- I) 152.1075, found, 152.1075. Anal. Calcd for $C_9H_{14}INO$: C, 38.73; H, 5.06; N, 5.02. Found: C, 38.57; H, 5.22; N, 4.86].

Procedure E: 5-[2-(4,5-Dihydro-2*H*-pyranyl)ethyl]-3-[1-((trimethylsilyl)oxy)ethyl]-2-isoxazoline (13a). A benzene (1 mL) solution of triethylamine (26 mg, 0.25 mmol) was added dropwise to a solution of 2-[(trimethylsilyl)oxy]-1-nitropropane (302 mg, 1.71 mmol), dihydropyran **10a** (472 mg, 3.41 mmol), and *p*-chlorophenyl isocyanate (524 mg, 3.41 mmol) in benzene (30 mL). The resulting solution was heated at reflux for 50 h and then cooled, filtered through Celite, and treated with water (25 drops). After 2 h of vigorous stirring, the mixture was again filtered through Celite, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by MPLC (Florisil column, 2:98 EtOAc:hexanes, 2.5 mL/min) gave **13a** (380 mg, 1.28 mmol, 75%) as a yellow oil: R_f = 0.68 (25/75 ethyl acetate/hexane); FT IR (neat) 2953, 1252, 1089, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9 H, $Si(CH_3)_3$), 1.32 (d, J = 6.3 Hz, 3 H, CH_3), 1.54-2.03 (m, 9 H), 2.50 (dd, J = 9, 15 Hz, 1 H, N=C*H*HCO), 2.92 (dd, J = 9, 15 Hz, 1 H, N=CH*H*CO), 3.86 (t, J = 3.2 Hz, 2 H, CH_2O), 4.42 (t, J = 2.6 Hz, 1 H, CH=), 4.60 (m, 1 H, HCO); HRMS calcd for $C_{15}H_{27}NO_3Si$ FAB+ 298.1838, found, 298.1839.

5-[2-(4,5-Dihydro-2*H*-pyranyl)propyl]-3-[1-((trimethylsilyl)oxy)ethyl]-2-isoxazoline (13b). Following procedure E, dihydropyran **10b** gave **13b** (411, 1.4 mmol, 70%) as a pale yellow oil: R_f = 0.68 (25/75 EtOAc/hexane); FT IR (neat) 2953, 1252, 1089, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9 H, $Si(CH_3)_3$), 1.18-2.22 (m, 13 H), 2.53 (dd, J = 7, 15 Hz, 1 H, N=CC*H*HCO), 3.13 (dd, J = 7, 15 Hz, 1 H, N=CCH*H*CO), 3.95 (t, J = 2.2 Hz, 2 H, CH_2O), 4.54 (br m, 2 H, HCO), 4.75 (m, 1 H, CH=); HRMS calcd for $C_{16}H_{29}NO_3Si$ 311.1917, found, 311.1916.

Procedure F: (5*S,6*R**,8*R**)- and (5*S**,6*R**,8*S**)-8-(Cyanomethyl)-5-iodo-1,7-dioxaspiro[5.4]decane (12a).** A solution of iodine (121 mg, 0.48 mmol) in methylene chloride (10 mL) was added in one portion to a methylene chloride (20 mL) solution of isoxazoline **13a** (94.8 mg, 0.318 mmol). The reaction mixture was stirred at room temperature for 5 h and then diluted with Et_2O (10 mL) and saturated aqueous sodium bisulfite solution (5 mL), and the layers separated. The aqueous phase was extracted with Et_2O (3 × 25 mL), and the combined organic extracts were washed with brine (1 × 10 mL), dried (Mg_2SO_4), filtered, and concentrated under reduced pressure. Purification by Chromatron (90/10 EtOAc/hexanes) gave spiroketal **12a** (55.7 mg, 0.18 mmol, 57%) as a pale yellow oil and inseparable 1:1 mixture of CH_2CN epimers; R_f = 0.57 (20/80 ethyl acetate/hexane); FT IR (neat) 2947, 2874, 2249 (CN), 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40-2.35 (m, 9 H), 2.58 (m, 2 H, CH_2CN), 3.69 (m, 1 H, C*H*HO), 3.86 (m, 1 H, CH*H*O), 4.35 (m, 1 H, *H*CO); ^{13}C ($CDCl_3$) δ 21.0/25.3, 26.0/26.8, 29.9/30.7, 34.4/34.5, 38.2/39.4, 62.8 (CH_2O), 72.8 (CHI), 75.3 (HCO), 106.7 (OCO), 117.6/117.7 (CN); HRMS calcd for ($C_{10}H_{14}NO_2$ - I) 180.1024, found 180.1025.

(2*S,6*R**,11*S**)-2-(Cyanomethyl)-11-iodo-1,7-dioxaspiro[5.5]undecane (12b).** Following procedure F, dihydropyran **13b** gave spiroketal **12b** (22 mg, 0.07 mmol, 25%) as a pale yellow oil: R_f = 0.33 (20/80 EtOAc/hexane); FT IR (neat) 2943, 2872, 2251 (CN), 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.09-1.17 (m, 11 H), 2.45 (d, J = 6.3 Hz, 2 H, CH_2CN), 3.65 (m, 2 H, CH_2O), 3.92 (m, 1 H, HCO); ^{13}C NMR ($CDCl_3$) δ 18.27, 18.30, 24.66, 25.10 (HCI), 30.23, 34.70, 35.37, 60.66 (CH_2O), 65.18 (HCO), 96.12 (OCO), 117.66 (CN); HRMS calcd for $C_{11}H_{16}INO_2$ 321.0225, found 321.0222.

