amine 1 in 1 mL of THF was added dropwise. The yellow mixture was stirred for 2.5 h and the solvent evaporated, leaving an orange oil. The oil was washed with ether and the ether discarded. The addition of fresh ether followed by 1 M NaOH (sufficient amount to dissolve the oil) left a yellow organic layer which was extracted with 10% HCl (3 × 5 mL), made alkaline with solid NaOH, and extracted again with ether, and the ether extracts were dried over potassium carbonate. The solvent was filtered and evaporated, leaving a yellow oil (70 mg, 71% yield) which by GLC analysis contained **6e** plus a small amount of **6a**. NMR ($CDCl_3$) for **6e:** δ 7.40 (m, 2 H), 7.25 (m, 3 H), 1.6–3.8 (m, 12 H). Mass spectrum, *m/e* (relative intensity) 219 (9, M^+), 110 (5), 109 (18), 108 (6), 84 (6), 83 (100), 55 (12).

Anal. Calcd for $C_{13}H_{17}NS$: M_r = 219.1082. Found: M_r = 219.1074.

Reaction of 1 with $PdCl_2(PhCN)_2$.[14] A solution containing 42 mg (0.38 mmol) of amine 1 in 5 mL of tetrahydrofuran was added dropwise to a mixture containing 150 mg (0.39 mmol) of $PdCl_2(PhCN)_2$ in 5 mL of THF at −40 °C with the immediate formation of a yellow precipitate. The yellow mixture was stirred for 1 h at room temperature, and triethylamine was added dropwise till the solution was clear with the formation of a black precipitate. After stirring for 2 h at room temperature, 25 mg (0.46 mmol) of potassium borohydride and 0.5 mL of 2 M NaOH were added and the solution was stirred for an additional 30 min. The clear solution was filtered from the palladium metal and extracted with 4 M HCl (3 × 5 mL). The aqueous layer was made alkaline with NaOH pellets and extracted with ether, and the ether extracts were dried over potassium carbonate. The sole product was determined by GLC to be **7** with identical spectral characteristics with those of azacyclooctane prepared by a separate route from cycloheptanone. No trace of either pyrrolizidine or starting material was observed.

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Registry No.—**1**, 57502-48-4; **3**, 65113-00-0; **4**, 65113-01-1; **5**, 65113-02-2; **6a**·HBr, 65113-05-5; **6a** picrate, 68225-94-5; **6b**, 643-20-9; **6d** picrate, 68201-07-0; **7**, 1121-92-2; **9**, 68201-08-1; diphenyl disulfide, 882-33-7; $PdCl_2(PhCN)_2$, 14220-64-5; diphenyl diselenide, 1666-13-3.

Supplementary Material Available: Figure 2 (numbering scheme for tables), Table III (fractional coordinates of atoms), Table IV (anisotropic thermal parameters), Table V (distances), Table VI (angles), and Table VII (torsion angles and structure factors) (6 pages). Ordering information is given on any current masthead page.

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Notes

Synthesis of 1,4,5,6-Tetrahydro-2-(hydroxymethyl)-4-oxo-3-pyridinecarboxylic Acid γ-Lactones

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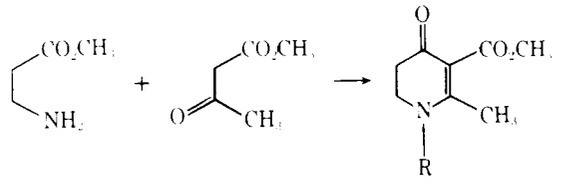
The tetrahydropyridine ring plays a central role in the construction of a variety of alkaloids.[1] Our own interest in the total synthesis of morphine alkaloids[2] required a practical synthesis of the previously unreported lactones **4a–c.** In this note, we describe an efficient synthesis of these and related compounds.

