25: mp 186 °C (dec, recryst from AcOEt); ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 9 H, Me_3), 2.53 (d, 1 H, J = 14.9 Hz, SiCH*H*), 3.73 (dd, 1 H, J = 7.5, 8.8 Hz, CHCH*H*-), 3.83 (d, 1 H, J = 14.9 Hz, SiC*H*H), 4.43 (d, 1 H, J = 4.4 Hz, NH), 4.47 (dd, 1 H, J = 3.2, 7.5 Hz, CHC*H*H-), 4.83-4.88 (m, 1 H, C*H*CH_2), 6.73-8.31 (m, 9 H, Ar H); IR (Nujol) 3280, 1670, 1620 cm^{-1}. Anal. Calcd for $C_{21}H_{24}N_4O_2Si$: C, 64.26; H, 6.16; N, 14.27. Found: C, 63.62; H, 6.16; N, 14.25.

General Procedure for Thermal Reaction of *N*-[(Trimethylsilyl)methyl]azinone 3 with *p*-Chloroacetophenone (6). A mixture of **6** (200 mg, 1.3 mmol) and **3** (1.2 molar equiv/mol of **6**) was stirred under the conditions described in Table I. Then 6 N HCl (2 mL) and MeOH (2 mL) were added and the mixture was stirred at room temperature for 6 h. The reaction mixture was poured into 5% NaOH and extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (entry 13) and recrystallization, and the results are summarized in Table I (entries 13 and 14).

Thermal Reaction of 1-[(Trimethylsilyl)methyl]-4-pyridone (3e) with Diethyl Acetylenedicarboxylate (27). A mixture of **3e** (200 mg, 1.1 mmol), **27** (235 mg, 1.6 mmol), and dry THF (1 mL) was refluxed for 8 h. The reaction mixture was evaporated to remove THF and chromatographed on silica gel. The fractions eluted with AcOEt-benzene (1:2) gave 24 mg (11%) of diethyl 7-hydroxyindolizine-1,2-dicarboxylate (**30**): mp 194-196 °C (MeOH-AcOEt); ^{1}H NMR (DMSO-d_6) δ 3.70 (s, 3 H, Me), 3.75 (s, 3 H, Me), 6.53 (dd, 1 H, J = 2.4 and 6.9 Hz, 6-position of indolizine ring) 7.24 (d, 1 H, J = 2.4 Hz, 8-position), 7.70 (s, 1 H, 3-position), 8.25 (d, 1 H, J = 6.9 Hz, 5-position); IR (Nujol) 3125, 1725, 1645, 1635 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.80; H, 4.51; N, 5.68.

Registry No. **3a**, 116059-99-5; **3b**, 116211-37-1; **3c**, 116211-38-2; **3d**, 116211-39-3; **3e**, 116211-40-6; **5**, 119-61-9; **6**, 99-91-2; **7**, 108-94-1; **8**, 2550-26-7; **9**, 116211-41-7; **10**, 116211-42-8; **11**, 116211-43-9; **12**, 116211-44-0; **14**, 104-88-1; **15**, 116211-45-1; **16**, 116211-46-2; **17**, 116211-47-3; **18**, 6285-05-8; **19**, 134-81-6; **20**, 116211-48-4; **21**, 116232-46-3; **22**, 116232-47-4; **23**, 116211-49-5; **24**, 116211-50-8; **25**, 116211-51-9; **27**, 762-21-0; **30**, 116211-52-0; TBAF, 429-41-4; 2-pyridone, 142-08-5; (chloromethyl)trimethylsilane, 2344-80-1; 2-quinolone, 59-31-4; 4-pyrimidinone, 4562-27-0; 4-quinazolinone, 491-36-1; 4-[(trimethylsilyl)oxy]pyridine, 27248-04-0; (iodomethyl)trimethylsilane, 4206-67-1.

