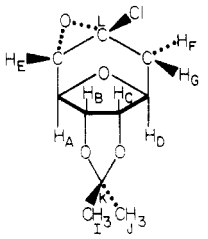
217.02487 (base peak) for $C_9H_{10}O_4Cl$ or $M^+ - CH_3$, 219.02350 for $C_9H_{10}O_4{}^{37}Cl$ or $M^+ - CH_3$, 139.03849 for $C_7H_7O_3$, 71.01330 for $C_3H_3O_2$, 111.04394 for $C_6H_7O_2$, etc.

The epoxide **2** had the following absorption characteristics: IR (CCl_4) 2990, 2930, 1420, 1380, 1330, 1270, 1220, 870 (epoxide ring) cm^{-1}; UV (CH_3OH) λ_{max} 210 nm (ϵ 244), 260 (63); ^1H NMR ($CDCl_3$) δ 4.90 and 4.68 (2 d, J_{BC} = 5.6 Hz, $J_{AB} = J_{CD}$ = 0, 2, B and C), 4.45 (d, J_{AE} = 1.5 Hz, J_{AB} = 0, 1, A), 4.15 (d, J_{DF} = 6.7 Hz, $J_{DG} = J_{CD}$ = 0, 1, D), 3.33 (t, $J_{AE} = J_{EF} \simeq$ 1.5, 1, E), 2.88 (ddd, J_{FD} = 6.7 Hz, $J_{FE} \simeq$ 1.2 Hz, J_{FG} = 15, 1, F), 2.10 (d, J_{FG} = 15 Hz, J_{GD} = 0, 1, G), 1.50 (s, 3, I), 1.35 (s, 3, J). Decoupling irradiation at the 4.45-ppm signal for A changed the 3.33-ppm triplet for E to a rough singlet. Irradiation at 3.33 ppm (E) changed the doublet at 4.45 ppm (A) to a singlet. Irradiation at 4.15 ppm (D) simplified the 2.88 ddd for F to dd.



The neglible vicinal couplings between A–B, C–D, and D–G correspond well to the respective dihedral angles (Dreiding model) of 90°. The A–E dihedral angle of 37°, according to the Karplus relation, should give rise to J_{AE} = 5.1 Hz, a value that does not agree with the J_{AE} = 1.5 observed. However, attention has been called[11] to the effect of an epoxide ring in decreasing vicinal coupling constants for such systems. Making use of the relevant equation[11] leads to a predicted J_{AE} of 3.5 Hz. The tetrahydrofuran oxygen attached to the carbon bearing the A hydrogen would reduce the A–E vicinal coupling still more and bring the predicted value even closer to that observed. The H_E triplet at 3.33 ppm involves not only vicinal coupling with A but also one other equal coupling with a remote hydrogen, possibly F.

The ^{13}C nuclear magnetic resonance curve was determined at 15 MHz with a JEOL FX 60 Q instrument and with $CDCl_3$ as solvent: δ 113.2 (s, C_K), 84.9 (d), 81.3 (d), 77.7 (d), 76.4 (d), 70.2 (s, C_L), 57.0 (d, J = 184, C_E), 36.6 (t, $J \simeq$ 133 Hz, C_{FG}), 26.2 (q, J = 127, C_I), 25.0 (q, J = 126, C_J). The four doublets from 84.9–76.4 ppm were assigned to the tetrahydrofuran ring carbons; each showed an approximate coupling constant of 155 Hz.

Ozonolysis of the chloroethylene **1** at 0 °C in ethyl acetate saturated with 1% aqueous potassium hydroxide afforded the epoxide in somewhat higher yield. Here the ozonolysis mixture was treated with borohydride in 1:1 water–dioxane at 0 °C, the volatiles were removed, and the residue in 8% aqueous acetic acid was held at 65 °C for 24 h. Again the solvents were removed, and in order to replace isopropylidene groups that the acetic acid might have removed, the product mixture was allowed to stand in dry acetone containing anydrous magnesium sulfate. Continued processing, including a toluene azeotrope with the intent of effecting lactonization to **4**, led to epoxide **2** (31%; mp 119–120 °C) as the only characterized product.

Treatment of Chloro Epoxide 2 with Base. A suspension of the epoxide **2** (0.100 g, 0.43 mmol) in 0.1 N aqueous sodium hydroxide (3 mL) was refluxed for 20 min. After neutralization at room temperature with 1 N hydrochloric acid, the heterogeneous mixture was stripped of all volatile material. Sublimation of the residual white solid at 120 °C (0.01 mm) afforded unchanged epoxide **2** (0.085 g, 85% recovery; mp 125–126 °C) with infrared and NMR spectra identical with those obtained with the starting material.

