cyclohexanone forms at room temperature in 30 min.[12]

Repetition of this preparation afforded material shown by ^{13}C NMR to be aromatic, with peaks at 157.5, 144.4, 106.1, and 104.8 ppm. In context, the chemical shifts and implied symmetry suggest that the product might well be sodium 3,5-dihydroxybenzenesulfonate, **10**. Preparation of this material by the sodium hydroxide fusion of 1,3,5-benzenetrisulfonic acid provided identical material.[13] The anomalous stability of the product is thus readily explained. Inasmuch as the molecular formulae of **9** and **10** differ by 1 mol of water, the elemental analysis implies that the material is isolated as a hydrate.

The question remains of whether or not phloroglucinol actually forms a sodium bisulfite addition compound. A solution of phloroglucinol in 4 M sodium bisulfite shows only two resonances in the ^{13}C spectrum, at 35.5 and 87.7 ppm, which appear in a coupled spectrum as a triplet and singlet respectively. The observation shows complete conversion to the tris addition compound, **11**. Addition of ethanol produced an oily layer which crystallized from aqueous ethanol. Combustion analysis showed that this material was grossly contaminated with sodium bisulfite, but the preparation allowed spectral examination in D_2O.

Attempts to prepare conventional derivatives of the material were frustrated by its insolubility in organic solvents and the ready reversibility of the formation in water. A D_2O solution of this material shows the carbon spectrum observed of the sodium bisulfite solution and, at proton frequencies, the AB system of the methylene group, observable at 300 MHz, δ 2.24 and 2.28, $J = -14.3$ Hz. The spectra gradually decreased in intensity as the result of exchange of the protons with the solvent, the process being essentially complete after about 45 min. The observation of the discrete methylene peaks and the slow exchange with solvent makes it clear that the peaks observed must therefore correspond to a single species, rather than the averaged resonances of rapidly exchanging species. Thus, within the limits of detection by the NMR spectra, only a single isomer of **11** is formed. It must be the all-cis isomer, for the ^{13}C spectrum of the cis-trans isomer must show four peaks. It seems reasonable to suppose that the conformation adopted must be that with the mutually repulsive sulfonic anions in the equatorial position.

Experimental Section

NMR spectra were run on a Varian XL200 and XL300 spectrometers. ^{13}C chemical shifts of aqueous solutions are relative to internal dioxane, $\delta = 67$ ppm; those of organic solutions are relative to $(CH_3)_4Si = 0$. Infrared spectra were run on KBr pellets on a Perkin-Elmer 1420 spectrometer.

Solutions of phloroglucinol in trifluoroethanol (ca. 1%) showed ^{13}C resonances at 159.39 and 97.50 ppm. Aqueous solutions (1%) showed peaks at 158.26 and 95.70 ppm. Neither solution had changed after 2 weeks.

Conversion of Phloroglucinol to 3,5-Dihydroxybenzenesulfonic Acid.[10] Ten grams of sodium bicarbonate was suspended in 30 mL of water while sulfur dioxide was bubbled through until the suspended solid dissolved and exit gases gave a strong acid reaction. The solution so prepared showed a pH of 1.2. A 5-g sample of phloroglucinol dihydrate was added and the solution was refluxed 3.5 days. A ^{13}C spectrum now showed peaks at 157.5, 144.4, 106.1, and 104.8 ppm. The solution was diluted with ethanol, allowed to stand overnight, and filtered, to provide 5.2 g of solid. An analytical sample was prepared by crystallization from ethanol. The infrared spectrum (KBr) was identical with that of material prepared by fusion of 1,3,5-benzenetrisulfonic acid:[13] 3608, 3450, 3370, 3240, 1630, 1596, 1515, 1495, 1380, 1305, 1220, 1195, 1167, 1110, 1052, 1003, 990, 837, 677, 645 cm^{-1}. Anal. Calcd for $C_6H_5SO_3Na \cdot 2H_2O$: C, 29.04; H, 3.66; S, 12.92. Obsd: C, 29.17; H, 3.48; S, 12.31.