Oxidative Coupling of Methyl 6-Hydroxyindole-2-carboxylate with Primary Amines: Preparation of 2-Substituted Methyl Pyrrolo[2,3-*e*]benzoxazole-5-carboxylates

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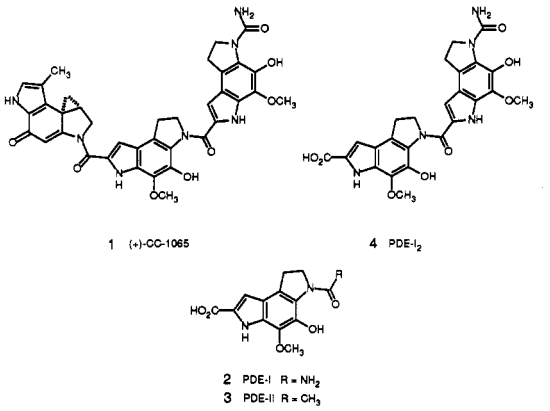
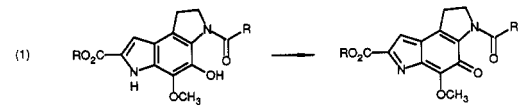
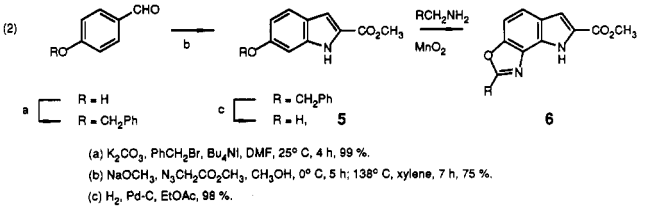
In the conduct of synthetic efforts on the antitumor antibiotic (+)-CC-1065 (**1**) and functionally related agents we have noted the instability of PDE-I (**2**), PDE-II (**3**), PDE-I dimer (**4**), and structurally related intermediates to mild, oxidative conditions.[2] We have suggested that the oxidative lability of the central and right-hand subunits of (+)-CC-1065 and structurally related agents may be due



to a mild oxidation of the 6-hydroxyindole-2-carboxylate structural subunit to an intermediate, extended *p*-quinonemethide imine, and subsequent capture by nucleophiles, eq 1.[3,4]



Herein we detail the related oxidative susceptibility of methyl 6-hydroxyindole-2-carboxylate (**5**),[5] its use in a mild regioselective, oxidative coupling with primary amines suitable for the preparation of fused oxazoles, eq 2,[6] and the apparent interception of an intermediate *o*-quinone monoimine generated enroute to the methyl pyrrolo[2,3-*e*]benzoxazole-5-carboxylates **6**.



In an initial survey of oxidants including silver(II) oxide,[7] lead(IV) dioxide,[8] nickle peroxide,[9] and manganese dioxide[6]

(1) (a) National Institutes of Health research career development award recipient, 1983-88 (CA 01134). Alfred P. Sloan research fellow, 1985-89. (b) Undergraduate research participant.

(2) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717. Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 1321. Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 4796. Boger, D. L.; Coleman, R. S. *Tetrahedron Lett.* **1987**, *28*, 1027.

(3) Boger, D. L.; Coleman, R. S.; Invergo, B. J. *J. Org. Chem.* **1987**, *52*, 1521.

(4) Like others, we suspected that this behavior may have been related to the delayed, fatal hepatotoxicity associated with the administration of (+)-CC-1065. Indirectly the oxidative lability of CC-1065 and its toxicity have been shown to not be related, cf.: Warpehoski, M. A.; Bradford, V. S. *Tetrahedron Lett.* **1988**, *29*, 131. Harbach, P. R.; Trzos, R. J.; Mazurek, J. H.; Zimmer, D. M.; Petzold, G. L.; Bhuyan, B. K. *Mutagenesis* **1986**, *1*, 407. Harbach, P. R.; Zimmer, D. M.; Mazurek, J. H.; Bhuyan, B. K. *Cancer Res.* **1988**, *48*, 32.