Boiling 0.100 g (0.43 mmol) of epoxide **2** in pyridine (3 mL) for 25 min, removing the solvent, and subliming the residue gave the epoxide as a white solid (0.090 g, 90% recovery) with unchanged melting point and infrared and ^1H NMR absorption spectra.

Acknowledgment. We acknowledge the sponsorship of the American Cancer Society, which through Grant No. T533 helped to support this work. We also thank Waters Associates, Inc., for their cooperation with several high-pressure liquid chromatography determinations. Professor David A. Forsyth very kindly provided the ^{13}C nuclear magnetic resonance data reported here; Dr. Catherine Costello performed the high-resolution mass spectral determination (Division of Research Resources, NIH Grant No. RR 00317 to Klaus Biemann at Massachusetts Institute of Technology).

Registry No. 1, 55036-18-5; 2, 76529-25-4; 3, 55036-19-6.

(11) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, 1964, p 100. In this connection, the total absence of gem coupling for the two hydrogen atoms on the ring methylene group of 2-chloro-2-*tert*-butyloxirane is noteworthy. (See the article to appear by Griesbaum et al. cited in ref 8.)

A New Approach to 4-Substituted Indoles

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As bifunctional reagents, 1*H*-4-carboxaldehyde (**4**) and 1*H*-indole-4-acetaldehyde are attractive starting materials for the synthesis of alkaloids related to the clavine family and lysergic acid. Aldehyde **4** has very recently been used in elegant syntheses of chanoclavine I and isochanoclavine I[1,2] and was prepared from 1*H*-indole-4-carboxylic acid methyl ester via oxidation of 1*H*-indole-4-methanol with either potassium permanganate[3] or manganese dioxide, pioneered by Plieninger[4] and recently adopted by Kozikowski.[5] Alternatively, **4** was synthesized by reduction of 1*H*-indole-4-carbonitrile[6] with lithium triethoxyaluminium hydride,[4] by catalytic hydrogenation and trapping of the aldehyde as a hydrazone,[4] or with sodium hypophosphite/Raney nickel.[7]

1-Acetyl-1*H*-indole-4-acetaldehyde has also been prepared before as follows. 1-Aminonaphthalene was reduced with sodium in ethanol to furnish 1-amino-5,8-dihydronaphthalene which was N-acetylated. The resulting *N*-(5,8-dihydro-2-naphthalenyl)acetamide was then ozonized, yielding *N*-[2,3-bis(2-oxoethyl)phenyl]acetamide. Acid-catalyzed cyclization and dehydration of this dialdehyde led to 1-acetyl-1*H*-indole-4-acetaldehyde which was isolated as the bisulfite adduct.[8] 1-(*p*-Toluenesulfonyl)-1*H*-indole-4-acetaldehyde was prepared in similar fashion.[9]

We now describe a short route to aldehyde **4** (Scheme I) based on the regiospecific benzylic oxidation of the inexpensive 2,3-dimethylnitrobenzene (**1**). It is then possible to either prepare **4** in a subsequent step or to elaborate the generated carboxaldehyde function, thus establishing a side chain at C-4 of indole prior to indole-

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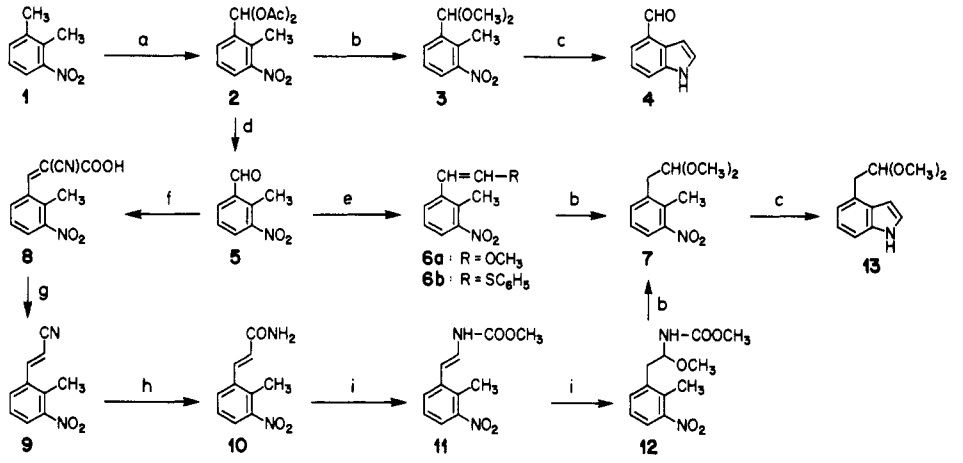
0022-3263/81/1946-1752$01.25/0

Scheme I[a]



[a] a, $CrO_3/H_2SO_4/AcOH/Ac_2O$; b, MeOH/HCl; c, (1) DMF/DMFDMA/pyrrolidine, (2) Raney Ni/hydrazine; d, EtOH/water/H_2SO_4; e, (methoxymethyl)tripyenylphosphonium chloride/phenyllithium or (phenylthiomethyl)triphenylphosphonium chloride/*n*-butyllithium; f, cyanoacetic acid/pyridine/THF; g, 2-methoxyethanol, 150 °C; h, H_2SO_4; i, NaOCl/MeOH.

nucleus formation. We illustrate the potential of this method by describing the synthesis of 4-(2,2-dimethoxyethyl)-1*H*-indole (**13**).