Acknowledgment. We are pleased to acknowledge support of this work by the National Science Foundation through Grant CHE-8704836.

Registry No. **1a**, 123622-54-8; **1b**, 123622-55-9; **1c**, 123622-56-0; **1d**, 123622-57-1; **1e**, 123622-58-2; **1g** (isomer 1), 123622-60-6; **1g** (isomer 2), 123622-61-7; **1h** (isomer 1), 123622-63-9; **1h** (isomer 2), 123622-64-0; *cis*-**2a**, 123622-65-1; *trans*-**2a**, 123622-66-2; *cis*-**2b**, 123622-68-4; *trans*-**2b**, 123622-69-5; *cis*-**2c**, 123622-70-8; *trans*-**2c**, 123622-71-9; *cis*-**3**, 123622-67-3; *trans*-**3**, 123622-87-7; **4**, 123622-72-0; (*E*,*E*)-**5**, 18152-31-3; (*Z*,*Z*)-**5**, 18680-11-0; **6**, 123622-73-1; **6** (4,5-regioisomer), 123622-88-8; 2,6-*cis*-**7a**, 123622-76-4; 2,6-*trans*-**7a**, 123622-77-5; **7b**, 123622-78-6; **8**, 123622-74-2; **8** (4,5-regioisomer), 123622-75-3; **9a**, 123622-79-7; **9b**, 123622-80-0; **9c**, 123673-08-5; **10a**, 123622-81-1; **10b**, 123622-83-3; **12a** (isomer 1), 123622-85-5; **12a** (isomer 2), 123673-09-6; **12b**, 123622-86-6; **13a**, 123622-82-2; **13b**, 123622-84-4; $Hg(CNO)_2$, 628-86-4; $Ph_3CC{\equiv}N^+O^-$, 13412-55-0; 1-hexene, 592-41-6; 1,5-hexadiene, 592-42-7; 1,6-heptadiene, 3070-53-9; 1,7-octadiene, 3710-30-3; (±)-2-[(trimethylsilyl)oxy]-3-methyl-1-nitrobutane, 123622-62-8; (±)-2-[(trimethylsilyl)oxy]-1-nitropropane, 123622-59-3; *tert*-butylhydroximic acid chloride, 3273-26-5.

Supplementary Material Available: Labeled drawings of **9a** and listings of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atom coordinates (6 pages). Ordering information is given on any current masthead page.

Oxidative Degradation of 6-Hydroxy-1,2,3,4-tetrahydroisoquinolines and 7-Hydroxy-2-benzazepines. A Novel Route to Heterocyclic Quinones

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A novel route toward 4,5-indolequinones and 5,8-quinolinequinones, based on the Fremy's salt promoted oxidative degradation of 6-hydroxy-1,2,3,4-tetrahydroisoquinolines and 7-hydroxy-2-benzazepines, is described.

The significant pharmacological properties associated with many synthetic and naturally occurring quinones has spurred much interest in the search for a new methodology for the synthesis of the quinone functionality.[1]

Our recent work in this field has led us to develop the so-called oxidative degradation approach (ODA) for the synthesis of simple 1,4-benzoquinones.[2] In essence, the success of this approach lies in the fact that the amino group of the starting phenolic *N*,*N*-dimethylbenzylamines serves two main purposes in the plan. As illustrated in Scheme I, it was first needed as a directing group for metalation (and subsequent functionalization) of the unprotected phenol,[3] and secondly, its role in the oxidative degradation process was to promote side-chain cleavage

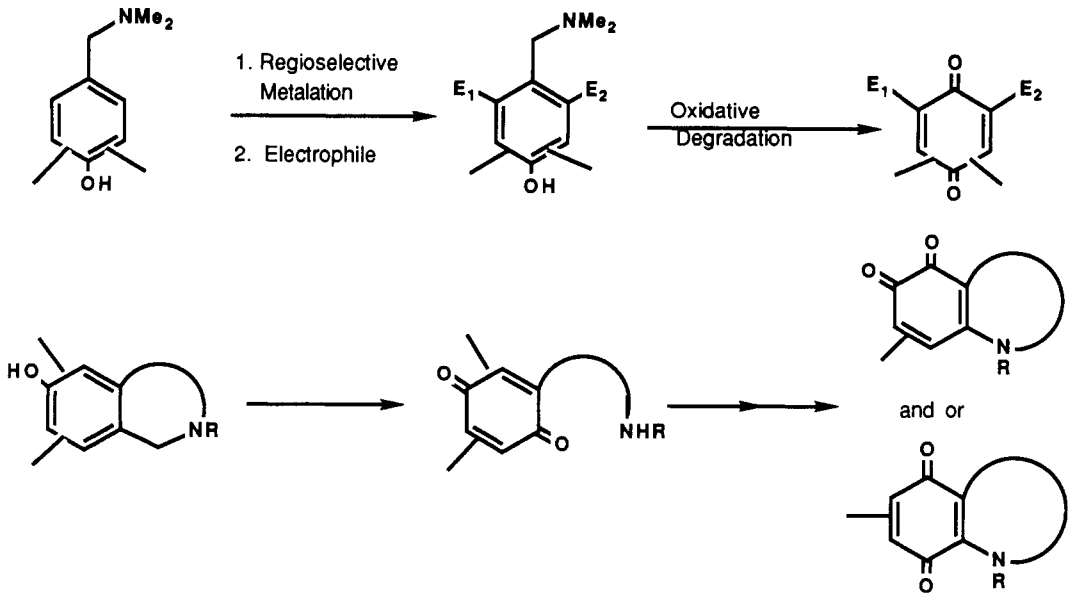
(1) *Chemistry of Quinones*; Rappoport, Z., Patai, S., Eds.; John Wiley: New York, 1988; Volume 2, Parts 1 and 2. *Methoden der Organischen Chemie (Houben Weyl)*; Georg Tieme Verlag: Stuttgart, 1977; Teil I, Band VII/3a. For some recent developments in the area, see: Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2795. Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. Moore, H. W.; Decker, O. H. *Chem. Rev.* **1986**, *86*, 821. Wulff, W. D.; Tang, P. C.; Chan, K. S.; McCallum, J. S.; Yang, D. C.; Gilberton, R. S. *Tetrahedron* **1985**, *24*, 5813. Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Spies, E. J.; Wulff, W.; Zask, A. *Tetrahedron*, **1985**, *24*, 5803.