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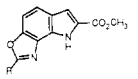
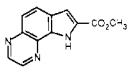
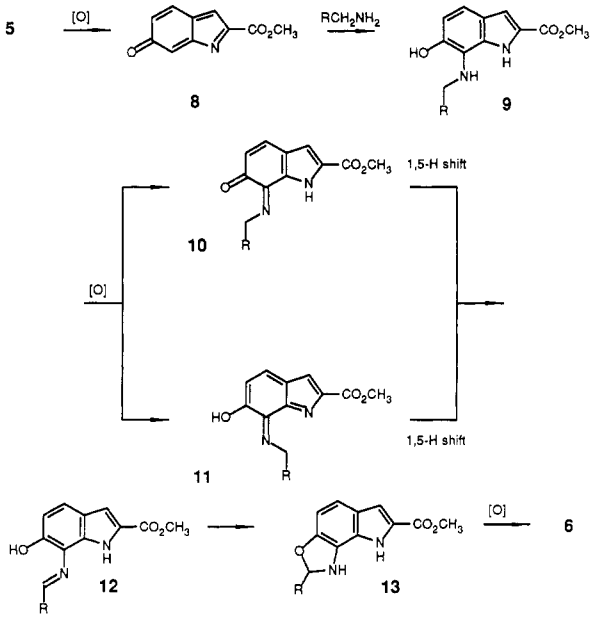
Table I. Oxidation and Reaction of Methyl 6-Hydroxyindole-2-carboxylate with Primary Amines

entry	amine (RCH_2NH_2)[a]	product	yield,[b] %
			
1	$CH_3(CH_2)_2$	**6a**	58
2	C_6H_5	**6b**	61
3	CH_2=CH	**6c**	41
4	$CH_3SCH_2CH_2$	**6d**	41
5	CH_3O_2C	**6e**	25
6	n-C_7H_{15}	**6f**	44[c]
7	$HOCH_2$	**6g**	34 (R = H)[d]
8	$HOCH_2CH_2$	**6h**	46
			
9	H_2NCH_2	7	42

[a] All reactions were conducted employing 1.2 equiv of amine, 35 wt equiv of MnO_2, DME, 25 °C; (entry 2, 20 wt equiv of MnO_2). [b] All yields are based on purified material isolated by chromatography (SiO_2). [c] See reference 11. [d] See reference 6a.

the rapid consumption of **5** was observed concurrent with the appearance of dimer (oligomer) oxidation products.[10] Initial attempts to isolate or characterize the intermediate, extended *p*-quinonemethide imine did not prove successful. Following a procedure introduced in related investigations,[6] the oxidation of **5** in the presence of primary amines (dimethoxyethane, methylene chloride, tetrahydrofuran; 25 °C, 10–35 wt equiv of manganese dioxide) proved to provide an effective, regioselective trap of the in situ generated *p*-quinonemethide imine and cleanly provided the 2-substituted methyl pyrrolo[2,3-*e*]benzoxazole-5-carboxylates **6**, eq 2. Table I summarizes the results of an investigation of this reaction. Dimethoxyethane (DME), methylene chloride (CH_2Cl_2), or tetrahydrofuran (THF) proved to be satisfactory solvents, the use of 10–15 wt equiv of manganese dioxide proved sufficient for complete oxidative coupling although the use of 35 wt equiv provided cleaner reaction products, and the rapid rate of consumption of **5** (3–14 h) was determined to occur concurrent with the appearance of **6** (1–7 h). Of the two, isomeric fused oxazole products potentially generated in the oxidative coupling reaction of **5** with primary amines (i.e., pyrrolo[2,3-*e*]benzoxazole versus pyrrolo[3,2-*f*]benzoxazole), the structure was firmly established as the former by ^1H NMR, J_{H7-H8} = 9 Hz. The isolation of a C-4/C-5,C-7 bis addition product in oxidations conducted in the presence of excess primary amine[11] and the

Scheme I



apparent intramolecular interception of the transient intermediate *o*-quinone monoimine **10** in the reaction of 1,2-diaminoethane (Table I, entry 9) with **5** provide solid evidence for the reaction mechanism provided in Scheme I. Consistent with a past observation, the coupling of **5** with ethanolamine provided predominantly the unsubstituted, fused oxazole **6g** in which deacylation accompanies or follows oxazole formation.[6a] Efforts to trap the in situ generated *p*-quinonemethide imine **8** with less reactive nucleophiles, e.g. methanol, acetic acid, and methyl *p*-hydroxybenzoate, have not proven successful.