Our synthesis of **4** started with 2-methyl-3-nitrobenzenemethanediol diacetate (**2**) which was obtained by Thiele oxidation of **1**[10] and converted to 1-(dimethoxymethyl)-2-methyl-3-nitrobenzene (**3**). A subsequent Batcho–Leimgruber sequence[11] with **3** involving formylation of the methyl group with *N,N*-dimethylformamide dimethyl acetal/pyrrolidine and reductive cyclization of the resulting enamine with Raney nickel/hydrazine,[12] yielded the deprotected product **4** in modest yield directly upon workup.

Similar to the synthesis of **4**, 4-(2,2-dimethoxyethyl)-1*H*-indole (**13**) was prepared from 1-(2,2-dimethoxyethyl)-2-methyl-3-nitrobenzene (**7**) in 67% yield. In contrast to the synthesis of **4**, the acetal function in **7** survived the conditions of the Batcho–Leimgruber sequence and workup. The required acetal **7** was synthesized from 2-methyl-3-nitrobenzaldehyde (**5**), available from **2**, by two procedures. A Wittig reaction with (methoxymethyl)triphenylphosphorane gave 1-(2-methoxyethenyl)-2-methyl-3-nitrobenzene (**6a**) which was converted to **7** with methanol and hydrogen chloride. Analogously, 2-methyl-3-nitro-1-[2-(phenylthio)ethenyl]benzene (**6b**) could be prepared in good yield from the corresponding phosphorane but remained unchanged under the same methanolysis conditions. Alternatively, a Knoevenagel reaction of **5** with cyanoacetic acid in pyridine led to 3-(2-methyl-3-nitrophenyl)-2-cyano-2-propenoic acid (**8**) which was readily obtained as the pyridinium salt. Prior isolation of this salt greatly facilitated the purification of 3-(2-methyl-3-nitrophenyl)-2-propenenitrile (**9**) obtained in the subsequent decarboxylation reaction of **8**. A Hofmann rearrangement in methanolic sodium hypochlorite solution of **10**, produced by hydrolysis of **9**, gave a mixture of methyl 2-(2-methyl-3-nitrophenyl)ethenylcarbamate (**11**) and its methanol adduct **12**. Methanolysis of this mixture also afforded **7**.

Experimental Section

IR (Digilab FTS-M) and NMR spectra (Varian XL-100) were recorded using the indicated solvents. EI mass spectra (Varian MAT CH5) were obtained at an ionizing voltage of 70 eV and a 250 °C ion-source temperature. TLC (silica gel, E. Merck) and column chromatograms (LiChroprep Si 60, E. Merck) were developed in the solvent systems stated. Melting points were determined on a Thermopan (Reichert) hot stage without corrections.

2-Methyl-3-nitrobenzenemethanediol Diacetate (2). The described Thiele oxidation of 1,2-dimethyl-3-nitrobenzene[10] was scaled up fourfold, allowing 1.3 h for the addition of the chromyl acetate solution at 5–10 °C. After being stirred for an additional 30 min at this temperature, the mixture was poured into an ice–water mixture (2 L) containing 50% sodium hydroxide solution (135 mL), stored in the refrigerator overnight, and worked up as described to yield **2** after recrystallization from ethanol–water (22.3 g, 52.5%); NMR ($CDCl_3$) δ 2.13 (s, 2 OAc), 2.54 (s, CH_3), 7.37 (t, H-5, $J_{4,5} = J_{5,6} = 8$ Hz), 7.74 (d, H-6, $J_{5,6} = 8$ Hz), 7.78 (d, H-4, $J_{4,5} = 8$ Hz), 7.87 (s, O–CH–O).

