Ketal Preparations. The procedures used to obtain the data in Table I were uniform for all the substrates. Representative examples are given of the better yield methods.

1,3-Dihydro-1-ethoxy-1-methylisobenzofuran (3a). (a) Reaction of 2 with Me_2Mg. Dimethylmagnesium was prepared by the dropwise addition of 34 mL of dioxane in 60 mL of ether to 109 mL of 2.75 M MeMgBr in ether, in a Schlenk flask at ambient temperature. After 20 h of stirring, the white solid was removed by filtration. An aliquot of the solution was titrated with 0.1 M HCl and found to be 0.65 M in Me_2Mg (83%). To a portion (15.5 mL, 10.0 mmol) of this solution at -78 °C was added 1.0 g (4.0 mmol) of **2** in one portion. The resulting slurry was allowed to warm gradually to 0 °C over 1.75 h and then quenched with $NaHCO_3$ solution. The usual workup gave 803 mg of crude material, which was chromatographed on basic alumina, using hexanes containing 0.5% Et_3N, to afford 355 mg (50%) of pure **3a**: ^1H NMR δ 1.11 (t, 3 H, J = 7 Hz), 1.72 (s, 3 H), 2.93-3.05 (m, 1 H), 3.33-3.45 (m, 1 H), 5.04 (d, 1 H, J = 13 Hz), 5.15 (d, 1 H, J = 13 Hz), 7.21-7.27 (m, 1 H), and 7.28-7.40 ppm (m, 3 H). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.88; H, 7.81.

(b) Reaction of 2 with MeLi. Commercial low halide MeLi (120 mL of 0.31 M in ether, 37.2 mmol) was placed in a 200-mL round-bottom flask with a stir bar and cooled to -78 °C. The salt **2** (7.5 g, 30.0 mmol) was added in one portion, and the resulting slurry was allowed to warm gradually to -10 °C, with stirring over a period of 26 h. It was then quenched by careful addition of 50 mL of saturated $NaHCO_3$ solution. The usual treatment gave 5.2 g of crude product as a yellow oil, which was distilled to give 2.96 g (55%) of pure **3a**, bp 54-57 °C (0.3 Torr).

(c) Reaction of Phthalide with MeLi. To 1.007 g (7.51 mmol) of phthalide in 50 mL of ether at -78 °C was added 5.9 mL (8.25 mmol) of MeLi (1.4 M in ether). After this mixture was stirred in the dry ice bath for 4 h, 5 mL of EtOH was added, and the majority of the solvent was removed by rotary evaporation. An additional 30 mL of EtOH was added, followed by 3 mL of glacial HOAc. This colorless solution was stirred at room temperature for 5 h, poured into 150 mL of saturated $NaHCO_3$, and extracted with CH_2Cl_2 (4 × 5 mL). The usual brine wash, drying, and evaporation gave 1.29 g of crude material. Chromatography as in (a) gave 1.02 g (76%) of pure **3a**.

1-Butyl-1,3-dihydro-1-ethoxyisobenzofuran (3b). (a) Reaction of 2 with *n*-BuLi. Commercial *n*-BuLi (18.75 mL, 1.6 M in hexane, 30 mmol) was placed in a round-bottom flask, and the hexane was removed under vacuum. Diethyl ether (80 mL) was added. After cooling as in (b) above, **2** (5.1 g, 20.4 mmol) was added, and the stirred mixture was allowed to warm to -10 °C over a period of 16 h. The usual workup gave 4.4 g of crude product. Short path distillation gave 180 mg (4%) of the diethyl ortho ester **7**, followed by 2.14 g (48%) of **3b**: colorless oil; bp 69-71 °C (0.07 Torr); ^1H NMR δ 0.84 (t, 3 H, J = 7 Hz), 0.96-1.42 (m, 4 H), 1.09 (t, 3 H, J = 7 Hz), 1.93-2.13 (m, 2 H), 2.93 (dq, 1 H, J = 9 and 7 Hz), 3.36 (dq, 1 H, J = 9 and 7 Hz), 5.03 (d, 1 H, J = 13 Hz), 5.16 (d, 1 H, J = 13 Hz), and 7.20-7.40 ppm (m, 4 H). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.42; H, 9.23.