Experimental Section[12]

Methyl 6-Hydroxyindole-2-carboxylate (5). A solution of 4-(benzyloxy)benzaldehyde (2.00 g, 9.43 mmol) and methyl α-azidoacetate[13] (10.8 g, 94.3 mmol, 10.0 equiv) in dry methanol (31 mL) was cooled to −23 °C (dry ice/CCl_4) under nitrogen and a solution of sodium methoxide in methanol (17.3 mL of 4.37 M, 75.4 mmol, 8 equiv) was added dropwise (5 min). The reaction mixture was warmed to 0 °C and was stirred for 5 h during which time a yellow precipitate was formed. The reaction mixture was diluted with saturated aqueous ammonium chloride (100 mL) and was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with saturated aqueous sodium chloride (50 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to afford crude methyl α-azido-4-(benzyloxy)cinnamate (2.70 g, 2.90 g theoretical, 93%) as an unstable yellow solid: ^1H NMR ($CDCl_3$, 80 MHz) δ 7.80 (d, 2 H, *J* = 8.8 Hz, C2, 6-H), 7.41 (m, 5 H), 7.00 (d, 2 H, *J* = 8.8 Hz, C3, 5-H), 6.90 (s, 1 H, C*H*=C), 5.12 (s, 2 H, CH_2Ph), 3.91 (s, 3 H, CO_2CH_3).

A solution of the crude azide (2.81 g, 9.09 mmol) in dry *p*-xylenes (190 mL) was warmed at reflux under nitrogen for 7 h.[14]

(9) Nakagawa, K.; Konaka, R.; Nakata, T. *J. Org. Chem.* **1962**, *27*, 1597. George, M. V.; Balachandran, K. S. *Chem. Rev.* **1975**, *75*, 491.

(10) Partial characterization of the dimer (oligomer) product: mp >230 °C dec (acetone); partial ^1H NMR ($CDCl_3$, 300 MHz) δ 11.45 (br s, 1 H), 11.30 (br s, 1 H), 8.69 (br s, 1 H), 7.79 (d, 1 H, *J* = 8.6 Hz), 7.75 (d, 1 H, *J* = 8.6 Hz), 7.42 (d, 1 H, *J* = 9.9 Hz), 7.21 (d, 1 H, *J* = 6.5 Hz), 7.08 (d, 1 H, *J* = 8.6 Hz), 6.87 (d, 1 H, *J* = 2.2 Hz), 6.80 (d, 1 H, *J* = 8.6 Hz), 5.99 (d, 1 H, *J* = 9.9 Hz), 3.79 (s, 3 H, CO_2CH_3), 3.07 (br m); IR (KBr) ν_{max} 3264, 2952, 1696, 1564, 1532, 1500, 1440, 1312, 1268, 1242, 1210, 1062, 998, 834 cm^{-1}.

(11) A bis amine addition product (21%) tentatively identified as methyl 7- or 8-(*n*-octylamino)-2-*n*-heptylpyrrolo[2,3-*e*]benzoxazole-5-carboxylate was isolated from the reaction of *n*-octylamine with **5**: mp 95–97 °C (EtOAc–hexane); ^1H NMR (DMSO-d_6, 300 MHz) δ 12.23 (br s, 1 H, NH), 7.61 (d, 1 H, *J* = 1.7 Hz, C6-H), 6.24 (s, 1 H, C7- or C8-H), 6.10 (br s, 1 H, ArNH), 3.78 (s, 3 H, CO_2CH_3), 3.10 (m, 2 H, ArNHCH_2), 2.82 (t, 2 H, *J* = 6.5 Hz, ArCH_2), 1.74 (p, 2 H, *J* = 6.4 Hz, ArNHCH_2CH_2), 1.60 (p, 2 H, *J* = 6.5 Hz, ArCH_2CH_2), 1.23 (m, 18 H), 0.81 (m, 6 H, ArNH$(CH_2)_7CH_3$ and Ar$(CH_2)_6CH_3$); IR (KBr) ν_{max} 3396, 3306, 2922, 2850, 1693, 1648, 1602, 1536, 1510, 1442, 1350, 1274, 1228, 1178, 1102, 994, 774 cm^{-1}; EIMS, *m/e* (relative intensity) 441 (M^+, base), 409 (14), 356 (3), 324 (15), 310 (7), 212 (11), 198 (8), 157 (22), 69 (14); CIMS (2-methylpropane), *m/e* 442 (M^+ + H, base).