Trisodium *cis,cis*-1,3,5-Trihydroxycyclohexane-1,3,5-trisulfonate. Phloroglucinol dihydrate, 2 g, was added to 40 mL of 4 M sodium bisulfite solution and stirred at room temperature for 3 h. The solution was transferred to a separatory funnel and diluted with 2 volumes of ethanol. The lower layer was separated, dissolved in 40 mL of ethanol–water (7:3), and chilled overnight. The solid was separated by filtration, washed with cold ethanol–water, and dried to afford 5.2 g of a white powder. Material so prepared showed strong absorption at 1130, 637, and 620 cm^{-1}, with small peaks at 1625 and 1511 cm^{-1} corresponding to phloroglucinol. The ^{13}C spectrum of an aqueous solution of this material showed peaks corresponding to phloroglucinol immediately, which increased with time.

Acknowledgment. We are indebted to Kathleen Gallagher for the 300-MHz spectrum and to Dr. James A. Ferretti for enlightening discussions.

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Multigram Preparation of 1,8-Diethyl-7-hydroxy-1,3,4,9-tetrahydropyrano-[3,4-*b*]indole-1-acetic Acid, a Phenolic Metabolite of the Analgesic and Antiinflammatory Agent Etodolac

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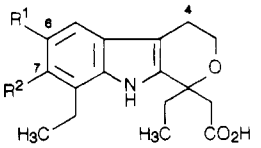
The hydroxypyranoindoles **2** and **3** are oxidative metabolites of the analgesic and antiinflammatory drug etodolac (**1**).[1,2] We recently required large amounts of 7-hydroxyetodolac (**2**). Although **2** is available through a



1(etodolac), $R^1 = H$; $R^2 = H$
2, $R^1 = H$; $R^2 = OH$
3, $R^1 = OH$; $R^2 = H$

nonselective microbial hydroxylation of **1** using *Cunninghamella blackesleeama*,[2] the low yields in this biotransformation make this process impractical. We now report a synthesis of **2** that utilizes as the key step the condensation of the lithio anion of *tert*-butyl acetate with isatin **9**. The twelve-step synthesis proceeds in 17% yield from *N*-(trimethylacetyl)-3-methoxyaniline (**4**)[3] and is readily adaptable to multigram quantities of **2** as demonstrated herein.

As shown in Scheme I, orthometalation of **4** with *n*-butyllithium[3] at 0 °C followed by an acetaldehyde quench at −78 °C provided crystalline alcohol **5** in 74% yield. Catalytic hydrogenation[4] and hydrolysis gave 2-ethyl-3-methoxyaniline (**6**), isolated as its HCl salt, in 86% yield. Aniline **6** was elaborated to tryptophol **11** via isatin **8**,