(b) Reaction of Phthalide with *n*-BuLi. A solution of 1.01 g (7.51 mmol) of phthalide in 50 mL of ether at -70 °C was treated with 5.1 mL (8.26 mmol) of *n*-BuLi in hexane. Subsequent treatment was the same as in (c) above; chromatography gave 1.01 g (61%) of pure **3b**.

1,3-Dihydro-1-ethoxy-1-phenylisobenzofuran (3c). (a) Reaction of 2 with $Ph_2CuCNLi_2$. The homogeneous reagent prepared from 790 mg (8.8 mmol) of CuCN and 10.4 mL (17.6 mmol) of PhLi (1.7 M in cyclohexane/ether) in 50 mL of ether was cooled in the usual way, and 2.0 g (8.0 mmol) of **2** was added on one portion. This slurry was stirred for 20 h while warming to 20 °C. Saturated NH_4Cl solution, brought to pH 8 by the addition of concentrated NH_4OH, was added. The layers were separated, and the aqueous phase was extracted with ether (3 × 30 mL). The usual treatment gave 2.02 g of crude product, which was chromatographed as above to furnish 938 mg (49%) of pure **3c** as a colorless oil: ^1H NMR δ 1.20 (t, 3 H, J = 7 Hz), 3.31 (dq, 1 H, J = 9 and 7 Hz), 3.50 (dq, 1 H, J = 9 and 7 Hz), 5.25 (d, 1 H, J = 13 Hz), 5.34 (d, 1 H, J = 13 Hz), 7.20-7.38 (m, 7 H), and 7.58-7.63 ppm (m, 2 H). Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.87; H, 6.62.

(b) Reaction of Phthalide with PhLi. The reaction was done on the same scale and in the same manner as for the aliphatic derivatives above, except for the use of PhLi. Chromatography gave 1.034 g (58%) of pure **3c**.

1,3-Dihydro-1-ethoxy-1-(4-pentenyl)isobenzofuran (3d). The method of Perry et al.[16] was used to convert commercial 4-penten-1-ol to 1-bromo-4-pentene. A solution of 12.5 g (0.084 mol) of the bromide in 10 mL of ether was added via syringe pump (0.5 h) to 2.4 g (0.35 mol) of finely dispersed Li in 35 mL of ether held in an ice bath. After 2 h of stirring at this temperature, the mixture was filtered under N_2 through Celite to give a clear solution of titre 0.85 M (56%). A portion of this material (48 mL, 40.8 mmol) and an additional 80 mL of ether was brought to -70 °C and treated with 8.0 g (32 mmol) of **2** in the usual way. Gradual warming to -10 °C over 12 h followed by the usual workup gave 8.6 g of yellow oil. Short-path distillation gave 4.20 g (56%) of ca. 90% pure **3d**: bp 73-75 °C (0.05 Torr); ^1H NMR δ 1.09 (t, 3 H, J = 7 Hz), 1.12-1.25 (m, 1 H), 1.41-1.56 (m, 1 H), 1.93-2.14 (m, 4 H), 2.88-2.98 (m, 1 H), 3.30-3.40 (m, 1 H), 4.87-4.99 (m, 2 H), 5.11 (d, 1 H, J = 13 Hz), 5.16 (d, 1 H, J = 13 Hz), 5.66-5.80 (m, 1 H), and 7.21-7.39 ppm (m, 4 H); MS calcd for $C_{15}H_{19}O_2$ (P-H) 231.1347, found, 231.1366.

Efforts to purify this material further by repeating the distillation and by chromatography were unsuccessful. Reactions of **3d** which assure the correctness of this structure have been reported previously.[13]

2-(2-(Hydroxymethyl)phenyl)-2-propanol (8). This diol was formed in essentially quantitative yield by the treatment of phthalide with excess MeMgBr or MeLi and constituted half of the material recovered from treatment of phthalide with 1 equiv of MeMgBr, as described in the text. It was characterized by ^1H NMR (60 MHz) δ 1.63 (s, 6 H), 3.80 (br s, 2 O-*H*), 4.74 (s, 2 H), and 7.23 (br s, 4 H).

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Varamines A and B, New Cytotoxic Thioalkaloids from *Lissoclinum vareau*

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The prolific variety of nitrogenous natural products obtained from tunicates (ascidians) portrays these marine animals as specialists in the production of unusual alkaloids. It is noteworthy that some 90% of reported tunicate secondary metabolites are nitrogenous,[1] most having highly modified amino acid or peptide structures.[2] Our interest in the chemistry of tunicates is drawn to these uncommon alkaloids, many with remarkable bioactivity. We report two new cytotoxic alkaloids, varamines A (**1**) and B (**2**).

