= 4.9:1.0 by ^{1}H NMR integration) solidified at -30 °C after purification by column chromatography (2% MeOH/CH_2Cl_2) and was recrystallized from hexane. Washing the pure solid with 50% ethyl acetate/hexane gave pure syn aldol product. R_f (5% MeOH/CH_2Cl_2) = 0.4 **16b** (syn). ^{1}H NMR: δ 7.31 (5 H, m), 4.72 (1 H, d, J = 6.6 Hz), 4.55 (2 H, m), 3.73 (1 H, br s), 3.24 (1 H, m), 2.12 (2 H, m), 1.94 (3 H, s), 1.12 (12 H, m). ^{13}C NMR: δ 209.9, 141.7, 128.4, 127.8, 126.4, 74.2 (d, J_{P-C} = 14.9 Hz), 70.6 (d, J_{P-C} = 6.8 Hz), 70.5 (d, J_{P-C} = 6.3 Hz), 54.4 (d, J_{P-C} = 3.2 Hz), 31.5, 25.0 (d, J_{P-C} = 143.1 Hz). ^{31}P NMR: +29.5 ppm. Mp: 74-77 °C. IR: 3331, 2981, 1713, 1456, 1387, 1231, 1012, 988 cm^{-1}. Exact mass calcd for $C_{17}H_{27}O_5P$ $(M)^+$ 342.1594, found 342.1633. **17b** (anti). ^{1}H NMR: δ 7.32 (5 H, m), 4.64 (1 H, d, J = 7.2 Hz), 4.53 (2 H, m), 3.12 (1 H, m), 2.12 (2 H, m), 2.24 (3 H, s), 1.13 (12 H, m). ^{13}C NMR: δ 210.8, 141.8, 128.5, 128, 126.5, 76.6 (d, J_{P-C} = 14.6 Hz), 70.6 (d, J_{P-C} = 6.7 Hz), 70.4 (d, J_{P-C} = 6.3 Hz), 52.7 (d, J_{P-C} = 3.0 Hz), 32.9, 26.5 (d, J_{P-C} = 143.7 Hz). ^{31}P NMR: +28.0 ppm. IR: 3331, 2981, 1713, 1456, 1387, 1231, 1012, 988 cm^{-1}. Exact mass calcd for $C_{17}H_{27}O_5P$ $(M)^+$ 342.1594, found 342.1633.

Preparation of Diethyl (3-Oxobutyl)phosphonate (7a). To the neat oxaphospholene **6a** (220 mg, 0.93 mmol) was added excess water (5 equiv) to produce an exothermic reaction. This reaction mixture was allowed to stir for 5 h at room temperature. The crude products were extracted with CH_2Cl_2 and purified by chromatography with 1% MeOH/CH_2Cl_2 to give a clear oil (180 mg, 0.87 mmol, 93% yield). R_f (5% MeOH/CH_2Cl_2) = 0.53. ^{1}H NMR: δ 4.12 (4 H, m), 2.75 (2 H, m), 2.23 (3 H, s), 2.01 (2 H, m), 1.32 (6 H, t, J = 7.1 Hz). ^{13}C NMR: δ 204.5 (d, J_{P-C} = 14.6 Hz), 60.5 (d, J_{P-C} = 6.4 Hz), 35.2 (d, J_{P-C} = 3.7 Hz), 28.6, 18.5 (d, J_{P-C} = 144.5 Hz), 15.5 (d, J_{P-C} = 5.9 Hz). ^{31}P NMR: +32.1 ppm. IR: 1723, 1238, 1059, 1023, 960 cm^{-1}. Exact mass calcd for $C_8H_{17}O_4P$ $(M)^+$ 208.0865, found 208.0874.

Preparation of Diisopropyl (3-Oxobutyl)phosphonate (7b). The hydrolysis of the oxaphospholene **6b** (210 mg, 0.75 mmol) was performed as described for **6a**. The crude products were extracted with CH_2Cl_2 and purified by chromatography with 1% MeOH/CH_2Cl_2 to give a clear oil (162 mg, 0.69 mmol, 92% yield). R_f (5% MeOH/CH_2Cl_2) = 0.54. ^{1}H NMR: δ 4.69 (2 H, m), 2.72 (2 H, m), 2.18 (3 H, s), 1.96 (2 H, m), 1.32 (12 H, t, J = 6.2 Hz). ^{13}C NMR: δ 205.8 (d, J_{P-C} = 15.7 Hz), 70.1 (d, J_{P-C} = 6.4 Hz), 36.5 (d, J_{P-C} = 3.6 Hz), 29.5, 23.9 (d, J_{P-C} = 3.5 Hz), 20.8 (d, J_{P-C} = 146.0 Hz). ^{31}P NMR: +30.2 ppm. IR: 1717, 1237, 1010, 993 cm^{-1}. Exact mass calcd for $C_{10}H_{21}O_4P$ $(M)^+$ 236.1176, found 236.1177.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for all compounds (32 pages). Ordering information is given on any current masthead page.