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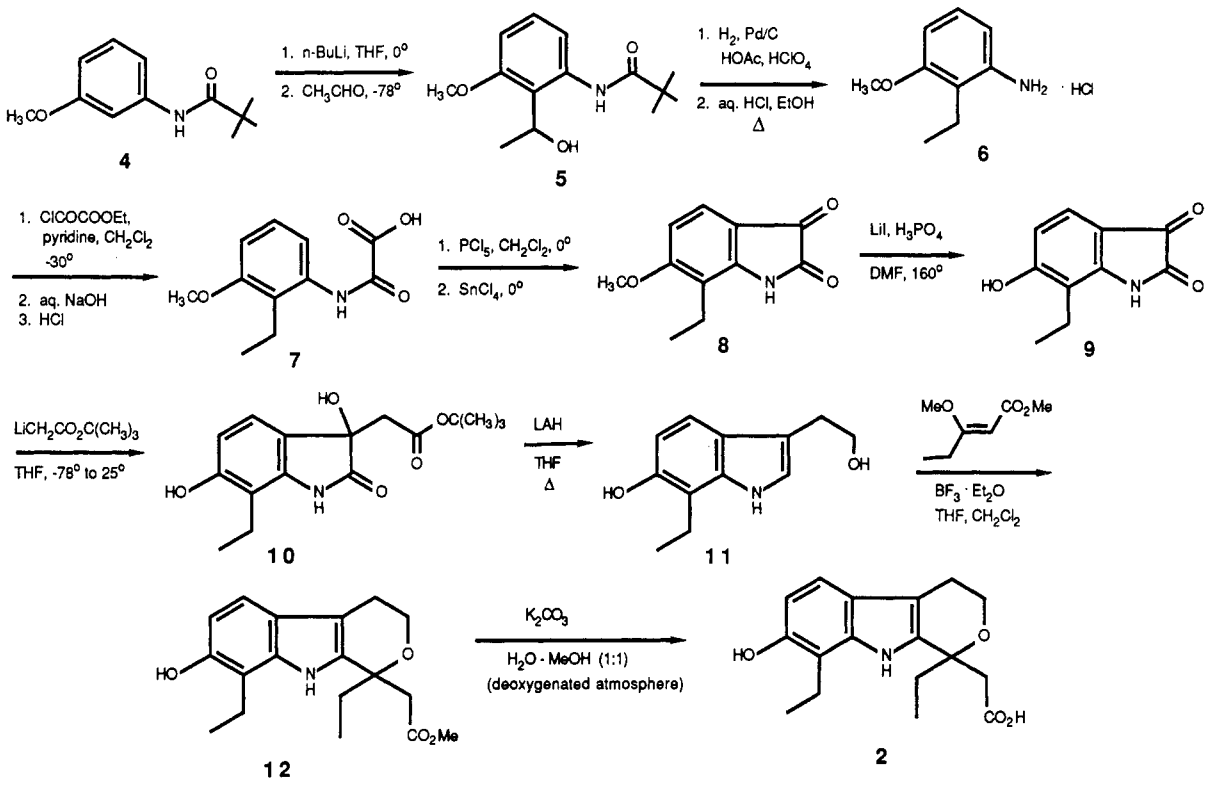
0022-3263/88/1953-2844$01.50/0

Scheme I



which was constructed in 77% yield according to the following sequence: (1) treatment of **6** with ethyl oxalyl chloride, (2) alkaline hydrolysis to oxamic acid **7**, (3) acid chloride formation with phosphorus pentachloride, and (4) $SnCl_4$-mediated cyclization.[5] Isatin **8** was submitted to lithium iodide demethylation in DMF[6] containing phosphoric acid to furnish hydroxyisatin **9** in 89% yield. In the absence of the acidic medium, products derived from N-methylation occurred.

Treatment of isatin **9** with approximately 15 equiv of the lithio anion of *tert*-butyl acetate provided in 77% yield the crystalline aldol adduct **10**,[7] which was reduced with lithium aluminum hydride to tryptophol **11** in 68% yield. Incomplete consumption of **9** was observed with <15 equiv of *tert*-butyl acetate anion. The synthesis was then completed by (1) pyranoindole formation to **12** with methyl 3-methoxy-2-pentenoate[8] and (2) hydrolysis of ester **12** with carbonate in 1:1 methanol–water in a degassed atmosphere. The crystalline metabolite **2**, so obtained in 76% yield from **11**, was identical with authentic material obtained from microbial oxidation of **1** as determined by 400-MHz spectrometry, IR spectroscopy, melting point determination, and TLC mobility. It should be noted that the use of hydroxide or the absence of a deoxygenated atmosphere in the hydrolysis step led to extensive decomposition.

Experimental Section

General. Melting points in capillary tubes were obtained on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 781 spectrophotometer. ^1H NMR spectra were obtained at either 200 or 400 MHz on a Varian XL-200 or Bruker AM-400 spectrometer, respectively, using Me_4Si as internal standard. Mass spectra were measured on either a Finnigan 8230 or Hewlett-Packard 5995A mass spectrometer. Elemental analyses were obtained on a Control Equipment 240-XA elemental analyzer.