Lissoclinum vareau (Monniot and Monniot, 1987), a bright red, thinly encrusting tunicate, was collected in shallow waters off the Yasawa island chain, in the Fiji Island group. Assay of the crude methanol extract of this tunicate revealed potent antifungal activity (zone of inhibition of 35 mm in a disk diffusion assay) and cytotox-

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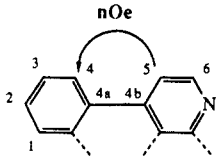
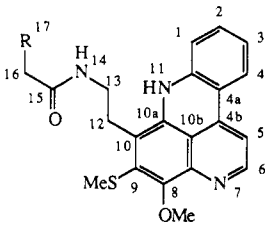
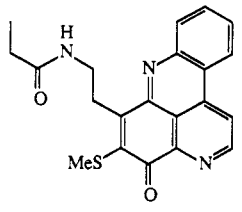


Figure 1.

icity against the L1210 murine leukemia cell line. Solvent partition of the crude extract and extensive chromatographic purification of the chloroform-soluble fraction allowed separation of two brilliant red pigments, varamine A (1) and varamine B (2), both isolated as trifluoroacetate salts. These were readily converted to their respective free bases upon treatment with potassium carbonate. Varamines A (1) and B (2) are tetracyclic heteroaromatic bases, an unusual departure from the secondary metabolites previously reported from *Lissoclinum* spp. which, typically, are modified thiazole-containing cyclic peptides[3] and macrolides.[4] In fact, 1 and 2 are members of a growing class of marine alkaloids, e.g. amphimedine, obtained from several unrelated marine organisms.[5]



1 R = Me
2 R = H



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Preliminary comparison of the spectral data of 1 and 2 showed the two compounds were related as homologues, and structure elucidation was carried out primarily on the trifluoroacetate salt of 1. Accurate mass measurement of the parent ion at m/z 394.1589 (MH^+; Δ = +0.3 mmu) in the fast atom bombardment mass spectrum of varamine A (1) provided the formula $C_{22}H_{23}N_3O_2S$. The ultraviolet spectrum of the free base of 1 was richly detailed and revealed strong bands from 232 to 494 nm. In particular, the striking color change from yellow to intense red upon acidification of the free base of 1 was correlated with a reversible bathochromic shift of λ_{max} 464 nm (ϵ 5170) to 527 (5670).

The ^1H NMR spectrum of the TFA salt of 1 displayed the best dispersion in methanol-d_4. Single frequency decoupling and double quantum filtered phase-sensitive COSY[6] verified four spin coupled networks. Six proton signals found between δ 7.20 and 8.30 ppm were assigned to deshielded protons in a heteroaromatic nucleus. The coupled one-proton signals at δ 7.52 (d, J = 6.5 Hz) and 8.21 (d, J = 6.5 Hz) were assigned to H-5 and H-6, respectively, in a trisubstituted pyridine (Figure 1). The spin system H-1,2,3,4 (8.09, d, J = 8.2 Hz; 7.27, dd, J = 8.2, 7.3 Hz; 7.66, dd, J = 8.3, 7.3 Hz; 7.77, d, J = 8.3 Hz) constituted signals of a disubstituted benzene. A strong nuclear Overhauser effect from H-5 to H-4 (14%) implied close proximity of the respective ring residues as shown in Figure 1. The remaining proton signals were an A_2B_2 system, assigned to a 1,2-disubstituted ethane (3.23, m, 2 H; 3.33, m, 2 H[7]), an aryl methoxyl group (4.00, s, 3 H), an aryl thiomethyl group (2.66, s, 3 H), two broad, exchangeable NH signals (6.2, 10.2), and a propionamide residue (2.35, q, 2 H, J = 7.6 Hz; 1.24, t, 3 H, J = 7.6 Hz). The latter was also supported by the infrared spectrum, which displayed an amide carbonyl stretching band at 1650 cm^{-1}, in addition to several NH stretching bands at 3450, 3280, and 3200 cm^{-1}.