1-(Dimethoxymethyl)-2-methyl-3-nitrobenzene (3). A solution of **2** (10 g, 37.42 mmol) in anhydrous methanol (500 mL) was cooled in a dry ice/ethanol bath, and, under vigorous stirring, thionyl chloride (50 mL) was added dropwise. The mixture was then stirred at room temperature for 1 h and poured into a stirred ice–water mixture containing sodium hydroxide (60 g). The solution was repeatedly extracted with dichloromethane, and the combined extracts were washed with water, dried (magnesium sulfate), evaporated, and distilled at a bath temperature of 80 °C (2 torr) to yield **3** as a yellow liquid (7.5 g, 95%): NMR ($CDCl_3$) δ 2.44 (s, CH_3Ar), 3.30 (s, $(CH_3O)_2$), 5.48 (s, O–CH–O), 7.30 (t, H-5, $J_{4,5} = J_{5,6} = 8$ Hz), 7.69 (d, H-6, $J_{5,6} = 8$ Hz), 7.77 (d, H-4, $J_{4,5} = 8$ Hz); mass spectrum *m/e* 210 (M − 1, <1%), 180 (M − OCH_3, 100%).

(1*H*)-Indole-4-carboxaldehyde (4). A solution of **3** (1 g, 4.73 mmol) in *N,N*-dimethylformamide (5 mL) was kept under nitrogen while *N,N*-dimethylformamide dimethyl acetal (0.73 mL) and pyrrolidine (0.46 mL) were added and the solution was heated at reflux, with stirring, in a 135 °C oil bath for 3 h. The dark red solution of the 3-nitro-2-[2-(1-pyrrolidinyl)ethenyl]benzaldehyde dimethyl acetal was then evaporated at 90 °C (18 torr) and the residue taken up in tetrahydrofuran–methanol (1:1, 10 mL). To this solution was added, under nitrogen, $^1/_4$ teaspoonful of Raney-nickel type 28, previously suspended in 2-propanol. The mixture was stirred at 30 °C while hydrazine hydrate (0.5 mL) was added dropwise. The temperature of the suspension increased and was kept at 45~50 °C in a preheated bath. Portions of hydrazine hydrate (0.5 mL) were added after 30 min and 1.5 h. The mixture was stirred for 2 h at 45~50 °C and then filtered through Celite. The filtrate and filter washings (dichloromethane) were evaporated and the residue was chromatographed on silica gel with dichloromethane as mobile phase to yield **4** (0.225 g, 33%): mp 142 °C (lit. mp 142–144 °C,[4] 138 °C,[5] 140–142 °C[7]); IR (KBr) 3250 (NH), 2740 (CH of CHO), 1670 (CO), and 758 cm^{-1} (1,2,3-trisubstituted benzene); NMR ($CDCl_3$) δ 7.32 (t, H-6, $J_{5,6} = J_{6,7}$

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= 7.5 Hz), 7.38 (m, H-2 and H-3), 7.64 and 7.67 (2 m, H-5 and H-7), 8.67 (br s, NH), 10.26 (s, CHO); mass spectrum m/e 145 (M, 100%), 116 (M − CHO, 74%). Anal. Calcd for C_9H_7NO (mol wt 145.16): C, 74.47; H, 4.86; N, 9.65. Found: C, 74.56; H, 4.95; N, 9.44.

(*E,Z*)-1-(2-Methoxyethenyl)-2-methyl-3-nitrobenzaldehyde (6a). A solution of phenyllithium in benzene–ether (1.9 M, 6.4 mL) was added dropwise to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (4.15 g, 12.1 mmol) in tetrahydrofuran (20 mL) at 0 °C under argon and the resulting mixture was stirred for 3 h at room temperature. A solution of aldehyde **5**[10] (1.0 g, 6.06 mmol) in tetrahydrofuran (10 mL) was then added dropwise below 30 °C with stirring. After 2 h, the mixture was diluted with water and extracted with diethyl ether three times. The combined extracts were washed with water, dried (sodium sulfate), and evaporated. The residue was chromatographed on silica gel with cyclohexane–dichloromethane (4:1) and dichloromethane as mobile phases, yielding **6a** as a mixture of *E* and *Z* isomers in the approximate ratio of 2:1 in the form of a straw-colored syrup (0.89 g, 76%) after evaporation of the solvent: NMR ($CDCl_3$) of (*E*)-**6** δ 2.41 (s, CH_3Ar), 3.74 (s, CH_3O), 5.96 (d, =CHAr, J = 15 Hz), 6.85 (d, =CH—O, J = 15 Hz), 7.20 (t, H-5, $J_{4,5} = J_{5,6}$ = 8 Hz), 7.45 (d, H-6, $J_{5,6}$ = 8 Hz), 7.54 (d, H-4, $J_{4,5}$ = 8 Hz); NMR ($CDCl_3$) of (*Z*)-**6** δ 2.40 (s, CH_3-Ar), 3.77 (s, CH_3O), 5.33 (d, =CHAr, J = 7 Hz), 6.28 (d, =CH—O, J = 7 Hz), 7.22 (t, H-5, $J_{4,5} = J_{5,6}$ = 8 Hz), 7.56 (d, H-4, $J_{4,5}$ = 8 Hz), 7.98 (d, H-6, $J_{5,6}$ = 8 Hz); mass spectrum of (*E,Z*)-**6**, m/e 193 (M, 100%), 176 (M − OH, 98%), 146 (176 − NO, 38%).