5-Nitro-3-(methoxymethyl)indole from the Cyanation of 5-Nitrogramine: Mechanistic Implications

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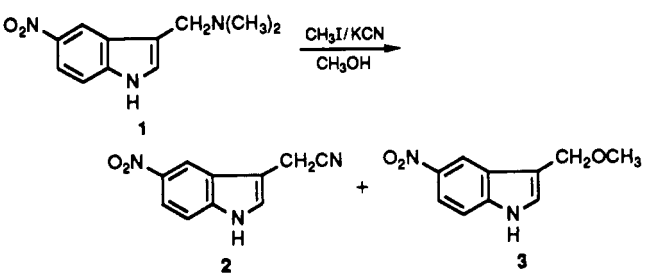
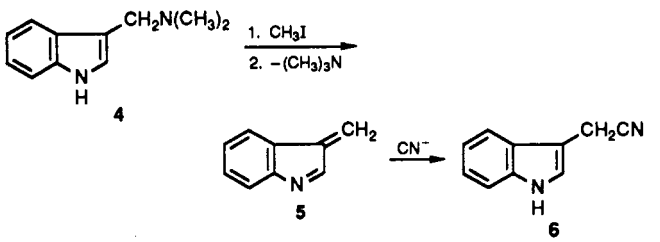
The cyanation of 5-substituted 1*H*-gramines forms 5-substituted indole-3-acetonitriles.[1] These are intermediates in the preparation of 5-substituted analogues of the pineal gland hormone melatonin which we were preparing for testing as potential cell mitosis inhibitors. During the preparation of 5-nitroindole-3-acetonitrile (**2**, Scheme I), an unexpected byproduct was isolated by soxhlet extraction of the crude product mixture with hexane. Infrared and NMR spectra confirmed the structure as 5-nitro-3-(methoxymethyl)indole (**3**). The proton NMR was most useful, showing a singlet for three protons at 3.35 ppm for the methyl group, a singlet for two protons at 4.65 ppm for the 3-indolyl methylene group, four aromatic protons scattered over the range 7.3-8.5 ppm, and a broad singlet for the amine proton at 11.3 ppm.

Scheme I



Scheme II



In 1952, Geissman and Armen[2] showed that such a compound as **3** came only from the direct involvement of a methoxide nucleophile rather than methylation of an intermediate 3-(hydroxymethyl)indole. Thus, in our mixture, compound **3** can only result from incidental reaction of a gramine intermediate with methanol as the nucleophile instead of cyanide ion. Thin-layer chromatography (TLC) has also indicated the presence of similar impurities in the crude product mixtures of the 5-bromo and 5-iodo analogues.

Compound **3** was unambiguously prepared by the reaction of 5-nitrogramine with methyl iodide and sodium methoxide in methanol.[2] To preclude the possibility that methanol itself was a strong enough base or nucleophile to initiate the reaction, a mixture of all reactants, except for methoxide ion, was stirred at room temperature for 48 h. TLC showed no reaction. Upon the addition of sodium methoxide the reaction proceeded to completion within 2 h. TLC samples were also taken at various stages in both the reaction and the normal workup sequence in order to determine just where the byproduct first appeared and was subsequently eliminated. With all other reactants present, the impurity was evident almost immediately after the addition of methyl iodide. It was effectively removed by washing the evaporate of the crude reaction mixture with either methanol or ether and water.

While examining the accepted mechanism of gramine alkylation, we realized that our finding presented an opportunity to highlight what appeared to be the last remaining detail of that mechanism. Work by several investigators[3-5] over 30 years ago showed that 1*H*-gramines

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(3) Snyder, H. R.; Eliel, E. *J. Am. Chem. Soc.* **1948**, *70*, 1703.
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Table I. Reaction Times (min) for (Methoxymethyl)indole Formation

substituent	temperature (°C) 20–25	5 to −5	−10 to −15
5-nitro	15	30	30
5-methoxy	15	90	165

alkylate via an elimination–addition mechanism (Scheme II). Methylation of the dimethylamino function of **4**, with subsequent elimination of trimethyl amine, first yields a 3*H*-pseudoindole intermediate **5** which then undergoes a Michael addition by a sufficiently nucleophilic species to yield the final product **6**. Albright and Snyder[6] used gramines with a chiral 3-substituent to investigate this mechanism, basing their kinetic results upon both the rate of amine evolution and the rate of racemization. They proposed two even more detailed mechanisms but could draw no specific conclusion about which of these was operating.

The major difference between these two variants was the point in the elimination sequence at which base abstracted the proton on the indole nitrogen. In one mechanism ("A") the rate-determining step was the formation of the pseudoindole **5** after the base abstracted the proton on the indole nitrogen in a fast step. In the alternative mechanism ("B"), the base abstraction of the indole nitrogen proton was the rate-determining step. The pseudoindole **5** then resulted from elimination of trimethylamine in a series of fast steps.