A thiomethyl group (SCH_3) is proposed to account for the deshielded methyl proton signal (2.66, s, 3 H), which correlated with the relatively high field carbon signal (18.7, q). The observation of only one COLOC correlation from δ 2.66 to an aromatic carbon (140.5, s) is more consistent with CH_3–X–Ar than CH_3–Ar. Additional evidence comes from $^1J_{CH}$ values for the methyl groups; these were most easily obtained by measuring the separation of the inner peaks of the methyl ^{13}C satellites in the proton spectra of 1 or 2. The moderately large one-bond coupling constant ($^1J_{CH}$ = 141 Hz) for the methyl carbon at 18.7 ppm is similar to that measured for the electronegative methoxyl group (60.4, s, $^1J_{CH}$ = 146 Hz). This contrasts with lower values measured for the acetamide methyl in varamine B (2) and toluene ($^1J_{CH}$ = 129 and 126 Hz, respectively). Clearly, the δ 2.66 methyl is attached to a heteroatom, X = S or N. This must be SCH_3 because the substitution on each of the three nitrogens has been accounted for.

The ^{13}C NMR spectrum of 1 (Table I) was assigned on the basis of heteronuclear correlation spectroscopy[8] (direct ^1H–^{13}C correlation[9] and COLOC[10]) and comparison with the spectral data of similar alkaloids. The observed correlations also verified the positions of some of the aromatic substituents. A three-bond correlation from the methoxyl proton signal (4.00, s, 3 H) was seen to C-8 (140.9, s). Long-range correlations were seen from protons of one of the unresolved H-12/H-13 methylene protons to the C-15 carbonyl group (178.8, s) as well as to C-9, C-10, and C-10a (140.5, s; 119.3, s; and 134.0, s, respectively). The C-9 signal was further correlated to the thiomethyl protons (2.65, s, 3 H); therefore, the vicinal C-12 and C-13 methylenes were positioned between the propionamide group and the heteroaromatic nucleus, ortho with respect to the thiomethyl ether as shown in 1. The latter arrangement is supported by the prominent mass spectral fragmentation ion at m/z 293.0746 (Δ = –0.3 mmu), due to loss of the

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(5) For example, the following alkaloids have been isolated from (i) sponges [(a) Amphimedine from *Amphimedon* sp. (Schmitz, F. J.; Agarwal, S. K.; Gunasekera, S. P.; Schmidt, P. G.; Shoolery, J. N. *J. Am. Chem. Soc.* **1983**, *105*, 4835). (b) Dercitin from *Dercites* sp. (Gunawardana, G. P.; Kohmoto, S.; Gunasekera, S. P.; McConnell, O. J.; Koehn, F. E. *J. Am. Chem. Soc.* **1988**, *110*, 4856). (c) Petrosamine from *Petrosia* sp. (Molinski, T. F.; Fahy, E.; Faulkner, D. J.; van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 1340)], from (ii) tunicates [(d) Shermilamine A from *Tridemnum* sp. (Cooray, N. M.; Scheuer, P. J.; Parkanyi, L.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 4619). (e) Segoline A (5), isosegoline A, and norsegoline from *Eudistoma* sp. (Rudi, A.; Benayahu, Y.; Goldberg, I.; Kashman, Y. *Tetrahedron Lett.* **1988**, *29*, 3861). (f) Ascididemin from *Didemnum* sp. (Kobayashi, J.; Cheng, J.; Nakamura, H.; Ohizumi, Y.; Hirata, Y.; Sasaki, T.; Ohta, T.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 1177)], and from (iii) the sea anemone *Calliactis parasitica* [(g) Calliactine (Cimino, G.; Crispino, A.; de Rosa, S.; de Stefano, S.; Gavagnin, M.; Sodano, G. *Tetrahedron* **1987**, *43*, 4023)].

(6) Rance, M.; Sørensen, O. W.; Bodenhausen, G.; Wagner, G.; Ernst, R. R.; Wüthrich, K. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 479.
(7) Resolved only at 500 MHz, in methanol-d_4. At lower field strength or in other solvents these signals were seen as a four-proton broad singlet or multiplet.
(8) Carried out at 50.3 MHz in CD_3OD.
(9) Bax, A.; Morris, G. *J. Magn. Reson.* **1981**, *42*, 501.
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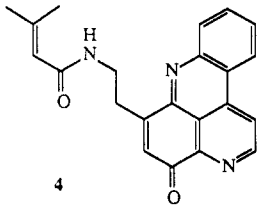
Table I. NMR Spectra of Varamine A (1)