(2) Saa, J. M.; Morey, J.; Costa, A. *Tetrahedron Lett.* **1985**, *27*, 5125.

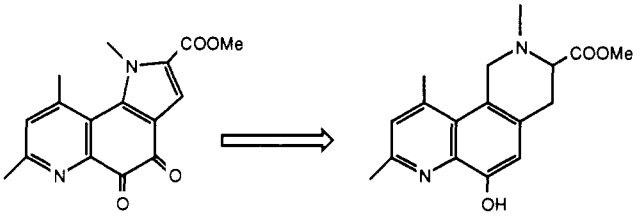
(3) Costa, A.; Saa, J. M. *Tetrahedron Lett.* **1987**, *28*, 5551. Saá, J. M.; Llobera, A.; García-Raso, A.; Costa, A.; Deyá, P. M. *J. Org. Chem.* **1988**, *53*, 4263.

0022-3263/90/1955-0288$02.50/0

Scheme I



Scheme II

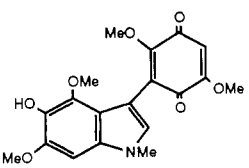


on the presumed 4,4-disubstituted cyclohexadienone intermediate, thus giving rise to a quinone depleted of the (dimethylamino)methyl side chain.[4]

As a further extension of the above methodology we would like now to report our results on the Fremy's salt (FS)[5] promoted oxidative degradation of some phenolic cyclic benzylamines such as 6-hydroxytetrahydroisoquinolines and 7-hydroxy-2-benzazepines. According to the proposed mechanism,[6] the title compounds should give rise to an intermediate (aminoalkyl)-1,4-benzoquinone which, on cyclization[7] and further oxidation,[8] should lead to heterocyclic quinones of the type shown in Scheme I, as a function of the cyclization mode (1,2 and/or 1,4). In passing, it is worth mentioning that the oxidation of phenolic indoles such as 5,7-dihydroxytriptamine is of great biological significance as it appears to be responsible for chemical denervation processes.[9] More specifically, we expected that this preliminary study would provide us with valuable information for our planned synthesis of the important cofactor methoxatin[10] (Scheme II) and other azaquinones. As illustrated in Scheme II, methoxatin could derive from the precursor shown which possesses the above mentioned 6-hydroxy-1,2,3,4-tetrahydroisoquinoline unit.

To this end, several simple 6-hydroxy-1,2,3,4-tetrahydroisoquinolines (**1**–**3**) were synthesized following a well-known methodology. Thus, **1** and **2** were easily available through the Bobbitt modification[11] of the Pomeranz–Fritsch cyclization, whereas **3** (which cannot be prepared as above) was eventually obtained by the Pictet–Spengler[12] cyclization of phenylephrine followed by chromatographic separation of the desired 6-hydroxy isomer, and final hydrogenolysis ($AcOH–ClO_4H$ (catalyst), 10% Pd/C, H_2, 40 psi, 96 h).[13] Treatment of the above 6-hydroxytetrahydroisoquinolines with excess Fremy's salt in a buffered (Na_2HPO_4–NaH_2PO_4, pH = 6.1) two-phase (CH_2Cl_2–H_2O) system, led to rapid consumption of starting material and formation of the corresponding 4,5-indoloquinones in low-to-medium isolated yields (15–50%) as blue–violet solids, thus proving that the major pathway for the Fremy's salt oxidative degradation of tetrahydroisoquinolines is 1,2 cyclization[7] (5-exo-trig, allowed according to the Baldwin rules[14]). Thus, **4** was isolated as the major product from **1** and **2**, although the latter compound also gave rise to a second minor byproduct believed to be a partially degraded dimer.[15] Somewhat as expected, the very reactive 4,5-indoloquinone **5** was obtained in low yield (15–25%) by oxidation of **3** followed by flash chro-