(*E,Z*)-2-Methyl-3-nitro-1-[2-(phenylthio)ethenyl]benzene (6b). A solution of *n*-butyllithium (1.6 M, 12.5 mL) was added dropwise under argon to a stirred suspension of (phenylthiomethyl)triphenylphosphonium chloride (8.4 g, 20 mmol) in tetrahydrofuran (25 mL) at −78 °C. The mixture was stirred at 23 °C for 1.5 h to yield an orange paste. A solution of **5** (1.65 g, 10 mmol) in tetrahydrofuran (10 mL) was then added and stirring was continued for 2 h at 23 °C. Water (50 mL) was added to the brown solution and the mixture extracted with ether (3 × 100 mL). The combined extracts were washed with brine, dried (magnesium sulfate), filtered, and evaporated. Most of the triphenylphosphine oxide was removed by trituration with ether–hexane. The resulting residue was purified by chromatography on silica gel with cyclohexane–dichloromethane (4:1) and dichloromethane as mobile phases to afford a mixture of *E* and *Z* isomers of **6b** in the approximate ratio of 1:1 (2.3 g, 85%): NMR (Me_2SO-d_6) δ 2.30 and 2.35 (s each, CH_3 of (*E*)-**6b** and (*Z*)-**6b**), 6.89 (s, H-1′ and H-2′ of (*Z*)-**6b**), 6.95 (d, H-1′ of (*E*)-**6b**, J = 15.5 Hz), 7.25 (d, H-2′ of (*E*)-**6b**, J = 15.5 Hz), 7.26∼7.93 (m, H-4∼6 and SC_6H_5 of (*E*)- and (*Z*)-**6b**); mass spectrum, m/e 271 (M, 3%), 69 (100%).

1-(2,2-Dimethoxyethyl)-2-methyl-3-nitrobenzene (7). From 6a. Thionyl chloride (0.5 mL) was added dropwise to an ice-cold, stirred solution of **6a** (0.43 g, 2.23 mmol) in anhydrous methanol (5 mL). The resulting solution was stirred at room temperature for 1 h and poured into ice-cold 2 N sodium hydroxide solution (15 mL). The mixture was extracted twice with dichloromethane. The combined extracts were washed with water, dried (magnesium sulfate), and evaporated to yield **7** as a straw-colored oil which slowly crystallized on standing (300 mg, 80%). The substance depositied as pale yellow needles at 62 °C (1.5 torr): mp 37∼39 °C, NMR ($CDCl_3$) δ 2.44 (s, CH_3Ar), 3.01 (d, CH_2Ar, J = 5.5 Hz), 3.35 (s, $(CH_3O)_2$), 4.50 (t, O–CH–O, J = 5.5 Hz), 7.23 (t, H-5, $J_{4,5} = J_{5,6}$ = 8 Hz), 7.42 (dd, H-6, $J_{5,6}$ = 8, $J_{4,6}$ = 2 Hz), 7.61 (dd, H-4, $J_{4,5}$ = 8, $J_{4,6}$ = 2 Hz); mass spectrum, m/e 224 (M − 1, <1%), 194 (M − OCH_3, 4%), 75 ($(CH_3O)_2CH^+$, 100%).

Anal. Calcd for $C_{11}H_{15}NO_4$ (mol wt 225.25): C, 58.66; H, 6.71; N, 6.22. Found: C, 58.40; H, 6.54; N, 6.33.

From 11 and 12. A solution of **11** and **12** (2:3, 500 mg, 1.92 mmol) in methanol (10 mL) was cooled to 0 °C and thionyl chloride (1 mL) was added dropwise with stirring. The resulting mixture was heated at reflux for 2 h, cooled, and poured into sodium hydroxide solution (1 N, 35 mL). This mixture was then extracted with dichloromethane (2 × 30 mL). The washed and dried (magnesium sulfate) extract was evaporated to give crude **7** as a yellow oil which was purified by chromatography on silica gel with dichloromethane as the mobile phase, yielding **7** as a pale yellow oil (310 mg, 72%).