Using the method of Becker,[3] keto ester **1a** is easily pre-



1a, R = H
b, R = CH_3
c, R = CO_2CH_3

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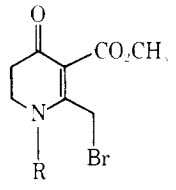
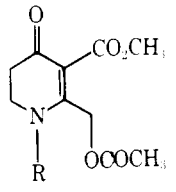
pared from β-alanine methyl ester and acetoacetic ester. Conversion of **1a** to the *N*-methyl derivative **1b** and urethane **1c** is accomplished by reaction of an alkali metal salt of **1a** with methyl iodide and methyl chloroformate, respectively.

Crystalline lactone **4a** may be obtained from **1b** in 65% isolated yield via allylic bromide **2a.** Thus, reaction of **1b** with *N*-bromosuccinimide (NBS) in dimethylformamide (DMF) at 0 °C gives **2a** in essentially quantitative yield. On the other hand photoinitiated allylic bromination of **1b** with NBS in carbon tetrachloride gives recovered **1b,** monobromide **2a,** and a substantial amount of a dibromide.

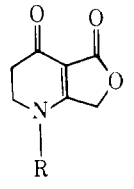
Treatment of **2a** with potassium acetate in DMF gives **3a,**[4] which is converted to lactone **4a** by reaction with a catalytic



2a, R = CH_3
b, R = CO_2CH_3



3a, R = CH_3
b, R = CO_2CH_3

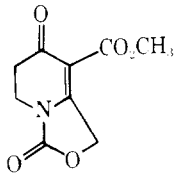


4a, R = CH_3
b, R = CO_2CH_3
c, R = H

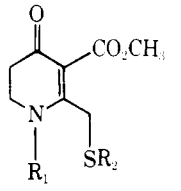
amount of sodium methoxide in methanol. Whereas allylic acetate **3a** is soluble in methanol at room temperature, lactone **4a** crystallizes as it is formed and after 10 min reaction time **4a** may be collected in 93% yield.

In a similar manner, **1c** is converted to the allylic acetate **3b.** However, treatment of **3b** with methanolic potassium hydroxide results in precipitation of a mixture of the potassium enolate of cyclic urethane **5** and a small amount of decarbomethoxylated lactone **4c** (^{1}H NMR analysis). While the enolate of **5** is soluble in aqueous ammonium chloride, **4c** is not; thus, pure **5** can be obtained by extraction of the aqueous layer.

The desired lactone **4b** is prepared in 86% isolated yield by reaction of acetate **3b** with methanolic hydrogen chloride. The expected sensitivity of **4b** to base (vide supra) is demonstrated by treatment of **4b** with potassium hydroxide in methanol solution, from which decarbomethoxylated lactone **4c** is formed.



5



6a, $R_1 = CH_3$; $R_2 = C_6H_5$
b, $R_1 = CO_2CH_3$; $R_2 = CH_3$
c, $R_1 = CO_2CH_3$; $R_2 = C_6H_5$

We also have prepared the allylic sulfides **6a–c** from the corresponding bromide. It is of interest to note that reaction of **2a** with benzenethiol (1 equiv) and triethylamine (1 equiv) in methanolic solution results in reduction to **1b,** recovery of **2a,** and formation of diphenyl disulfide. Evidently, reaction of benzenethiol with **6a**[5] is favored over that with **2a.** In any event, by simply changing to DMF solvent, **2a** undergoes smooth displacement with benzenethiol and no reduction to **1b** is detected.[6]

Experimental Section

General. ^{1}H NMR spectra were obtained on a Varian A-60A or EM-390 NMR spectrometer (tetramethylsilane internal standard, deuteriochloroform solvent). Infrared spectra were recorded on a Perkin-Elmer 257 grating spectrometer and melting points were measured on a calibrated Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectra were obtained on a Finnigan 3300 gas chromatograph–mass spectrometer and microanalyses were carried out by Spang Microanalytical Laboratory, Eagle Harbor, Mich.