(4) Saa, J. M.; Llobera, A.; Deyâ, P. M. *Chem. Lett.* **1987**, 771. Saâ, J. M.; Morey, J.; Rubido, C. *J. Org. Chem.* **1986**, *51*, 447.
(5) Zimmer, H.; Lankin, D. C.; Horgan, H. *Chem. Rev.* **1971**, *71*, 229.
(6) See: Deyâ, P. M.; Dopico, M.; García-Raso, A.; Morey, J.; Saa, J. M. *Tetrahedron* **1987**, *43*, 3523, and references therein.
(7) For examples of 1,2 cyclization of (aminoethyl)-1,4-benzoquinones and related compounds, see ref 5 and the following: (a) Teuber, H. J.; Glosauer, O. *Chem. Ber.* **1965**, *98*, 2648. (b) Teuber, H. J.; Glosauer, O. *Chem. Ber.* **1965**, *98*, 2939. (c) Chen, C.-P.; Shih, C.; Swenton, J. S. *Tetrahedron Lett.* **1986**, *27*, 1891. For examples of 1,2 cyclization of (aminopropyl)-1,4-benzoquinones, see c.
(8) The FS oxidation of 5-hydroxyindoles to the corresponding 4,5-indolequinones has been reported. See, for example: Teuber, H. J.; Thaler, G. *Chem. Ber.* **1958**, *91*, 2253.
(9) See: Dryhurst, G.; Anne, A.; Wrona, M. Z.; Lemordant, D. *J. Am. Chem. Soc.* **1989**, *111*, 719.
(10) Duine, J.; Frank, J.; Jongejan, J. A. In *Advances in Enzymology and Related Areas of Molecular Biology*; Meister, A., Ed.; Wiley: New York, 1987; pp 169–212.
(11) (a) Bobbitt, J. M.; Kiely, J. M.; Khanna, K. L.; Ebermann, R. *J. Org. Chem.* **1965**, *30*, 2247. (b) Bobbitt, J. M.; Roy, D. N.; Marchand, A.; Allen, C. W. *J. Org. Chem.* **1967**, *32*, 2225. (c) Bobbitt, J. M.; Steinfield, A. S.; Weisgraber, K. H.; Dutta, S. *J. Org. Chem.* **1969**, *34*, 2478.
(12) Bates, H. A.; Bagheri, K.; Vertino, P. M. *J. Org. Chem.* **1986**, *51*, 3061.
(13) Tallent, W. H.; Horning, E. C. *J. Am. Chem. Soc.* **1956**, *78*, 4469.
(14) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.
(15) The structure of this minor byproduct has been tentatively established as the following:



matography of the crude material on a short silica gel column (Scheme III). Attempts at reducing the extensive yield losses produced during purification of **5** by rapidly derivatizing the crude reaction mixture ($S_2O_4Na_2$, followed by Ac_2O/pyridine) led to a marginal yield improvement (20–30%) in the expected 4,5-diacetoxy-1-methylindole.

As a useful candidate for studying the FS oxidative degradation of 7-hydroxy-2-benzazepines, (–)-sanguinine **6**, a naturally occurring *Amaryllidaceae* alkaloid,[16] was selected. Treatment of a buffered (pH = 6.1) solution (EtOH:$CHCl_3$, 1:9) of **6** with FS yielded a mixture of **7** and **8** as red–violet solids in 54% combined yield (isolated). Furthermore, when the reaction was carried out in MeOH:$CHCl_3$, the methoxy analogue **9** was obtained as the major product together with minor amounts of **7** (Scheme III). On the other hand, only **7** and trace amounts of other minor components were obtained when the oxidation was run in chloroform containing some acetone. The structure (including its relative stereochemistry) of the above tetrahydroquinoline-5,8-diones was unambiguously established for the case of compound **8** by employing the usual decoupling techniques. The location of the OEt group on the quinone skeleton was deduced from a long-distance ^{13}C–^1H correlation.

The formation of **7**, **8**, and **9** can be easily understood as a consequence of the preferred 1,4 cyclization (addition–elimination; 6-endo-trig, allowed[14]) of the intermediate (aminoalkyl)-1,4-benzoquinone, followed by further oxidation of the resulting phenolic tetrahydroquinoline to the parent quinone **7**. This compound eventually undergoes a not too common oxidative addition of the alcoholic solvent, a process that we assume to take place by addition to the β position of the unsaturated ketone (the other unit is a vinylogous amide). Accordingly, compound **7** has been proven to undergo oxidative addition of ethanol, in the presence of FS, to give **8**.

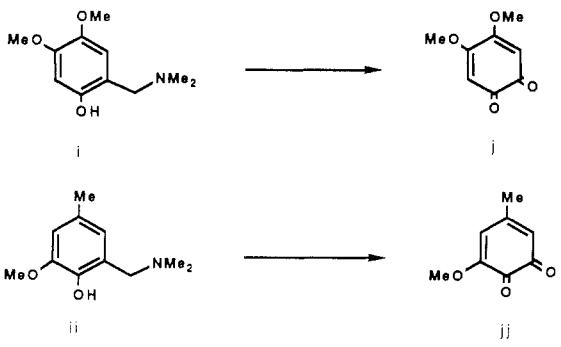
In an effort to further extend the above methodology to 8-hydroxy-5,7-disubstituted tetrahydroisoquinolines, compound **10**[17] was submitted to FS oxidative degradation. We hoped that this operation would lead us to 7-hydroxy-4,6-disubstituted indoles, therefore opening a potentially valuable new access to mitomycins and related compounds. This expectation was based on recent observations in regard to the FS oxidative degradation of simple *o*-hydroxybenzylamines[18] and related compounds[6] to the corresponding 1,2-benzoquinones. Unfortunately **10** was found to be almost inert (70% recovery after 48 h) to the standard reaction conditions (Scheme III).