Thin-layer chromatography (TLC) analyses were performed on glass-backed (2.5 × 7.5 cm) silica gel 60 F254 plates (0.25 mm). Visualization of spots was effected with UV light and one of the following stains: 10% phosphomolybdic acid in ethanol, ceric ammonium sulfate (100 mg/mL of 35% H_2SO_4), or iodine-impregnated silica gel. R_f refers to the ratio of the distance of the spot from the origin to that of the solvent front. Solvents for TLC are indicated.

Flash chromatography refers to the technique described by Still.[9] Silica gel 60 (400–230 mesh) was used throughout. Reactions requiring anhydrous conditions were performed under N_2.

3′-Methoxy-2,2-dimethylpropionanilide (4). To a vigorously stirred suspension of *m*-anisidine (500 g, 3.94 mol) and sodium carbonate (1060 g, 10.0 mol) in water (2.4 L) and CH_2Cl_2 (2.4 L) was added dropwise over 1 h trimethylacetyl chloride (482 g, 3.96 mol) at a rate such that the temperature was maintained below 25 °C. After stirring at room temperature for 3 h, the reaction mixture was diluted further with water (3000 mL) and CH_2Cl_2 (1000 mL). The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 1000 mL). The combined organic extracts were filtered through Celite, dried ($MgSO_4$), concentrated to a thick slurry, and triturated with hexane. The resulting solid was collected, rinsed with hexane, and dried in vacuo at 40 °C to provide 660 g (81%) of the title compound as a white solid: mp 125–126 °C (lit.[3] mp 123–125 °C); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.39 (t, 1 H, J = 2.2 Hz), 7.3 (bs, 1 H, NH), 7.20 (t, 1 H, J = 7.8 Hz), 6.96 (bd, 1 H, J = 7.0 Hz), 6.67 (bd, 1 H, J = 8.3 Hz), 3.81 (s, 3 H, OCH_3), 1.32 (s, 9 H, *tert*-butyl); R_f (CH_2Cl_2) 0.35.

2′-(α-Hydroxyethyl)-3′-methoxy-2,2-dimethylpropionanilide (5). To 100 g (0.483 mol) of **4** in THF (700 mL; Aldrich anhydrous) at 0 °C was added in a slow, steady stream over 10 min 475 mL (1.12 mol) of *n*-butyllithium (2.36 M in hexanes). After 1 h, the reaction mixture was cooled to −78 °C and to it was added a solution of 45 mL (0.806 mol) of acetaldehyde in THF (70 mL). After 10 min, an additional portion of acetaldehyde (10

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mL, 0.18 mol) was added. The cold bath was removed, and stirring was continued for 15 min. The reaction mixture was quenched with water (300 mL) and diluted with brine (700 mL). The organic phase was separated and the aqueous phase was extracted with methylene chloride (3 × 500 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and combined with an identical run using 45 g of 4. The crude product was dissolved in a minimal amount of a methylene chloride–methanol solution and was triturated with petroleum ether at −40 °C. Filtration and drying in vacuo at 45 °C provided 131 g (74%) of analytically pure product as a colorless powder: mp 160–162 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.87 (bs, 1 H, NH), 7.94 (d, 1 H), 7.19 (t, 1 H), 6.60 (d, 1 H), 5.68 (dq, 1 H, OCH_3), 3.79 (s, 3 H, OCH_3), 2.48 (d, 1 H, OH), 1.49 (d, 3 H, CH_3), 1.30 (s, 9 H, *tert*-butyl); IR (KBr) 3340, 3270, 1655 cm^{-1}; mass spectrum, *m/e* 251, 166; R_f (10% ether–CH_2Cl_2) 0.43. Anal. Calcd for $C_{14}H_{21}NO_3 \cdot {}^1/_4H_2O$: C, 65.71; H, 8.49; N, 5.48. Found: C, 65.83; H, 8.25; N, 5.32.