Methyl 1,4,5,6-Tetrahydro-1,2-dimethyl-4-oxo-3-pyridinecarboxylate (1b). To 2.27 g (55.4 mmol) of potassium hydride suspended in 250 mL of tetrahydrofuran was added 9.36 g (55.4 mmol) of methyl 1,4,5,6-tetrahydro-2-methyl-4-oxo-3-pyridinecarboxylate (**1a**) at room temperature. The mixture was heated to reflux for 20 min and cooled to room temperature. Dimethylformamide (30 mL) was added followed by addition of 6.9 mL (15.7 g, 0.111 mol) of iodomethane. After stirring 2 h at room temperature, the mixture was filtered and concentrated to 15.6 g of oil. The oil was dissolved in water and extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated to 10.3 g of oil which crystallized in ethyl acetate–petroleum ether (3:1) to give the pyridinone **1b** (6.75 g, 67%, mp 76–77 °C): IR ($CHCl_3$) 1715, 1690 (shoulder), 1635, 1555 cm^{-1}; NMR δ 3.76 (s, 3 H), 3.57 (t, 2 H), 3.20 (s, 3 H), 2.50 (t, 2 H), 2.23 (s, 3 H).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15. Found: C, 58.92; H, 7.14.

Methyl 1,4,5,6-Tetrahydro-2-(bromomethyl)-1-methyl-4-oxo-3-pyridinecarboxylate (2a). To 3.66 g of pyridinone **1b** (20 mmol) in 18 mL of dimethylformamide cooled to 0 °C was added 3.56 g of *N*-bromosuccinimide (20 mmol) followed by 2 mL of dimethylformamide. After stirring 2 h at 0 °C, the dimethylformamide was removed at about 0.1 mmHg. The residue was dissolved in dichloromethane and washed consecutively with 1% $Na_2S_2O_3$ and water and dried ($MgSO_4$). Concentration gave 5.14 g of oil which crystallized from ethyl acetate–dichloromethane to give the bromide **2a** (3.45 g, 66%, mp 112–113 °C): IR ($CHCl_3$) 1715, 1695, 1645, 1560 cm^{-1}; NMR δ 4.38 (s, 2 H), 3.80 (s, 3 H), 3.60 (t, 2 H), 3.26 (s, 3 H), 2.50 (t, 2 H).

Anal. Calcd for $C_9H_{12}NO_3Br$: C, 41.24; H, 4.62. Found: C, 41.23; H, 4.69.

Methyl 1,4,5,6-Tetrahydro-2-[(acetyloxy)methyl]-1-methyl-4-oxo-3-pyridinecarboxylate (3a). A mixture of 1.31 g of bromide **2a** (5.0 mmol), 10 mL of dimethylformamide, and 0.98 g of potassium acetate (10 mmol) was stirred for 2 h at room temperature. The solvent was removed at about 0.1 mmHg and the residue taken up in water and extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated to 1.17 g of solid. Recrystallization of the solid from ethyl acetate–petroleum ether (1:1) gave the acetate **3a** (0.97 g, 81%, mp 102.5–103.5 °C): IR ($CHCl_3$) 1750, 1722, 1647, 1565 cm^{-1}; NMR δ 4.97 (s, 2 H), 3.78 (s, 3 H), 3.60 (t, 2 H), 3.20 (s, 3 H), 2.52 (t, 2 H), 2.10 (s, 3 H).

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27. Found: C, 54.79; H, 6.25.

1,4,5,6-Tetrahydro-2-(hydroxymethyl)-1-methyl-4-oxo-3-pyridinecarboxylic Acid γ-Lactone (4a). To 1.25 g of acetate **3a** (5.2 mmol) in 10 mL of methanol was added 0.5 mL of 0.5 M sodium methoxide (0.25 mmol) in methanol at room temperature. After stirring 10 min the mixture was cooled to 0 °C and filtered to give the lactone **4a** (0.81 g, 93%, mp 223–224 °C): IR (Nujol) 1765, 1640 cm^{-1}; NMR δ 4.74 (s, 2 H), 3.72 (t, 2 H), 3.10 (s, 3 H), 2.59 (t, 2 H).

Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43. Found: C, 57.46; H, 5.45.