In summary, appropriately substituted cyclic benzylamines can be considered useful synthons for a series of valuable heterocyclic quinone skeletons present in such interesting molecules as methoxatin[10] or discorhabdins.[19] Further work on the application of this strategy for the synthesis of some naturally occurring heterocyclic quinones is being studied with emphasis in improving the yield of the oxidative degradation.

(16) (–)-Sanguinine was isolated in our laboratories from *Leucojum aestivum sub. pullchelum* as needles: mp 215–6 °C; $[a]_D$ = –136° (*c* = 0.23, EtOH). Its spectroscopic data were found to be identical with those (kindly provided by Prof. Kobayashi) reported for (–)-sanguinine. See: Kobayashi, S.; Takeda, S.; Ishikawa, H.; Matsumoto, H.; Kihara, M.; Shingu, T.; Numata, A.; Uyeo, S. *Chem. Pharm. Bull.* **1976**, *24*, 1537.

(17) Bobbitt, J. M.; Dutta, C. P. *J. Org. Chem.* **1969**, *34*, 2001.

(18) Fremy's salt oxidative degradation of 6-[(dimethylamino)methyl]-3,4-dimethoxyphenol (i) and 6-[(dimethylamino)methyl]-2-methoxy-4-methylphenol (ii) under the above standard conditions furnishes 4,5-dimethoxy-1,2-benzoquinone j and 3-methoxy-5-methyl-1,2-benzoquinone jj in 90% and 52% yields, respectively; unpublished results.



Experimental Section

General Methods. All melting points are uncorrected and were taken on a capillary melting point apparatus. Proton and carbon NMR spectra were obtained on a Varian FT-80A and Brucker WM-250 spectrometers in $CDCl_3$, unless otherwise noted, with Me_4Si as internal standard. Electron impact mass spectra were recorded on a Hewlett-Packard 5988A GC MS operating at 70-eV ionizing energy. Infrared spectra were obtained on a Hitachi 260-10 infrared spectrophotometer. High-resolution mass spectra were recorded on a VG Micromass ZAB-2F or a Kratos MS-50 (U. de la Laguna, Tenerife, and U. de Santiago de Compostela, La Coruña, Spain). Column chromatographies were performed on silica gel (Macherey Nagel 70–230 mesh).

***N*-Methyl-6-hydroxy-5,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2).** This compound was prepared in 53% isolated yield following Bobbitt's procedure:[11] mp (hydrochloride) 190–202 °C (dec); IR (hydrochloride, KBr) 3420, 2930, 1610, 1495, 1455, 1320, 1160, 1110, 950 cm^{-1}; ^1H NMR 6.43 (s, 1 H), 3.94 (s, 6 H), 3.59 (s, 2 H), 2.81 (m, 4 H), 2.55 (s, 3 H) ppm; ^{13}C NMR 146.12, 144.81, 136.60, 124.37, 119.22, 103.92, 58.97, 56.71, 55.36, 51.80, 44.87, 22.48 ppm; EIMS, *m/e* (%) 223(M^+, 0.7), 206 (26), 149 (100), 132 (13), 91 (69); HRMS calculated for $C_{12}H_{17}O_3N$ 223.1208, found 223.1203.

***N*-Methyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (3).** *N*-Methyl-4,6-dihydroxy-1,2,3,4-tetrahydroisoquinoline (1.08 g, 5 mmol), itself prepared from phenylephrine hydrochloride as described by McLaughlin,[20] was dissolved in 40 mL of AcOH:MeOH (3:1) containing a few drops of perchloric acid. To this, 10% Pd/C (0.5 g) was added, and the mixture was then hydrogenated (Parr apparatus) at 40 psi during 96 h. The catalyst was filtered, and the solution, after neutralization, was extracted with chloroform. The extracts were washed, dried, and finally evaporated to dryness, thus providing 0.6 g (74%) of **3**: mp 180–2 °C (lit.[21] mp 180–2 °C); ^1H NMR ($CDCl_3$ + CD_3OD) 6.83 (d, J = 7.8 Hz, 1 H), 6.55 (d, J = 7.8 Hz, 1 H), 6.50 (s, 1 H), 3.53 (s, 2 H), 2.75 (m, 4 H), 2.44 (s, 3 H) ppm.