2-Ethyl-3-methoxyaniline Hydrochloride (6). A suspension of 100 g (0.398 mol) of **5**, acetic acid (1000 mL), 70% perchloric acid (33 mL), and 20 g of 10% Pd/C was hydrogenated (Parr shaker) at 45 psi of H_2 for 20 h. The reaction mixture was filtered through Solka-Floc,[10] and the filtrate was concentrated. Water was added to the residue, and concentrated ammonium hydroxide was added slowly to the chilled slurry until pH 9 was obtained. The white precipitate was filtered and washed thoroughly with water. The product was used without further purification.

Wet crude product (360 g), obtained from a total of 189 g of **5** was refluxed in a solution of concentrated HCl (1.4 L) and ethanol (1.4 L) for 16 h. An additional portion of concentrated HCl (300 mL) was added and reflux was continued for additional 24 h. After concentration to ca. one-third volume, the mixture was cooled to 0 °C. The precipitate was filtered, washed well with ether, and dried in vacuo at 40 °C to provide 130 g (86%) of pure **6** (mp 242 °C dec) as a colorless solid: ^{1}H NMR (DMSO, 200 MHz): δ 9.75 (bs, 3 H, NH), 7.21 (t, 1 H), 6.95 (d, 2 H), 3.78 (s, 3 H, OCH_3), 2.61 (q, 2 H), 1.08 (t, 3 H, CH_3); IR (free base, $CHCl_3$) 3490, 3400 cm^{-1}; mass spectrum (free base), *m/e* 151, 136; R_f (free base, CH_2Cl_2) 0.36. Anal. Calcd for $C_9H_{13}NO \cdot HCl$: C, 57.60; H, 7.52; N, 7.46. Found: C, 57.21; H, 7.24; N, 7.07.

***N*-(2-Ethyl-3-methoxyphenyl)oxamic Acid (7).** To a solution of 232 g (1.24 mol) of **6** in CH_2Cl_2 (3.2 L) containing 296 mL (3.66 mol) of pyridine was added over 1 h ethyl oxalyl chloride (195 mL, 1.74 mol) at a rate such that the reaction temperature was maintained below 30 °C. After 1 h at room temperature, the reaction mixture was washed with 1 N HCl, dried over magnesium sulfate, and concentrated to a thick oil. Ethanol (300 mL) and 600 mL (1.5 mol) of 2.5 N NaOH were added. After 10 min, the reaction mixture was filtered through Celite, and the filter cake was rinsed with water (2 × 100 mL). The filtrate was acidified with 2 N HCl to pH 2. The resulting precipitate was washed with water and dried in vacuo at 40 °C to provide 248 g (90%) of pure product as a colorless solid. An analytical sample (mp 162–163 °C) was obtained by recrystallization from ethanol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.03 (bs, 1 H, NH), 7.61 (d, 1 H), 7.23 (t, 1 H), 6.80 (d, 1 H), 3.85 (s, 3 H), 2.71 (q, 2 H), 1.15 (t, 3 H); IR (KBr) 3280, 1780, 1680 cm^{-1}; mass spectrum, *m/e* 223, 178; R_f (1% HOAc–THF) 0.50. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 58.83; H, 5.56; N, 6.51.

6-Methoxy-7-ethylisatin (8). To a suspension of 248 g (1.11 mol) of **7** and CH_2Cl_2 (3.5 L) at 0 °C was added portionwise phosphorus pentachloride (254 g, 1.22 mol). After 30 min at 0 °C, 160 mL (1.37 mol) of $SnCl_4$ was added over 2 h to the resulting solution, maintaining the temperature at 0 °C. After 16 h at room temperature, 1.7 L of 2 N HCl was added portionwise to the reaction mixture at 0 °C, and then the mixture was diluted with an additional 860 mL of THF. The organic phase was removed and the aqueous layer extracted with 6 × 2 L of 2:8 THF–CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), concentrated to a slurry, and triturated with ether to provide 196 g (86%) of product as an orange solid: mp 229–230 °C; ^{1}H NMR (DMSO, 200 MHz) δ 11.21 (s, 1 H, NH), 7.58 (d, 1 H), 6.83 (d, 1 H), 4.05 (s, 3 H), 1.17 (t, 3 H); IR (KBr) 3165, 1730 cm^{-1}; mass spectrum, *m/e* 205, 177, 149; R_f (10% ether–CH_2Cl_2) 0.25. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.24; H, 5.29; N, 6.72.

