **1979**, *44*, 1761.

(7) For examples of alkaloid syntheses involving carbon nucleophile interactions at the α-carbon sites of *N*-alkylpyridinium salts, see: Wanner, M. J.; Koomen, G. J.; Pandit, U. K. *Heterocycles* **1980**, *14*, 643; **1981**, *15*, 377; *Tetrahedron* **1982**, *38*, 2741; **1983**, *39*, 3673.

(8) Besselièrre, R.; Cosson, J. P.; Das, B. C.; Husson, H.-P. *Tetrahedron Lett.* **1980**, *21*, 63.