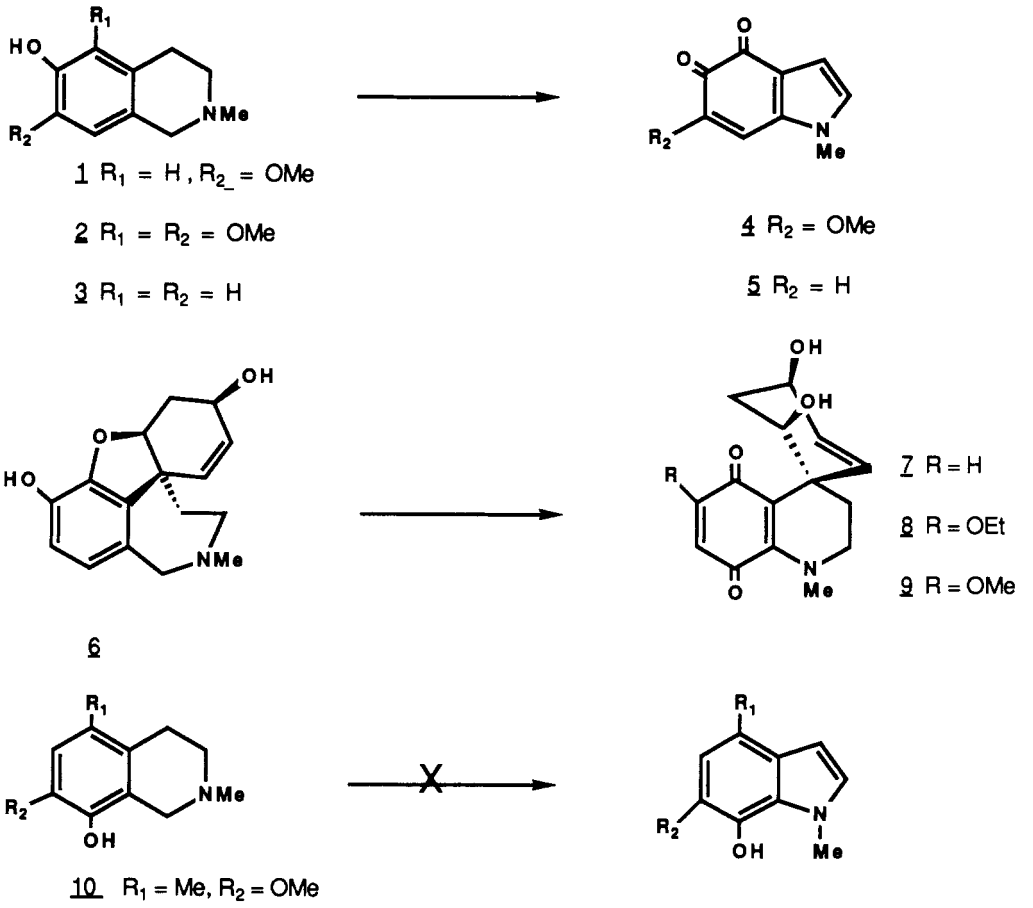
General Procedure for the Fremy's Salt Oxidative Degradation of 6-Hydroxytetrahydroisoquinolines and 7-Hydroxybenzazepines. Preparation of *N*-Methyl-6-methoxy-4,5-indoloquinone (4) by Oxidation of 1. To a vigorously stirred solution of 1.7 g of Fremy's salt in 20 mL of buffer, pH = 6.1 (Na_2HPO_4, NaH_2PO_4), a methylene chloride solution of **1**[11c] (0.23 g, 1 mmol) was added. Stirring was continued for 15 min, during which time the mixture turned dark blue. The organic phase was separated, and the aqueous solution further extracted (5 × 20 mL). The combined extracts were washed, dried over anhydrous Na_2SO_4, and evaporated to dryness. The dark solid obtained was chromatographed on silica gel. Elution with methylene chloride yielded **4** in 52–65% yield as dark violet crystals, mp 236–8 °C ($CHCl_3$); λ_{max} (EtOH) 230, 355, 570 nm; IR (KBr) 1650, 1645, 1632, 1600, 1500, 1452, 1265, 1230, 1090, 1060 cm^{-1}; ^1H NMR 6.48 (s, 2 H), 6.11 (s, 1 H), 3.72 (s, 3 H), 3.60 (s, 3 H) ppm; ^{13}C NMR (DMSO-d_6) 179.10, 170.86, 150.25, 139.37, 127.14, 116.88, 108.93, 102.40, 56.01, 33.56 ppm; EIMS, *m/e* (%) 191(M^+, 39), 163 (36), 148(100), 120(21), 92(34); HRMS calculated for $C_{10}H_9O_3N$ 191.0582, found 191.0564.

(19) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Higa, T.; Sakai, R. *J. Org. Chem.* **1988**, *53*, 4127.

(20) Ranieri, R. L.; McLaughlin, J. L. *J. Org. Chem.* **1976**, *41*, 319.

(21) Menachery, M. D.; Lavanier, G. L.; Wetherly, M. L.; Guinaudeau, H.; Shamma, M. *J. Nat. Prod.* **1986**, *49*, 745.

Scheme III



Preparation of *N*-Methyl-6-methoxy-4,5-indoloquinone (4) by Oxidation of 2. Treatment of **2** (0.1 g, 0.51 mmol) with Fremy's salt, as above, yielded a dark solid showing mainly a blue and a yellow spot in TLC, the latter being rapidly converted into a second blue spot on exposure to air and light. Chromatography on silica gel preparative plates (successive elutions with methylene chloride were carried out to allow for total conversion of the yellow spot) yielded **4** in 39% yield as dark violet crystals, mp 236–8 °C ($CHCl_3$), identical with the one obtained above. A dark blue crystalline material of unknown structure[15] was isolated as a minor byproduct: mp 211–6 °C; λ_{max} (EtOH) 220, 370, 555 nm; IR (KBr) 3310, 1685, 1640, 1620, 1045, 885 cm^{-1}; ^1H NMR (CD_3Cl + CD_3OD) 8.5 (s, 1 H, OH), 7.01 (d, 1 H, J = 1.4 Hz), 6.61 (s, 1 H), 5.93 (s, 1 H), 3.90 (s, 3 H), 3.85 (s, 3 H), 3.78 (s, 3 H), 3.71 (s, 3 H) ppm; EIMS, m/e (%) 359 (M^+, 100), 316 (32), 273 (31), 245 (11), 230 (9); HRMS calculated for $C_{18}H_{17}O_7N$ 359.3366, found 359.1106.