(12) Melting points are uncorrected. *N,N*-Dimethylformamide (DMF) was distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium methoxide. Dimethoxyethane (DME) was distilled from sodium benzophenone ketyl and methylene chloride (CH_2Cl_2) was distilled from phosphorus pentoxide. Flash chromatography[12b] was performed on 230–400-mesh silica gel. All extraction and chromatographic solvents (ethyl acetate (EtOAc), ethyl ether (Et_2O), and hexane) was distilled prior to use. Activated manganese dioxide was obtained from Aldrich Chemical Company and freshly dried (120 °C, 12 h) prior to use. *p*-Xylene was obtained from Eastman Kodak. All reactions requiring anhydrous conditions or an inert atmosphere were performed under a positive atmosphere of nitrogen (N_2) or argon. (b) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(13) Forster, M. O.; Fierz, H. E. *J. Chem. Soc.* **1908**, *93*, 72.

The solvent was removed in vacuo and flash chromatography (SiO_2, 3 × 15 cm, 10% EtOAc–hexane) afforded methyl 6-(benzyloxy)indole-2-carboxylate (2.00 g, 2.65 g theoretical, 75% overall) as a white solid: mp 137–137.5 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.70 (br s, 1 H, NH), 7.56 (d, 1 H, J = 8.5 Hz, C4-H), 7.38 (m, 5 H), 7.16 (d, 1 H, J = 1.6 Hz, C3-H), 6.92 (d, 1 H, J = 8.5 Hz, C5-H), 6.90 (s, 1 H, C7-H), 5.12 (s, 2 H, CH_2Ph), 3.92 (s, 3 H, CO_2CH_3); IR (KBr) ν_{max} 3315, 3028, 2952, 1687, 1622, 1527, 1509, 1256, 1210, 1163, 1116, 1020, 770, 734 cm^{-1}; EIMS, m/e (relative intensity) 281 (M^+, 13), 190 (14), 158 (7), 130 (8), 102 (6), 91 (base), 76 (5), 65 (16); CIMS (2-methylpropane), m/e 282 (M^+ + H, base); HRMS, m/e 281.1049 ($C_{17}H_{15}NO_3$ requires 281.1052).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.59; H, 5.33; N, 4.98. Found: C, 72.71; H, 5.53; N, 4.87.

A solution of methyl 6-(benzyloxy)indole-2-carboxylate (1.45 g, 5.16 mmol) in 100 mL of EtOAc containing 0.87 g of 10% palladium on carbon was shaken in a Parr apparatus under a hydrogen atmosphere of 30 psi for 12 h. The catalyst was removed by filtration through Celite and the solvent was removed in vacuo. Flash chromatography (SiO_2, 2 × 15 cm, 35% EtOAc–hexane) afforded **5** (0.97 g, 0.99 g theoretical, 98%) as a white solid: mp 171–172 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.47 (br s, 1 H, OH), 9.37 (s, 1 H, NH), 7.43 (dd, 1 H, J = 5.6 Hz, C4-H), 7.03 (s, 1 H, C3-H), 6.77 (d, 1 H, J = 1.5 Hz, C7-H), 6.61 (dd, 1 H, J = 8.6 Hz, 2.0 Hz, C5-H), 3.82 (s, 3 H, CO_2CH_3); IR (KBr) ν_{max} 3335, 2949, 1697, 1628, 1530, 1507, 1441, 1299, 1247, 1212, 1159, 1117, 852, 765 cm^{-1}; EIMS, m/e (relative intensity) 191 (M^+, base), 159 (78), 131 (36), 105 (27), 76 (12), 59 (6), 51 (10); CIMS (2-methylpropane), m/e 192 (M^+ + H, base); HRMS, m/e 191.0576 ($C_{10}H_9NO_3$ requires 191.0582).

Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.58; H, 4.69; N, 7.49.