Methyl 1,4,5,6-Tetrahydro-1-(methoxycarbonyl)-2-methyl-4-oxo-3-pyridinecarboxylate (1c). To a mechanically stirred suspension of sodium hydride (6.2 g of a 57% oil dispersion, 0.147 mol) in 250 mL of tetrahydrofuran was added 25.0 g (0.147 mol) of methyl 1,4,5,6-tetrahydro-2-methyl-4-oxo-3-pyridinecarboxylate (**1a**) at room temperature. Dimethylformamide (50 mL) was added and the mixture heated to reflux for 5 h. Tetrahydrofuran (100 mL) was added and the heating continued for 2 h. A solution of 13.9 g (0.147 mol) of methyl chloroformate in 50 mL of tetrahydrofuran was added at room temperature and the mixture was stirred for 12 h. The suspension was filtered and concentrated to give an oil which crystallized in ethyl acetate–petroleum ether (1:1) to give pyridinone **1c** (24.4 g, 73%, mp 55–57 °C): IR ($CHCl_3$) 1750–1715, 1670, 1585 cm^{-1}; NMR δ 4.10 (t, 2 H), 3.85 and 3.83 (2 s, 6 H), 2.55 (t, 2 H), 2.35 (s, 3 H).

Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.76. Found: C, 53.01; H, 5.79.

Methyl 1,4,5,6-Tetrahydro-2-(bromomethyl)-1-methoxycarbonyl-4-oxo-3-pyridinecarboxylate (2b). A suspension of 1.14 g (5.0 mmol) of pyridinone **1c** and 1.07 g (6.0 mmol) of *N*-bromosuccinimide in 5 mL of carbon tetrachloride was heated to reflux and irradiated with a 150 W sunlamp for 0.5 h. The mixture was cooled and filtered with dichloromethane. The filtrate was washed consecutively with 1% $Na_2S_2O_3$ and water and dried ($MgSO_4$). The solution was concentrated to 1.73 g of oil which was crystallized in ether to give bromide **2b** (0.96 g, 63%, mp 69–70 °C); alternatively, crude bromide **2b** could be used directly for subsequent reactions: IR ($CHCl_3$)

1745–1720, 1680, 1590 cm^{-1}; NMR δ 4.70 (s, 2 H), 4.12 (t, 2 H), 3.85 (ds, 6 H), 2.60 (t, 2 H).

Anal. Calcd for $C_{10}H_{12}NO_5Br$: C, 39.24; H, 3.95. Found: C, 39.28; H, 3.93.

Methyl 1,4,5,6-Tetrahydro-2-[(acetyloxy)methyl]-1-methoxycarbonyl-4-oxo-3-pyridinecarboxylate (3b). The crude bromide **2b** (prepared from 11.3 g, 50 mmol, of pyridinone **1c**) was stirred with 9.8 g (100 mmol) of potassium acetate in 150 mL of dry dimethylformamide at room temperature for 5 h. Water was added and the aqueous solution extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated to 6.8 g of solid. The aqueous solution was further extracted with dichloromethane. The dichloromethane extract was dried ($MgSO_4$) and concentrated to 6.7 g of red oil which was chromatographed on 100 mL dry volumn of silica gel (*ICN Pharmaceuticals* Act III for dry column chromatography). Elution with dichloromethane–ethyl acetate (2:1) gave 4.45 g of crystalline acetate **3b.** Further elution gave 0.7 g of yellow solid which was combined with the ether extract and recrystallized from ethyl acetate to 4.7 g of the acetate **3b** (9.15 g, 64%, mp 100–101 °C): IR ($CHCl_3$) 1755–1725, 1680, 1600 cm^{-1}; NMR δ 5.10 (s, 2 H), 4.10 (t, 2 H), 3.85 (s, 6 H), 2.62 (t, 2 H), 2.05 (s, 3 H).

Anal. Calcd for $C_{12}H_{15}NO_7$: C, 50.53; H, 5.30. Found: C, 50.71; H, 5.30.