Preparation of *N*-Methyl-4,5-indoloquinone (5) by Oxidation of 3. Oxidation of **3** (0.08 g, 0.49 mmol) as illustrated previously furnished crude **5**, which on flash chromatography on a short silica gel column (to avoid decomposition), gave pure **5** in 15–25% yield, as dark violet crystals: mp 113–4 °C (CH_2Cl_2); λ_{max} (EtOH) 239, 310, 348, 500 nm; IR (KBr) 1650, 1640 cm^{-1}; ^1H NMR 7.16 (d, 1 H, J = 10 Hz), 6.61 (s, 2 H), 5.96 (d, 1 H, J = 10 Hz), 3.66 (s, 3 H) ppm; ^{13}C NMR (DMSO-d_6) 183.6, 173.1, 130.4, 127.7, 123.7, 122.8, 110.8, 31.3 ppm; EIMS, m/e (%) 163 (M^+ + 2, 10), 162 (M^+ + 1, 9), 161 (M^+, 56), 133 (94), 105 (100), 78 (79); HRMS calculated for $C_9H_7O_2N$ 161.0476, found 161.0450.

In another experiment, the crude reaction mixture from the oxidation of **3** was treated with sodium dithionite. After a few minutes, the resulting colorless mixture was separated and the aqueous phase further extracted with chloroform. The combined extracts were washed, dried over anhydrous sodium sulfate, and evaporated to dryness. The crude material was then treated with excess acetyl anhydride (1 mL) in pyridine (1 mL) for 3 h. Standard workup provided the expected 4,5-diacetoxy-1-methylindole as crystals (CH_2Cl_2): mp 108–9 °C; ^1H NMR 7.28 (d, 1 H, J = 8.8 Hz), 7.02 (d, 1 H, J = 3 Hz), 7.00 (d, 1 H, J = 8.8 Hz), 6.35 (d, 1 H, J = 3 Hz), 3.74 (s, 3 H), 2.35 (s, 3 H), 2.29 (s, 3 H) ppm; EIMS, m/e (%) 247 (M^+, 27), 205 (26), 164 (24), 163 (100), 162 (48), 134 (35), 78 (22); HRMS calculated for $C_{13}H_{13}O_4N$ 247.0844, found 247.0832.

Fremy's Salt Oxidation of Sanguinine (6). Treatment of a $CHCl_3$–EtOH solution of sanguinine (**6**,0.06 g) with excess Fremy's salt as indicated in the general procedure yielded a crude mixture (29–40%) of a major, **8**, and a minor product, **7**, which were separated by preparative TLC chromatography (silica gel, chloroform).

7: wine-red prisms, mp 121–3 °C ($CHCl_3$); λ_{max} (EtOH) 310, 360, 510 nm; IR (KBr) 3400, 1665, 1625, 1535, 1400, 1380, 1330, 1100 cm^{-1}; EIMS, m/e (%) 275 (M^+, 13), 259 (62), 228 (44), 202 (69), 188 (36); ^1H NMR (250 MHz) 6.63 (d, 1 H, J = 9.9 Hz), 6.48 (d, 1 H, J = 9.9 Hz), 5.96 (ddd, 1 H, J = 10.1, 4.7, 1.5 Hz), 5.66 (1 H, s), 5.49 (ddd, 1 H, J = 10.1, 1.0, 1.6 Hz), 4.1 (m, 1 H), 3.98 (m, 1 H), 3.32 (s, 3 H), 2.27 (ddt, 1 H, J = 15.1, 4.3, 1.5, 1.5 Hz), 2.10 (ddd, 1 H, J = 15.1, 5.47, 2.0 Hz) ppm.

Treatment of a $CHCl_3$–EtOH solution of **7** (0.005 g) with Fremy's salt as above yielded **8** (0.003 g) identical (UV, IR, NMR, MS, TLC) with an authenticated sample (vide infra). **8**: wine-red prisms, mp 153–7 °C ($CHCl_3$); λ_{max} (EtOH) 307, 505 nm; IR (KBr) 3495, 3230, 1640, 1615, 1520, 1420, 1395, 1330, 1305, 1225, 1115 cm^{-1}; EIMS, m/e (%) 319 (M, 48), 301 (68), 272 (81), 246 (100), 218 (23), 216 (14), 202 (4), 190 (5); HRMS calculated for $C_{17}H_{21}O_5N$ 319.1418, found 319.1412; ^1H NMR (250 MHz) 5.96 (ddd, 1 H, J = 10.1, 4.7, 1.4 Hz), 5.66 (s, 1 H), 5.49 (ddd, 1 H, J = 10.1, 1.0, 1.5 Hz), 4.74 (d, OH), 4.1 (m, 1 H), 4.0 (m, 1 H), 3.9 (2 H, q, J = 7 Hz), 3.38 (s, 3 H), 3.08 (m, OH), 2.28 (ddt, 1 H, J = 15.0, 4.3, 1.6, 1.6 Hz), 2.08 (ddd, 1 H, J = 15.0, 5.4, 2.1 Hz), 1.48 (t, 1 H, J = 7 Hz) ppm; ^{13}C NMR ($CDCl_3$) 169.70 (s), 163.38 (s), 146.48 (s), 139.14 (s), 134.35 (d), 126.47 (d), 112.48 (s), 104.08 (d), 72.89 (d), 65.10 (d), 62.75 (t), 49.05 (t), 43.18 (q), 40.21 (t), 33.96 (t), 32.33 (t), 13.7 (q) ppm.