atom no.	^{1}H NMR (200 MHz, multiplicity, J in Hz) TFA salt, CD_3OD	^{1}H NMR (200 MHz, multiplicity, J in Hz) free base, $CDCl_3$	^{13}C NMR (50.3 MHz) TFA salt, CD_3OD	^{13}C NMR (50.3 MHz) COLOC[10]
1	8.09 (d, 8.2)	7.87 (dd, 8.4, 1.2)	126.2 d	C-11a, C-3
2	7.27 (dd, 8.2, 7.3)	7.04 (td, 8.4, 1.3)	124.8 d	
3	7.66 (dd, 8.3, 7.3)	7.43 (td, 8.4, 1.2)	136.5 d	
4	7.77 (d, 8.3)	7.51 (d, 8.4, 1.3)	119.5 d	C-11a, C-2
4a			116.0 s[b]	
4b			132.6 s	
5	7.52 (d, 6.5)	7.30 (d, 5.2)	106.4 d	C-10b or C-4a
6	8.21 (d, 6.5)	8.67 (d, 5.2)	143.8 d	C-7a, C-4b
7a			150.5 s	
8			140.9 s	
9			140.5 s	
10			119.3 s	
10a			134.0 s	
10b			120.6 s[b]	
11		10.2 (bs)		
11a			142.2 s	
12	3.23 (m)[a]	3.3 (m)	29.3 t	C-10a, C-9
13	3.33 (m)[a]	3.3 (m)	38.8 t	C-15, C-10, C-12
14		6.22 (bs)		
15			178.8 s	
16	2.35 (q, 7.6)	2.38 (q, 6.5)	30.0 t	
17	1.24 (t, 7.6)	1.29 (t, 6.5)	10.4 q	
O-Me	4.00 (s)	4.05 (s)	60.4 q	C-8
S-Me	2.66 (s)	2.53 (s)	18.7 q	C-9

[a] Resolved at 500 MHz. [b] Assignments with the same superscript are interchangeable.

$C_5H_{10}NO$ side chain from the molecular ion.

The methoxyl group was also best placed ortho to the thiomethyl ether. Conclusive evidence that it resided at C-10 was provided by oxidative demethylation[11] of 1 (ceric ammonium nitrate, 2:1 CH_3CN/H_2O, 25 °C) to afford imino quinone **3** (mp 205–207 °C) in high yield. The FAB mass spectrum of **3** gave a parent ion (m/z 380) corresponding to a reduced species, $MH^+ + H_2$, a feature common to related iminoquinones.[12,13] Iminoquinone **3** retained the *S*-methyl group (δ_H 2.65 s, 3 H; δ_C 17.9 q) but lacked the methoxyl signal (4.00 s, 3 H), present in **1**. Furthermore, the ^{13}C NMR spectrum of the new compound **3** now displayed a conjugated ketone signal at 179.6 ppm (ν 1660 cm^{-1}). The UV and ^{13}C NMR spectra of **3** are more consistent with a *p*-iminoquinone and are analogous to those of cystodytin A (**4**), recently reported[13] from the tunicate, *Cystodytes dellechiajei*, collected in Okinawa. In addition the ^{13}C NMR spectrum of **1** is very similar to that of segoline A (**5**).[5e] Consequently, structure **1** was favored for varamine A over alternative isomers.



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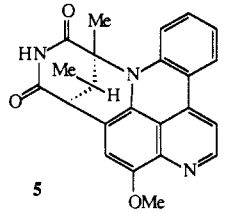

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Varamine B (**2**) gave UV, IR, ^{1}H NMR, and ^{13}C NMR spectral data almost identical with those of **1** with the following differences. FAB mass spectroscopic measurements (m/z 380, MH^+) gave a formula of $C_{21}H_{21}N_3O_2S$, and therefore varamine B (**2**) was a lower homologue of **1**. The ^{1}H NMR and ^{13}C NMR spectra of **2** lacked the ethyl side chain signals of **1** and displayed signals, ascribed to an acetamido side chain (δ_H 2.08, s, 3 H: δ_C 22.5, q; 175.2, s). The remainder of the spectra were essentially identical with those of **1**.