4-(2-Dimethoxyethyl)-1*H*-indole (13). Aldehyde **7** was converted to **13** by the procedure described for the synthesis of **4**. Chromatography on silica gel with dichloromethane as the mobile phase gave **13** as pale yellow syrup (200 mg, 67.5%): NMR ($CDCl_3$) δ 3.21 (d, CH_2, J = 6 Hz), 3.34 (s, $(OCH_3)_2$), 4.75 (t, O–CH–O J = 6 Hz), 6.61 (m, H-3), 7.00 (d, H-5, $J_{5,6}$ = 7 Hz), 7.14 (t, H-6, $J_{5,6} = J_{6,7}$ = 7 Hz), 7.20 (d, H-2, $J_{2,3}$ = 3 Hz), 7.28 (d, H-7, $J_{6,7}$ = 7 Hz), 8.15 (br, NH); mass spectrum, m/e 205 (M, 12%), 174 (M − OCH_3, 8%), 130 (M − $(CH_3O)_2CH$, 15%), 75 ($(CH_3O)_2CH^+$, 100%).

Anal. Calcd for $C_{12}H_{15}NO_2$ (mol wt 205.26): C, 70.22; H, 7.37; N, 6.82. Found: C, 69.95; H, 7.20; N, 6.76.

(*E*)-3-(2-Methyl-3-nitrophenyl)-2-propenenitrile (9). A solution of aldehyde **5** (3.30 g, 0.020 mol) and cyanoacetic acid (1.95 g) in pyridine (2 mL) and tetrahydrofuran (6 mL) was kept at 50 °C. After 40 h, the solution had solidified to a crystalline mass which was throughly mixed with diethyl ether (6 mL) and refrigerated. The suspension was filtered and the solids were washed with ether to yield a mixture of **8** and its pyridinium salt (4 g) which gradually lost pyridine upon drying; NMR (Me_2SO-d_6) δ 2.38 (s, CH_3), 7.39 (m, H-3 and H-5 of pyridinium ion), 7.60 (t, H-5, J_o = 8 Hz), 7.81 (m, H-4 of pyridinium ion), 8.01 (2 d, H-4 and H-6, J_o = 8 Hz), 8.55 (s, —CH=), 8.56 (br, H-2 and H-6 of pyridinium ion).

The partial pyridinium salt of **8** (4 g) was decarboxylated in 2-methoxyethanol (4 mL) by heating at 150 °C for 11 h. The mixture was evaporated and the crystalline residue recrystallized from ethanol to give **9** as white prisms (1.60 g, 42.5%): mp 136–137 °C; IR (KBr) 2220 cm^{-1} (CN); NMR ($CDCl_3$) δ 2.49 (s, CH_3), 5.84 (d, H-2, $J_{2,3}$ = 16.5 Hz), 7.38 (t, H-5′, J_o = 8 Hz), 7.64 (dd, H-6′, J_o = 8 and J_m = 2 Hz), 7.71 (d, H-3, $J_{2,3}$ = 16.5 Hz), 7.82 (dd, H-4′, J_o = 8 and J_m = 2 Hz); mass spectrum, m/e 188 (M, 33%), 116 (M − NO_2 − CN, 100%).

Anal. Calcd for $C_{10}H_8N_2O_2$ (mol wt 188.18): C, 63.83; H, 4.29; N, 14.89. Found: C, 63.61; H, 4.13; N, 14.88.

(*E*)-3-(2-Methyl-3-nitrophenyl)-2-propenamide (10). Concentrated sulfuric acid (10 mL) was added to nitrile **9** (2.00 g, 10.6 mmol) and the mixture heated on the steam bath for 3 min with gentle agitation. The resulting solution was cooled in ice and added to a stirred ice–water mixture (150 mL). The precipitate was filtered off and washed consecutively with chilled water, a small amount of water containing a few drops of concentrated ammonium hydroxide solution and water. Drying at 60 °C (1 torr) gave a microcrystalline powder (2.11 g, 96%) which was used directly in the next step. For analysis, a 50-mg sample was purified by preparative TLC (dichloromethane–methanol, 8:1), and crystallized from ethanol: mp 158–159 °C; IR (KBr) 3360, 3180 (NH_2), 1668 cm^{-1} (C=O); NMR ($CDCl_3$/Me_2SO-d_6, 20:1) δ 2.50 (s, CH_3), 6.45 (d, H-2, $J_{2,3}$ = 16 Hz), 7.32 (t, H-5′, J_o = 8 Hz), 7.68 (d, H-6′, J_o = 8 Hz), 7.73 (d, H-4′, J_o = 8 Hz), 7.91 (d, H-3, $J_{2,3}$ = 16 Hz); mass spectrum, m/e 206 (M, 33%), 189 (M − 17, 81%), 172 (M − 17 − 17, 41%), 159 (M − HNO_2, 12%), 115 (M − HNO_2 − $CONH_2$, 100%).

Anal. Calcd for $C_{10}H_{10}N_2O_3$ (mol wt 206.20): C, 58.25; H, 4.89; N, 13.59. Found: C, 58.12; H, 4.79; N, 13.65.