6-Hydroxy-7-ethylisatin (9). To 2.6 L of DMF was added portionwise 692 g (5.17 mol) of lithium iodide (exothermic reaction) followed by 14 mL of 85% H_3PO_4 and 173 g (0.843 mol) of **8**. After stirring at 160 °C (internal temperature) for 8 h, the reaction mixture was quenched at 10 °C with 1 L of 1 N HCl and water (20 L) and then extracted with ethyl acetate (7 × 1 L). The organic extracts were dried over $MgSO_4$ and then diluted further with an equal volume of methylene chloride. The extracts were divided equally and each was passed through a thick pad of flash silica gel (8-in. height × 6-in. width), followed by a 2-L rinse of 1:1 CH_2Cl_2–ethyl acetate. Concentration of the filtrate and trituration with hexane provided 144 g (89%) of the title compound as a brown-red solid: mp 285 °C dec; ^{1}H NMR (DMSO, 200 MHz): δ 11.1 (s, 1 H), 10.96 (s, 1 H), 7.27 (d, 1 H), 6.49 (d, 1 H), 2.5 (q, 2 H), 1.03 (t, 3 H); IR (KBr) 3200, 1750, 1705 cm^{-1}; mass spectrum, *m/e* 191, 163, 135; R_f (ether) 0.41. Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.72; H, 4.68; N, 7.44.

***tert*-Butyl 2,3-Dihydro-3,6-dihydroxy-7-ethyl-2-oxo-1*H*-indole-3-acetate (10).** At −78 °C to 607 g (5.23 mol) of *tert*-butyl acetate in 2 L of THF (Aldrich anhydrous) was added over 2 h 5.23 L (5.23 mol) of lithium bis(trimethylsilyl)amide (1 M in THF). Approximately one-third of the ester anion was added to a slurry of 66.2 g (0.346 mol) of **9** in THF (4 L) at room temperature. After 4 h an additional one-third of the ester anion solution was added to the reaction mixture. After 16 h of stirring at ambient temperature, **9** was still evident by TLC analysis. To the resulting solution was added the remainder of the ester anion. TLC analysis indicated no presence of **9**. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of 6 N HCl until pH 2 was obtained. The reaction mixture was extracted with two portions of ether, and the organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo at 30 °C. The residue was triturated to give 62 g (77%) of product as a lavender solid (mp 191–192 °C dec). An analytical sample (mp 193 °C dec) was obtained by recrystallization from hexane–ethyl acetate: ^{1}H NMR (DMSO, 200 MHz) δ 10.2 (s, 1 H), 9.3 (s, 1 H), 6.9 (d, 1 H), 6.35 (d, 1 H), 5.83 (s, 1 H), 2.73 (q, 2 H), 2.5 (q, 2 H), 1.08 (s, 9 H), 1.05 (t, 3 H); R_f (ether) 0.33. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.20; H, 6.54; N, 4.64.

6-Hydroxy-7-ethyltryptophol (11). At 0 °C to a solution of 83.6 g (0.272 mol) of **10** in 1.6 L of THF (Aldrich anhydrous) was added dropwise 800 mL (0.80 mol) of lithium aluminum hydride (1 M in THF). After stirring at reflux for 2 h, the reaction mixture was cooled to 0 °C and quenched carefully with 400 mL of 3 N HCl. Additional water was added and the reaction mixture was extracted with two portions of ether. The combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting solid was rinsed with 360 mL of ether to provide 18.5 g of **11** (mp 144–145 °C). The ethereal filtrate was flash chromatographed (Et_2O–CH_2Cl_2, 1:4 and 1:1) to provide an additional 19.4 g of pure **11** (68%; mp 144–146 °C). An analytical sample (mp 145–146 °C) was obtained by recrystallization from hexane–ethyl acetate: ^{1}H NMR (DMSO, 200 MHz): δ 10.34 (s, 1 H), 8.55 (s, 1 H), 7.08 (d, 1 H), 6.88 (s, 1 H), 6.56 (d, 1 H), 4.56 (bs, 1 H), 3.57 (t, 2 H), 2.70 (bs, 4 H), 1.08 (t, 3 H); IR (KBr) 3420, 3150 cm^{-1}; R_f (ether) 0.59. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.02; H, 7.55; N, 6.67.