Neither varamine A (**1**) or varamine B (**2**) was active against *Candida albicans*. Both compounds, however, were shown to be cytotoxic towards L1210 murine leukemia cells with IC_{50}'s of 0.03 ad 0.05 μg/mL, respectively. The varamines are about 1 order of magnitude more toxic than the cystodytins, which possess the same heteroaromatic carbon skeleton but lack the thiomethyl group.[13]

Experimental Section[14]

Lissoclinum vareau (Monniot and Monniot, 1987) was collected at −10 m in the Yasawa island group, Fiji (November 1987), and frozen until used. Freeze-dried animals (71.2 g) were homogenized in a blender with methanol and filtered, and the clear red filtrate was concentrated to approximately 500 mL. The methanol extract was successively extracted with a modified Kupchan partition with hexanes, carbon tetrachloride, chloroform, and 1-butanol. The chloroform extract (480 mg) inhibited the growth of *Candida albicans*. Elution of this extract through a column of Sephadex LH20 (90 × 2 cm), with methanol, afforded a bright red glass (122.8 mg). A portion of this material (100 mg) was separated by flash chromatography (C-18 bonded silica; 60% methanol in water to 100% methanol) to give, in order of elution, two active fractions; A (49.1 mg) and B(42.1 mg), and a nonpolar inactive fraction. Fraction B was separated by HPLC (Dynamax C_{18}, 55% acetonitrile/0.1% aqueous trifluoroacetic acid) to give an active component followed by varamine B (**2**, 15.0 mg, 0.026% of dry weight) and varamine A (**1**, 21.9 mg, 0.038%), each obtained as the trifluoroacetate salt (bright red glass). Treatment of a solution of either **1** or **2** in 1:9 methanol/dichloromethane with potassium carbonate followed by filtration through a short column of silica gave the respective free base (orange solid) after removal of solvent.

Varamine A (1): $C_{22}H_{23}N_3O_2S$; UV (MeOH, free base) λ_{max} 232 (ϵ 31 500), 275 (25 800), 292 (sh), 324 (sh), 382 (3530), 464 (5170), 494 (sh); (pH 2) 224 (24 400), 228 (sh), 240 (sh), 263 (sh), 280 (sh), 291 (31 100), 339 (20 400), 359 (4520), 376 (4640), 527 (5670), 552 (sh); IR ($CHCl_3$) ν_{max} 3450, 3280, 3200, 1650, 1615 cm^{-1}; ^{1}H NMR and ^{13}C NMR, see Table I; FABMS m/z 394 (MH^+, 100), 293 ($M^+ - C_5H_{10}NO$, 43); HRMS found m/z 394.1592 (MH^+), $C_{22}H_{24}N_3O_2S$ requires 394.1589.

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Varamine B (2): $C_{21}H_{21}N_3O_2S$; UV (MeOH, free base) λ_{max} 234 nm (ϵ 25900), 274 (21400), 292 (sh), 324 (sh), 382 (3040), 462 (4320), 491 (sh); (pH 2) 223 (20570), 238 (sh), 266 (sh), 282 (sh), 294 (27400), 311 (17300), 362 (sh), 379 (4190), 529 (4720), 552 (4230); IR ($CHCl_3$) ν_{max} 3450, 3280, 3200, 1650, 1617 cm^{-1}; ^1H NMR (TFA salt, CD_3OD), identical with that of 1 except for δ 2.08 (s, 3 H, H-16) and absence of H-17 (see Table I); ^{13}C NMR (TFA salt, CD_3OD), identical with that of 1 except for δ 22.5 (s, C-16), 175.2 (s, C-15), and the absence of C-17 (see Table I); FABMS m/z 380 (MH^+, 100); HRMS found m/z 380.1420 (MH^+), $C_{21}H_{22}N_3O_2S$ requires 380.1433.

Oxidative Demethylation of Varamine A (1). Aqueous ceric ammonium nitrate (0.28 mL, 0.31 M, 87 μmol) was added to a stirred solution of varamine A TFA salt (1, 11.3 mg, 26.3 μmol) in 2:1 acetonitrile/water (5.0 mL) at 25 °C. After 1 min the red solution turned yellow, and TLC indicated the absence of starting material. After 6 min the mixture was diluted with water and extracted twice with ethyl acetate. The combined organic extracts were washed with brine and dried over sodium sulfate, and the solvent was removed to give iminoquinone **3** (9.0 mg, 90%). Chromatography over silica (2% methanol in dichloromethane) and crystallization from methanol gave compound **3** as fine golden needles.