Methyl 1,5,6,7-Tetrahydro-3,7-dioxo-3*H*-oxazolo[3,4-*a*]pyridine-8-carboxylate (5). To 285 mg of acetate **3b** (1 mmol) in 3 mL of methanol was added 1.0 mL of 1 M potassium hydroxide in methanol (1 mmol) at −20 °C. After stirring 1.3 h, the mixture was filtered and washed with cold methanol to give 174 mg of the potassium enolate of **5:** NMR (Me_2SO-d_6) δ 6.62 (s), 2.2 (t), the spectrum also showed a singlet at δ 4.72 due to a small amount of lactone **4c;** IR (KBr) 1715, 1645, 1605 cm^{-1} (identical to that of the potassium enolate prepared by treatment of the urethane **5** with potassium hydroxide in methanol). The white solid was partially dissolved in aqueous ammonium chloride and extracted with dichloromethane. The extracts were dried ($MgSO_4$) and concentrated to give pure urethane **5** (98 mg, 46%, mp 152–153 °C): IR ($CHCl_3$) 1815, 1748, 1692, 1600 cm^{-1}; NMR δ 5.48 (s, 2 H), 4.0 (t, 2 H), 3.80 (s, 3 H), 2.70 (t, 2 H); mass spectrum *m/e* (rel intensity) 211 M^+ (73), 180 (100), 179 (80), 153 (34), 151 (18), 59 (13), 55 (43).

Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30. Found: C, 51.20, H, 4.24.

1,4,5,6-Tetrahydro-2-(hydroxymethyl)-1-(methoxycarbonyl)-4-oxo-3-pyridinecarboxylic Acid γ-Lactone (4b). To 2.85 g of acetate **3b** (10 mmol) in 40 mL of methanol was added hydrogen chloride gas at room temperature. After stirring 4 h the mixture was cooled to 0 °C and filtered to give the lactone **4b** (1.82 g, 86%, mp 227–228 °C): IR (KBr) 1770, 1745, 1675, 1585 cm^{-1}; NMR δ 5.25 (s, 2 H), 4.22 (t, 2 H), 3.96 (s, 3 H), 2.69 (t, 2 H); chemical ionization mass spectrum *m/e* (rel intensity) 212 (100).

Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30. Found: C, 51.23; H, 4.40.

1,4,5,6-Tetrahydro-2-(hydroxymethyl)-4-oxo-3-pyridinecarboxylic Acid γ-Lactone (4c). To 211 mg of lactone **4b** (1 mmol) in 3 mL of methanol was added 1.0 mL of 1 M potassium hydroxide in methanol at room temperature. After 1.6 h the mixture was cooled to 0 °C and 1.1 mL of 1 N hydrochloric acid was added. After 10 min the mixture was filtered to give 146 mg of solid which was recrystallized from methanol–water (1:1) to give the lactone **4c** (76 mg, 50%, decomposition without melting at 340 °C): IR (KBr) 3210, 1740, 1615 cm^{-1}; NMR (Me_2SO-d_6) 8.95 (bs, 0.8 H), 4.80 (s, 2 H), 3.65 (t, 2 H), 2.35 (t, overlaps with Me_2SO-d_5); chemical ionization mass spectrum *m/e* (rel intensity) 154 (100).

Anal. Calcd for $C_7H_7NO_3$: C, 54.90; H, 4.61. Found: C, 54.96; H, 4.71.

Methyl 1,4,5,6-Tetrahydro-1-methyl-4-oxo-2-[(phenylthio)methyl]-3-pyridinecarboxylate (6a). To a mixture of 131 mg of bromide **2a** (0.5 mmol), 70 μL of triethylamine (0.5 mmol), and 2 mL of dimethylformamide was added 57 μL of benzenethiol (0.55 mmol) at 0 °C. After stirring 2 h at 0 °C and 3 h at room temperature, the solvent was removed at about 0.1 mmHg. The residue was taken up in water and extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated to 143 mg of oil which crystallized in ether to give the sulfide **6a** (93 mg, 64%, mp 49–51 °C): IR ($CHCl_3$) 1690, 1640, 1553 cm^{-1}; NMR δ 7.3 (m, 5 H), 4.07 (s, 2 H), 3.58 (s, 3 H), 3.50 (t, 2 H), 3.10 (s, 3 H), 2.40 (t, 2 H).

Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88. Found: C, 61.82; H, 5.85.

Methyl 1,4,5,6-Tetrahydro-2-[(methylthio)methyl]-1-(methoxycarbonyl)-4-oxo-3-pyridinecarboxylate (6b). Lithium thiomethoxide (3.24 g, 60 mmol) was added to a solution of 15.9 g of crude bromide **2b** (50 mmol) in 200 mL of tetrahydrofuran at room temperature. After stirring 6 h, brine was added and the aqueous solution extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated to 11.8 g of oil which was chromatographed on 600 mL dry volume of silica gel (ICN Pharmaceuticals Act III for dry column chromatography). Elution with 1 L of ethyl acetate–petroleum ether (3:1) gave 1.1 g of a mixture of **1c** and the methyl sulfide **6b.** Elution with 1.2 L of ethyl acetate–petroleum ether (2:1) gave the methyl sulfide **6b** (8.0 g, 59%, mp 83–84.5 °C): IR ($CHCl_3$) 1745–1715, 1675, 1585 cm^{-1}; NMR δ 4.10 (t, 2 H), 3.90 and 3.82 (2 s, 8 H), 2.60 (t, 2 H), 2.05 (s, 3 H).

Anal. Calcd for $C_{11}H_{15}NO_5S$: C, 48.34; H, 5.53. Found: C, 48.37; H, 5.64.

Methyl 1,4,5,6-Tetrahydro-1-(methoxycarbonyl)-4-oxo-2-[(phenylthio)methyl]-3-pyridinecarboxylate (6c). Benzenethiol (2.29 g, 20.8 mmol) was added to a solution of 6.36 g (20.8 mmol) of bromide **2b** and 2.1 g (20.8 mmol) of triethylamine in 70 mL of methanol at room temperature. After stirring 17 h the mixture was concentrated, dissolved in water, and extracted with dichloromethane. The extract was concentrated to an oil which crystallized from ethyl acetate–hexane to give the phenyl sulfide **6c** (4.9 g, 70%, mp 87–88 °C): IR ($CHCl_3$) 1745–1715, 1675, 1585 cm^{-1}; NMR δ 7.35 (m, 5 H), 4.30 (s, 2 H), 3.90 (t, 2 H), 3.80 (s, 3 H), 3.62 (s, 3 H), 2.50 (t, 2 H).

Anal. Calcd for $C_{16}H_{17}NO_5S$: C, 57.30; H, 5.11. Found: C, 57.28; H, 5.09.

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Registry No.—**1a,** 68185-61-5; **1b,** 68185-62-6; **1c,** 68185-63-7; **2a,** 68185-64-8; **2b,** 68185-65-9; **3a,** 68185-66-0; **3b,** 68185-67-1; **4a,** 68185-68-2; **4b,** 68185-69-3; **4c,** 68185-70-6; **5,** 68185-71-7; **6a,** 68185-72-8; **6b,** 68185-73-9; **6c,** 68185-74-0; β-alanine methyl ester, 4138-35-6; methyl acetoacetate, 105-45-3; methyl chloroformate, 79-22-1; benzenethiol, 108-98-5; lithium thiomethoxide, 35638-70-1.

References and Notes

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Attempted Benzophenanthridine Syntheses through Chemical and Electrochemical Cyclizations of Naphthylamines and Naphthylimines[1]

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We have synthesized[2] numerous benzophenanthridines using the Kessar cyclization[3] as a key step. This cyclization involves treatment of a bromoimine (e.g., **2**) with $NaNH_2$ in liquid NH_3 and the yields of benzophenanthridines were usually on the order of 30%. We considered that it might be possible to effect the same cyclization in better yield with chemical or electrochemical oxidations. It might also be possible to perform the cyclization directly on the imine (e.g., **1**) and thus obviate the need for preparation of a bromo derivative. We report here the results of VOF_3 and anodic oxidation of **1, 3,** and **4.**

Imine **1** gave benzophenanthridine **5** in a maximum of 30% yield by oxidation with VOF_3 in trifluoroacetic acid (TFA)/

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