The oxidation of sanguinine **6** in $CHCl_3$–MeOH in otherwise identical conditions as above yielded a mixture of **7** and **9**. The major product **9** was isolated as a wine-red amorphous powder; λ_{max} (EtOH) 305, 510 nm; MS, m/e (%) 305 (M^+, 30), 289 (20), 258 (80), 232 (100), 188 (36); ^1H NMR (80 MHz) 6.01 (dd, 1 H,

J = 10.0, 3.5 Hz), 5.67 (s, 1 H), 5.55 (b s, 1 H), 5.44 (b s, 1 H), 3.80 (s, 3 H), 3.38 (s, 3 H) ppm.

Attempted Fremy's Salt Oxidation of 10. Treatment of a methylene chloride solution of **10**[17] with Fremy's salt as illustrated in the general procedure yielded recovered starting material. Neither operating at different pH (in the range of 4–10) nor using longer reaction times (up to 48 h) led to any improvement, starting material being recovered unchanged in ca. 70% yield.

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Registry No. 1, 13871-59-5; **2**, 123752-57-8; **3**, 14097-39-3; **4**, 123752-58-9; **5**, 123752-59-0; **6**, 60755-80-8; **7**, 123775-12-2; **8**, 123752-60-3; **9**, 123752-61-4; *N*-methyl-4,6-dihydroxy-1,2,3,4-tetrahydroisoquinoline, 23824-24-0; 4,5-dihydroxy-1-methylindole, 123752-62-5; 4,5-diacetoxy-1-methylindole, 123752-63-6; 6-[(dimethylamino)methyl]-3,4-dimethoxyphenol, 115320-11-1; 6-[(dimethylamino)methyl]-2-methoxy-4-methylphenol, 123752-64-7; 4,5-dimethoxy-1,2-benzoquinone, 21086-65-7; 3-methoxy-5-methyl-1,2-benzoquinone, 60824-63-7.

Synthesis and Synthetic Utility of 1-Acyl-5-(trialkylsilyl)-1,2-dihydropyridines. Synthesis of (±)-Elaeokanine A

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The regioselective addition of Grignard reagents to the phenoxycarbonyl salts of 3-(trialkylsilyl)pyridines was studied. Most of the 3-(trialkylsilyl)pyridine salts gave a mixture of dihydropyridines on reaction with aliphatic Grignard reagents. However, all reactions using alkyl or aryl Grignard reagents and the 1-phenoxycarbonyl salt of 3-(triisopropylsilyl)pyridine, or 4-chloro-3-(triisopropylsilyl)pyridine, gave exclusively 1,2-dihydropyridines resulting from attack of the Grignard reagents at the C-6 position of the pyridinium salt. Vilsmeier–Haack formylation of 2-alkyl(aryl)-1-(phenoxycarbonyl)-5-(triisopropylsilyl)-1,2-dihydropyridines **8g,h** and **10h** occurs at C3. Friedel–Crafts acylation of 5-(trialkylsilyl)dihydropyridines **10** gave C-5 acylation via ipso substitution. In contrast, acylation of **10f,h,i** with acyl triflates gives C-3 substitution. The triisopropylsilyl group of the C-3 acylated 1,2-dihydropyridines could be removed on reaction with HBr/HOAc in methylene chloride. The methodology developed for the regiospecific formation and acylation of 5-(triisopropylsilyl)-1,2-dihydropyridines was utilized in the total synthesis of the indolizidine alkaloid, (±)-elaeokanine A. The synthesis was achieved in a regiospecific manner from 3-(triisopropylsilyl)pyridine in six steps.

Over the years there has been considerable interest in 1-acyl-1,2-dihydropyridines as intermediates for the synthesis of substituted pyridines[2,3] and natural products.[2,4] Fowler's discovery that pyridine could be reduced by sodium borohydride in the presence of an alkyl chloroformate provided synthetic chemists with convenient access to 2-unsubstituted 1-(alkoxycarbonyl)-1,2-dihydropyridines.[5] These relatively stable dihydropyridines proved to be interesting dienes for the Diels–Alder reaction and have been utilized by several research groups for the synthesis of alkaloids and novel ring systems. Although Fraenkel and co-workers[6] reported in 1970 that Grignard reagents react with 4-picoline in the presence of ethyl chloroformate to provide 2-substituted 1-(ethoxycarbonyl)-1,2-dihydropyridines, this reaction was not utilized until recently for natural product synthesis. One of the reasons for this slow development is the lack of regioselectivity found with aliphatic Grignard reagents. Although aryl,[7] vinyl,[8] and alkynyl[8,9] Grignard reagents give mainly 1,2-dihydropyridines, most alkyl[7a] Grignard reagents give mixtures of 1,2- and 1,4-dihydropyridines. The synthetic potential of 1-acyl-2-alkyl-1,2-dihydropyridines prompted us to develop a regiospecific synthesis of these heterocycles from alkyl Grignard reagents, a chloroformate, and 4-(trimethylstannyl)pyridine.[4g] The trimethylstannyl substituent acts as a removable blocking group. We also

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