Methyl 1,8-Diethyl-7-hydroxy-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetate (12). To a solution of 43.7 g (0.213 mol) of **11** in THF (410 mL; Aldrich anhydrous) and CH_2Cl_2 (410 mL) and methyl 3-methoxy-2-pentenoate (30.7 g, 0.213 mol) was added in small portions over 90 min 26.2 mL (0.213 mol) of $BF_3 \cdot Et_2O$. TLC analysis showed incomplete consumption of **11**. Additional $BF_3 \cdot Et_2O$ (4.0 mL) and methyl 3-methoxy-2-pentenoate (0.70 g) were added portionwise over 4.5 h. After 6 h at room temperature, the reaction mixture was added to a mixture of ice and aqueous saturated $NaHCO_3$. The mixture was extracted into CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$) and concentrated. The dark green residue was dissolved in CH_2Cl_2 and passed through a thick pad (6 in. × 6 in.) of flash silica gel, using CH_2Cl_2 (5 L) elution. Concentration and trituration with hexane provided 53.3 g (79%) of the title product (mp 127–130 °C). An analytical sample, obtained as a colorless crystal (mp 130–131 °C) was

(10) James River Corp., Berlin, NH 03570.

prepared by recrystallization from ether: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.89 (bs, 1 H, NH), 7.18 (d, 1 H), 6.64 (d, 1 H), 4.60 (s, 1 H, OH), 3.7–4.1 (m, 2 H), 3.71 (s, 3 H, OCH_3), 2.5–3.1 (m, 3 H), 1.9–2.2 (m, 2 H), 1.29 (t, 3 H, CH_3), 0.83 (t, 3 H, CH_3); IR (KBr) 3420, 1735 cm^{-1}; mass spectrum, *m/e* 317, 288, 244; R_f (ether–petroleum ether) 0.57. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.02; H, 6.98; N, 4.28.

1,8-Diethyl-7-hydroxy-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic Acid (2). A degassed solution of potassium carbonate (480 g, 3.47 mol) in water (1.7 L) and methanol (1.7 L) was added to 53.7 g (0.169 mol) of **12**. The flask was evacuated and then filled with N_2 (procedure repeated three times). The reaction mixture was heated at 50 °C. During the reaction period, the reaction flask was evacuated and fresh N_2 was introduced at 1-h intervals. After 3 h, 240 g (1.74 mol) of K_2CO_3 was added. After evacuation and N_2 introduction, the reaction mixture was heated at 50 °C for 5 h. The red solution was cooled to 0 °C and treated with degassed 4 N HCl (2.68 mL, 10.7 mol) until pH 2 was obtained. The resulting tan crystals were collected, washed thoroughly with water, and dried in vacuo at 25 °C to provide 49.3 g (96%) of analytically pure title compound as a beige solid: mp 180 °C dec; ^{1}H NMR (DMSO, 400 MHz) δ 11.1 (s, 1 H), 10.1 (s, 1 H), 6.96 (d, 1 H), 6.54 (d, 1 H), 3.8–4.0 (m, 2 H), 2.87 (d, 1 H), 2.7 (d, 1 H), 1.10 (t, 3 H), 0.59 (t, 3 H); IR (KBr) 3350, 1690 cm^{-1}; mass spectrum, *m/e* 303, 259; R_f (33% acetone–CH_2Cl_2; on 1% H_3PO_4–MeOH pretreated plates) 0.5. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.02; H, 6.71; N, 4.87.