General Procedure for the Preparation of 2-Substituted Methyl Pyrrolo[2,3-*e*]benzoxazole-5-carboxylates: Preparation of Methyl 2-Phenylpyrrolo[2,3-*e*]benzoxazole-5-carboxylate (6b). A solution of methyl 6-hydroxyindole-2-carboxylate (**5**, 100 mg, 0.524 mmol) and benzylamine (69 μL, 0.628 mmol, 1.2 equiv) in dry dimethoxyethane (DME, 37 mL) under argon was cooled to 0 °C and 20 wt equiv of activated manganese(IV) dioxide (MnO_2) was added. The reaction mixture was allowed to stir at 25 °C for 4 h. The MnO_2 was removed by filtration through Celite and the residue was washed with EtOAc (5 × 100 mL). The solvent was removed in vacuo and flash chromatography (SiO_2, 1.5 × 15 cm, 15–20% EtOAc–hexane) afforded **6b** (93 mg, 153 mg theoretical, 61%) as a white solid: mp 235–235.5 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 10.12 (br s, 1 H, NH), 7.72 (d, 1 H, J = 8.8 Hz, C8-H), 7.61 (m, 5 H), 7.47 (d, 1 H, J = 8.8 Hz, C7-H), 7.40 (d, 1 H, J = 2.1 Hz, C6-H), 3.99 (s, 3 H, CO_2CH_3); IR (KBr) ν_{max} 3317, 2949, 1712, 1552, 1539, 1445, 1353, 1284, 1262, 1233, 1205, 701, 687, 662 cm^{-1}; EIMS, m/e (relative intensity) 292 (M^+, 72), 260 (base), 232 (12), 204 (4), 130 (11), 101 (9), 77 (4); CIMS (2-methylpropane), m/e 293 (M^+ + H, base); HRMS, m/e 292.0846 ($C_{17}H_{12}N_2O_3$ requires 292.0848).

Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 68.95; H, 4.15; N, 9.59. Found: C, 68.90; H, 3.78; N, 9.48.

Methyl 2-*n*-Propylpyrrolo[2,3-*e*]benzoxazole-5-carboxylate (6a). Reaction conditions: 25 °C, 3 h, mp 139–140 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.68 (br s, 1 H, NH), 7.61 (d, 1 H, J = 8.8 Hz, C8-H), 7.36 (d, 1 H, J = 8.8 Hz, C7-H), 7.35 (d, 1 H, J = 2.2 Hz, C6-H), 3.96 (s, 3 H, CO_2CH_3), 3.00 (t, 2 H, J = 7.4 Hz, $ArCH_2$), 1.97 (sextet, 2 H, J = 7.4 Hz, $ArCH_2CH_2$), 1.08 (t, 3 H, J = 7.4 Hz, CH_3); IR (KBr) ν_{max} 3297, 2965, 1696, 1573, 1541, 1440, 1348, 1308, 1261, 1209, 1192, 787, 765 cm^{-1}; EIMS, m/e (relative intensity) 258 (M^+, 85), 226 (base), 211 (20), 198 (95), 183 (4), 170 (11), 149 (12), 129 (12), 114 (7), 101 (24), 85 (8), 71 (18); CIMS (2-methylpropane), m/e 259 (M^+ + H, base); HRMS, m/e 258.1004 ($C_{14}H_{14}N_2O_3$ requires 258.1004).

Methyl 2-Vinylpyrrolo[2,3-*e*]benzoxazole-5-carboxylate (6c). Reaction conditions: 25 °C, 3 h, mp 178–179 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.77 (br s, 1 H, NH), 7.64 (d, 1 H, J = 9 Hz, C8-H), 7.37 (d, 1 H, J = 9 Hz, C7-H), 7.35 (s, 1 H, C6-H), 6.78 (dd, 1 H, J = 18 Hz, 11 Hz, CH=CH_2), 6.47 (d, 1 H, J = 18 Hz, CH=CHH_t), 5.84 (d, 1 H, J = 11 Hz, CH=CH_cH), 3.96 (s, 3 H, CO_2CH_3); IR (KBr) ν_{max} 3306, 1706, 1537, 1356, 1272, 1210, 822, 781, 750, 667 cm^{-1}; EIMS, m/e (relative intensity) 242 (M^+, 59), 210 (base), 182 (26), 156 (7), 129 (7), 101 (17), 75 (10); CIMS (2-methylpropane), m/e 243 (M^+ + H); HRMS, m/e 242.0691 ($C_{13}H_{10}N_2O_3$ requires 242.0691).

Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.13; N, 11.57. Found: C, 64.71; H, 4.07; N, 11.44.