Methyl (*E*)-[2-(2-Methyl-3-nitrophenyl)ethenyl]carbamate (11) and Methyl [1-Methoxy-2-(2-methyl-3-nitrophenyl)ethyl]carbamate (12). A solution of amide **10** (2.06 g, 10 mmol) in methanol (75 mL) was cooled to 5 °C and a sodium hypochlorite solution (12.8 mL, prepared by adding 5.5 g of chlorine to a solution of 10 g of sodium hydroxide in ca. 20 mL of water at 0–5 °C and adjusting the volume to 100 mL with water)[13] was added. The solution was heated on the steam bath for 10 min, filtered, concentrated to a volume of ca. 8 mL, and refrigerated overnight, affording a crystalline mixture of **11** and **12** in the ratio of 2:3 (2.06 g, 79%): NMR of **11** ($CDCl_3$) δ 2.36 (s, CH_3), 3.79 (s, $COOCH_3$), 6.15 (d, H-2, $J_{1,2}$ = 14 Hz), 7.08 (d, H-1, $J_{1,2}$ = 14 Hz), 7.24 (t, H-5′, J_o = 8 Hz), 7.56 (d, H-6′, J_o = 8 Hz), 7.63 (d, H-4′, J_o = 8 Hz); NMR of **12** ($CDCl_3$) δ 2.43 (s, CH_3), 3.03 (d, CH_2, $J_{1,2}$ = 6 Hz), 3.29 (s, OCH_3), 3.67 (s, $COOCH_3$), 5.06 (br, HNCH–O), 7.24 (t, H-5′, J_o = 8 Hz), 7.41 (d, H-6′, J_o = 8 Hz), 7.63 (d, H-4′, J_o = 8 Hz).

Registry No. **1**, 83-41-0; **2**, 23876-11-1; **3**, 76499-33-7; **4**, 1074-86-8; **5**, 23876-12-2; (*E*)-**6a**, 76499-34-8; (*Z*)-**6a**, 76499-35-9; (*E*)-**6b**, 76499-36-0; (*Z*)-**6b**, 76499-37-1; **7**, 76499-38-2; **8**, 76499-39-3; **8** pyridinium

salt, 76499-40-6; (*E*)-9, 76499-41-7; (*E*)-10, 76499-42-8; (*E*)-11, 76499-43-9; 12, 76499-44-0; 13, 76499-45-1; 3-nitro-2-[2-(1-pyrrolidinyl)ethenyl]benzaldehyde dimethyl acetal, 76499-46-2; (methoxymethyl)triphenylphosphonium chloride, 4009-98-7; (phenylthiomethyl)triphenylphosphonium chloride, 13884-92-9; cyanoacetic acid, 372-09-8.

Structure of a Byproduct Formed during Use of the Robinson Annulation Reaction with 6-Methoxy-1-methyl-2-tetralone[1]

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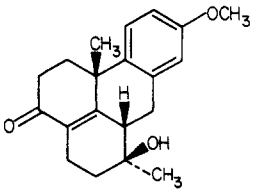
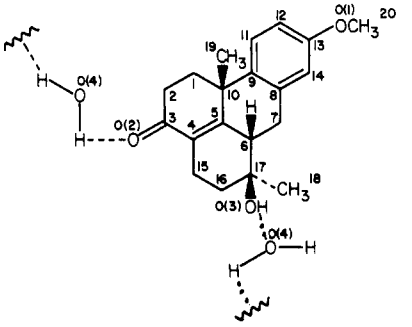
As part of another synthetic program, the methoxy tetralone **1** was subjected to a Robinson annulation procedure to form the enone **3** by following the procedure of Howell and Taylor.[3] In addition to the enone **3**, isolated in 78% yield, a crystalline C-20 byproduct was isolated in 10% yield. The spectral properties of this byproduct (a conjugated ketone containing a hydroxyl function) were reminiscent of a C-19 crystalline byproduct isolated by Howell and Taylor[3a] when the Robinson annulation procedure was applied to the tetralone **4**. These authors suggested that their byproduct may be derived from the dialkylated product **5** and might have structure **6b**. By analogy, the byproduct from tetralone **1** could be formulated as **6a** or **7** (Scheme I). Alternatively, the initial product **3** could have reacted with more methyl vinyl ketone to form successively the diketone **8** and the hydroxy enone **9** (or one of its stereoisomers).

Since the spectral properties of our byproduct did not unambiguously distinguish among various structures such as **6a**, **7**, and **9**, the structure was determined to be **9** by X-ray crystallographic analyses. The molecule crystallized as a monohydrate with water molecules in the crystal located as shown in structure **10**. A perspective view of the structure of the byproduct **9** is presented in Figure 1.