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Registry No. **1**, 41340-25-4; **2**, 101901-07-9; **4**, 56619-93-3; **5**, 114274-14-5; **6**, 114274-15-6; **6** (free base), 114274-16-7; **7**, 114274-17-8; **8**, 114274-18-9; **9**, 114274-19-0; **10**, 114274-20-3; **11**, 114274-21-4; **12**, 114274-22-5; CH_3CHO, 75-07-0; $Cl(CO)_2OEt$, 4755-77-5; *m*-anisidine, 536-90-3; trimethylacetyl chloride, 3282-30-2; *N*-(*tert*-butylcarbonyl)-2-ethyl-3-methoxyaniline, 114274-23-6; *tert*-butylacetate, 540-88-5; methyl 3-methoxy-2-pentenoate, 104065-67-0.

Isoquinoline Quinones. Preparation of Saframycin Intermediates and a Total Synthesis of Mimosamycin

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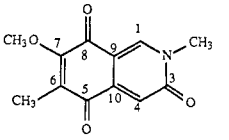
The isoquinoline quinones comprise a new structural class of naturally occurring antibiotics.[1] Mimosamycin (**1**),[2] one of the "monomeric" isoquinoline quinones, was found to have antitubercular activity.[3] Saframycin A (**2**),[4] which represents the more complex "dimeric" members of the class, exhibits antitumor activity.[5]



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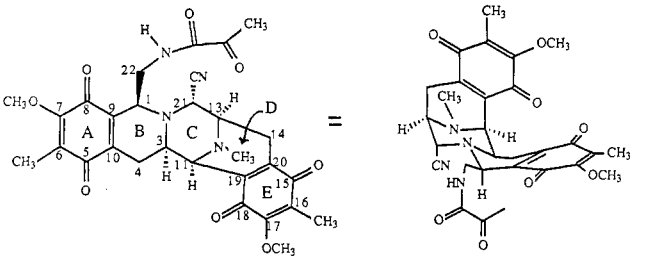

2

In earlier work directed toward the synthesis of the saframycins, the strategy of conjugate addition to quinone monoketal **3** was used to introduce functionality for the A/B ring system.[6] We imagined that this approach might also be employed to construct precursors to the functionally similar D/E ring system of saframycin A and to the natural product, mimosamycin.

For example, conjugate addition of a one-carbon nucleophile to the readily available quinone monoketal **3**[6] would append a functionalized carbon-11 to the latent E ring of saframycin. In the same fashion, we might add a functionalized carbon-1 to the latent quinone of mimosamycin. Then allylation (Scheme I) would provide the basis for the elaboration of the side chains required (C-14, C-13, and C-21 of saframycin and C-4 and C-3 of mimosamycin). In this paper, we report the preparation of allylbenzonitriles **6**, regarded as potential intermediates in a total synthesis of saframycin A,[7] and the elaboration of nitrile **6c** (X = H) to the antibiotic mimosamycin (**1**).

Cyanide addition to a naphthoquinone monoketal (KCN, methanol, reflux) has been demonstrated by Semmelhack and co-workers.[9] In our hands, the conversion of quinone ketal **3** to benzonitrile **4** was improved (60% yield) when potassium cyanide (slightly more than 1 equiv) was added in the presence of 1 equiv of 18-crown-6 in THF.

Our first attempts to introduce the acetic acid side chain of mimosamycin were based on oxidative cleavage of a haloallyl substituent.[10,11] Both bromo and chloro substitution were examined in this application.

The haloallyl side chain was to be introduced into the sixth position on the aromatic nucleus by Claisen rearrangement. Alkylation of phenol **4** with the appropriate

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(6) Parker, K. A.; Cohen, I. D.; Babine, R. E. *Tetrahedron Lett.* **1984**, *25*, 3543.

(7) Of the saframycins, only saframycin B has been prepared: Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957.

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(9) Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W. *J. Org. Chem.* **1985**, *50*, 5566.

(10) For similar approaches using cyano-substituted olefins, see: Schroder, M. *Chem. Rev.* **1980**, *80*, 187–213.

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