Our reasoning was that if mechanism B represents both the role of the base and the correct rate determining step, then the presence of the methoxy group "para" to the indole nitrogen should reduce the acidity of this proton. Thus, base abstraction of this proton would proceed slowly, especially at reduced temperatures. With a "para" nitro group the reaction should proceed faster. If mechanism A was the correct one, then the rate of reaction of the nitro compound would be decreased by resonance stabilization of the newly formed anion.

A very elementary rate study to compare the rate of reaction of 5-nitrogramine to that of 5-methoxygramine was undertaken. Standard reaction conditions were developed and followed with each compound. The appropriate gramine was dissolved in anhydrous methanol containing potassium cyanide. This mixture was treated with methyl iodide, and the reaction was followed by TLC. Samples were taken at 15-min intervals, and the times at which the methoxymethyl impurity first appeared were observed at room temperature, 5 to −5 °C, and −10 to −15 °C.

The results in Table I show that the methoxy group in position 5 of the indole ring slows the reaction rate considerably while the reaction proceeds with no significant rate change when the nitro group is in the same position. This strongly suggests that the overall mechanism of alkylation by 1*H*-gramines proceeds by the base abstraction, rate-determining-step sequence, mechanism B. This is detailed for gramine in Scheme III showing the incorporation of methanol to yield the methoxymethyl type byproduct.

Experimental Section

Melting points were obtained on a Thomas-Hoover Unimelt apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 710B spectrophotometer and the NMR spectra on a Hitachi/Perkin-Elmer R-21B instrument using tetramethylsilane as internal reference with chemical shifts expressed in ppm. Chromatography was on Kodak Chromagram silica gel strips using a 1:1 ether/hexane–10% ethanol solvent system. Analyses were performed by Atlantic Microlab, Inc.

5-Methoxygramine was purchased from Aldrich Chemical Co.

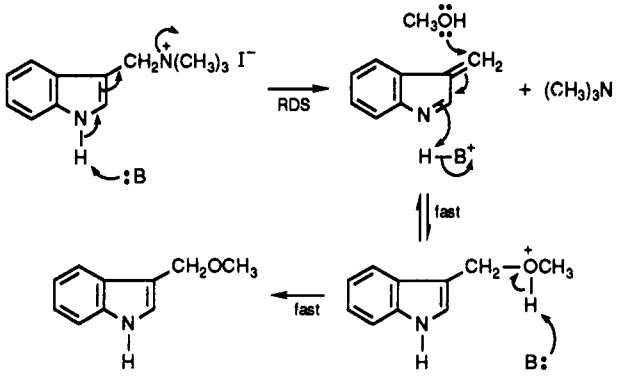
5-Nitrogramine (1) was prepared following the basic procedure of Cavallini and Ravenna.[7]

5-Nitro-3-(methoxymethyl)indole (3). 5-Nitrogramine (11.0 g, 0.05 mol) and methanol (250 mL) were introduced to a 500-mL Erlenmeyer flask and stirred. Excess methyl iodide was added, and after about 15–20 min a solid appeared. This mixture was allowed to stir at room temperature for another 48 h. TLC showed nothing above the origin. Sodium methoxide (3.25 g, 0.06 mol) was then added, and the mixture was stirred for 15 min when TLC showed product forming. The mixture was stirred for 4 h and filtered. The filtrate was evaporated, and the resulting solid was stirred with water and refiltered to give 10 g (96%) of dull yellow solid. Recrystallization from methanol gave bright yellow crystals: mp 133–134 °C; IR (KBr) ν 3200 (N–H), 1520 and 1330 (NO_2), 1055 cm^{-1} (C–O); ^1H NMR (Unisol) δ 3.35 (3 H, s, CH_3), 4.65 (2 H, s, CH_2), 7.35–7.5 (s and d overlapping, 2 H, $J_{6,7}$ = 5 Hz, C-2 and C-7), 8.0 (1 H, dd, $J_{6,7}$ = 5 Hz, C-6), 8.55 (1 H, s, $J_{4,6}$ = 3 Hz, C-4), 11.3 (br s, 1 H, NH).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.22; H, 4.89; N, 13.58. Found: C, 58.13; H, 4.91; N, 13.50.

Standard Reaction Conditions for Rate Study Using 5-Nitrogramine and 5-Methoxygramine. A stock solution of the gramine (0.005 mol) in methanol was prepared in a 50-mL volumetric flask. To potassium cyanide (0.002 mol) was added 10 mL (0.001 mol of gramine) of this stock solution. The mixture was stirred, and to it was added (0.002 mol) of methyl iodide. The reaction was followed by TLC, and the times at which the methoxymethyl impurity first appeared were observed at room temperature, 5 to −5 °C, and −10 to −15 °C.

Scheme III



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Asymmetric Alkylation of Oxindoles: An Approach to the Total Synthesis of (−)-Physostigmine

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(−)-Physostigmine (1) is a clinically useful anticholinesterase agent that has been used in the treatment of glaucoma and myasthenia gravis.[1] More recently, selected

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