Imino quinone 3: mp 205–207 °C; $C_{21}H_{19}N_3O_2S$; UV (MeOH) λ_{max} 262 nm (ϵ 25000), 299 (15200), 322 (sh), 373 (5300), 447 (3700); IR ($CHCl_3$) ν_{max} 3450, 3000, 1668, 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7.6 Hz), 2.14 (q, 2 H, J = 7.6 Hz), 2.65 (s, 3 H), 3.76 (m, 4 H), 6.30 (b s, 1 H, NH), 7.82 (td, 1 H, J = 8.0, 1.4 Hz), 7.95 (td, 1 H, J = 8.0, 1.4 Hz), 8.29 (dd, 1 H, J = 8.0, 1.4 Hz), 8.45 (d, 1 H, J = 5.6 Hz), 8.52 (dd, 1 H, J = 8.0, 1.4 Hz), 9.15 (d, 1 H, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 9.7 (q), 17.9 (q), 29.6 (t), 29.9 (t), 39.8 (t), 117.4 (s), 119.4 (d), 121.5 (s), 122.9 (d), 129.8 (d), 131.8 (d), 131.9 (d), 137.2 (s), 143.3 (s), 145.6 (s), 146.7 (s), 149.7 (s), 149.9 (d), 151.8 (s), 174.1 (s), 179.6 (s); FABMS m/z 380 ($MH^+ + H_2$, 100), 378 (MH^+, 25).

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Using Electron-Transfer Reactions To Propagate Radical Chain Processes[1]

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The invention of radical-based methods for organic synthesis is an activity that has flourished over the last decade.[2,3] Many of the advances have depended upon a thorough knowledge of the relevant reaction kinetics so that highly reactive radical intermediates could be used in a controlled way. Designing new reactions using kinetic data is highly attractive since it allows the practitioner to select viable schemes with minimal expenditure of labor. While this approach has been highly refined for simple radical reactions, there exists an entire class of processes that are amenable to quantitative design and yet which appear not to have been exploited in a systematic way. These are single-electron-transfer reactions involving organic free radicals and neutral molecules.[4] In principle, the reaction thermodynamics are accessible from redox potentials and the reaction rate constants can be estimated by Marcus theory.[5]

Table I. Kinetic Chain Lengths, kcl, for the Electron-Transfer Chain Reduction of Isopropyl Bromoacetate by Isopropyl Alcohol[a]

time, min	[I-Br], mM	[I-H], mM	kcl
	$(CH_3)_2CHOH$		
0	200.0	0	58.3
10	74.3	91.6	23.2
20	31.1	147.7	9.2
30	2.6	168.8	3.7
	$(CD_3)CDOD$		
0	200.0	0	14.7
10	173.0	16.0	15.4
20	151.8	30.6	16.0
30	132.1	42.3	16.7
60	96.6	69.3	19.0
90	66.9	91.6	21.6

[a] kcl = R_p/R_i = (-d[I-Br]/dt)/(-d[benzophenone]/dt).

In this work, we have designed some simple radical chain reactions that incorporate an electron-transfer step. The radical, $(CH_3)_2\dot{C}OH$, was chosen as a reactant since it is very readily oxidized.[6-11] In fact, its oxidation potential versus the saturated calomel electrode (SCE) is −0.60 V in acetonitrile,[12,13] −1.11 V in isopropyl alcohol/acetonitrile (3:1, v/v),[12] and −1.3 V in water.[14] The values are below the reduction potentials of several possible substrates. Of these, we selected bromoacetates since, on reduction, they form carbon-centered radicals by loss of bromide ion. Reduction potentials for bromoacetates are ≥−0.88 V versus SCE[15] so that in isopropyl alcohol/acetonitrile mixtures, electron transfer between radical and substrate will be exothermic by at least 0.2 eV (5 kcal mol^{-1}). However, poorly defined values of the reorganization energy (λ_0) preclude calculation of an accurate reaction rate constant using Marcus theory.[5]

The efficacy of the reaction was tested by photolyzing (350 nm, Rayonet reactor at 30 °C) a mixture of benzophenone (0.01 M) and isopropyl bromoacetate, I-Br (0.20 M), in isopropyl alcohol hydrogen bromide formed in the reaction, eq 1–5 (R = CH_3). The rates of product formation were monitored as a function of time by using quan-

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