9



10

Experimental Section[4]

Robinson Annulation with Tetralone 1. A cold (0 °C) solution of 6.71 g (46.9 mmol) of 1-(diethylamino)-3-butanone in 12 mL of Et_2O was treated with 15 mL of MeI in 8 mL of Et_2O and the resulting mixture was stirred at 0 °C for 1 h. After the Et_2O and excess MeI had been removed under reduced pressure, the residual salt **2** was mixed with 10.0 g (53.6 mmol) of the tetralone **1** in 60 mL of PhH. This mixture was cooled to ca. 0 °C and a solution of NaOMe, prepared from 2.4 g (0.1 mol) of Na and 60 mL of anhydrous MeOH, was added. The resulting dark red solution was stirred at 0 °C for 2 h and then refluxed for 10 min. After the reaction mixture had cooled, it was diluted with H_2O and acidified with aqueous 30% H_2SO_4. The organic layer was separated, the aqueous phase was extracted with Et_2O, and the combined organic layers were washed with aqueous NaCl, dried, and concentrated. After the residual oil had been triturated with Et_2O, the solid that separated was recrystallized from an Et_2O–petroleum ether (bp 40–60 °C) mixture. The enone **3** separated as 9.91 g (78%) of crystalline solid: mp 107–108 °C (lit.[3a] mp 106–108 °C); IR (KBr pellet) 1670 cm^{-1} (conjugated C=O); NMR (CCl_4) δ 6.46–7.20 (3 H, m, aryl CH), 5.76 (1 H, s, vinyl CH), 3.72 (3 H, s, OCH_3), 1.52 (3 H, s, CH_3).

Concentration of the mother liquors from the crystallization of the enone **3** separated 1.61 g (10%) of the crude hydroxy enone **9**, mp 96–101.3 °C. This byproduct was recrystallized from an Et_2O–$CHCl_3$ mixture to separate the monohydrate of hydroxy enone **9** as colorless prisms, mp 98.2–104.6 °C.

Anal. Calcd for $C_{20}H_{24}O_3 \cdot H_2O$: C, 72.70; H, 7.93. Found: C, 72.53; H, 8.14.

After the sample had been dried at 80 °C under reduced pressure for 8 days, the sample melted at 90–92.5 °C. The composition of the sample (Found: C, 75.73; H, 7.94. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74) indicated that about 75% of the water of hydration had been removed. The spectral properties of the monohydrate of hydroxy enone **9** follow: IR ($CHCl_3$) 3685, 3600, 3480 (OH), 1670, 1658 (conjugated C=O), 1626 cm^{-1} (conjugated C=C); UV max (95% EtOH) 229 nm (ϵ 13 400), 247 (15 300), 286 (2030); mass spectrum, *m/e* (relative intensity) 312 (M^+, 55), 297 (49), 280 (20), 279 (100), 241 (25), 239 (25), 237 (35), 227 (21), 43 (33); ^1H NMR ($CDCl_3$) δ 6.5–7.3 (3 H, m, aryl CH), 3.79 (3 H, s, OCH_3), 1.6–3.2 (11 H, m, aliphatic CH), 1.55 (3 H, s, CH_3), 1.37 (3 H, s, CH_3); ^{13}C NMR (Me_2SO-d_6, multiplicity in off-resonance decoupling), 196.0 (s), 160.5 (s), 156.1 (s), 136.4 (s), 135.1 (s), 127.3 (s), 126.6 (d), 112.5 (d), 112.1 (d), 67.4 (s), 54.6 (q), 44.0 (d), 36.5 (t), 34.7 (t), 33.7 (t), 29.6 (q), 27.8 (s), 26.3 (t), 19.5 ppm (t). The last ^{13}C NMR signal may be obscured by absorption of the solvent, Me_2SO-d_6, in the region 37–41 ppm.

Crystal Structure of the Hydroxy Enone 9. A. Data Collection. A crystal of the enone **9** with approximate dimensions 0.75 × 0.35 × 0.35 mm was mounted on a glass fiber, using epoxy cement, such that the longest crystal dimension, 0.75 mm, was approximately parallel to the fiber axis. Unit cell parameters and the orientation matrix were determined on a Syntex $P2_1$ four-circle diffractometer equipped with a graphite monochromator (Bragg 2θ angle = 12.2°), using Mo Kα radiation at a takeoff angle of

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(3) (a) Howell, F. H.; Taylor, D. A. H. *J. Chem. Soc.* **1958**, 1248. (b) also see: Stork, G.; Meisels, A.; Davies, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 3419.

(4) All melting points are corrected; $MgSO_4$ was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer Model 299 infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with a Perkin-Elmer Model 202 recording spectrophotometer. The ^1H NMR spectra were determined at 60 MHz with a Varian Model T-60A NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in γ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with a Varian MAT, Model 112S, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

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