Methyl 2-[2-(Methylthio)ethyl]pyrrolo[2,3-*e*]benzoxazole-5-carboxylate (6d). Reaction conditions: 25 °C, 9 h, mp 130–131 °C (Et_2O–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.67 (br s, 1 H, NH), 7.60 (d, 1 H, J = 8.8 Hz, C8-H), 7.35 (d, 1 H, J = 8.8 Hz, C7-H), 7.34 (s, 1 H, C6-H), 3.96 (s, 3 H, CO_2CH_3), 3.31 (t, 2 H, J = 7.4 Hz, $ArCH_2CH_2SCH_3$), 3.06 (t, 2 H, J = 7.4 Hz, $ArCH_2CH_2SCH_3$), 2.18 (s, 3 H, SCH_3); IR (KBr) ν_{max} 3313, 2926, 1687, 1568, 1540, 1444, 1342, 1268, 1232, 1208, 1190, 784 cm^{-1}; EIMS, m/e (relative intensity) 290 (M^+, 62), 275 (5), 258 (6), 243 (26), 229 (12), 211 (22), 197 (59), 191 (9), 159 (9), 114 (7), 101 (4), 75 (13), 61 (base); CIMS (2-methylpropane), m/e 291 (M^+ + H, base); HRMS, m/e 290.0726 ($C_{14}H_{14}N_2O_3S$ requires 290.0725).

Methyl 2-(Methoxycarbonyl)pyrrolo[2,3-*e*]benzoxazole-5-carboxylate (6e). Reaction conditions: 25 °C, 14 h, 2.2 equiv of K_2CO_3, mp 247–248 °C dec (EtOAc–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.65 (br s, 1 H, NH), 7.83 (d, 1 H, J = 8.9 Hz, C8-H), 7.48 (d, 1 H, J = 8.9 Hz, C7-H), 7.39 (d, 1 H, J = 2.1 Hz, C6-H), 4.12 (s, 3 H, CO_2CH_3), 3.98 (s, 3 H, CO_2CH_3); IR (KBr) ν_{max} 3294, 2924, 1748, 1702, 1532, 1436, 1362, 1338, 1276, 1218, 1194, 1148, 672 cm^{-1}; EIMS, m/e (relative intensity) 274 (M^+, 97) 242 (base), 183 (8), 170 (5), 155 (9), 127 (7), 101 (6), 83 (5), 69 (6), 57 (15), 55 (12); CIMS (2-methylpropane), m/e 275 (M^+ + H, base); HRMS, m/e 274.0590 ($C_{13}H_{10}N_2O_5$ requires 274.0590).

Methyl 2-*n*-Heptylpyrrolo[2,3-*e*]benzoxazole-5-carboxylate (6f). Reaction conditions: 25 °C, 2 h, mp 107–107.5 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.63 (br s, 1 H, NH), 7.58 (d, 1 H, J = 8.8 Hz, C8-H), 7.35 (d, 1 H, J = 8.8 Hz, C7-H), 7.34 (d, 1 H, J = 2.1 Hz, C6-H), 3.96 (s, 3 H, CO_2CH_3), 2.99 (t, 2 H, J = 7 Hz, $ArCH_2$), 1.91 (p, 2 H, J = 7 Hz, $ArCH_2CH_2$), 1.38 (m, 8 H), 0.88 (t, 3 H, J = 6.7 Hz, CH_3); IR (KBr) ν_{max} 3299, 2949, 2925, 2865, 2851, 1702, 1541, 1443, 1348, 1259, 1223, 1203, 1187, 758 cm^{-1}; EIMS, m/e (relative intensity) 314 (M^+, 90), 285 (17), 272 (20), 254 (17), 239 (5), 230 (50), 225 (6), 211 (32), 198 (base), 184 (4), 170 (9); CIMS (2-methylpropane), m/e 315 (M^+ + H, base); HRMS, m/e 314.1630 ($C_{18}H_{22}N_2O_3$ requires 314.1630).

Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.79; H, 7.01; N, 8.92. Found: C, 68.54; H, 7.41; N, 8.68.

Methyl Pyrrolo[2,3-*e*]benzoxazole-5-carboxylate (6g). Reaction conditions: 25 °C, 4 h, mp 244 °C dec (EtOAc–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 10.21 (br s, 1 H, NH), 8.34 (s, 1 H, C2-H), 7.69 (d, 1 H, J = 8.8 Hz, C8-H), 7.45 (d, 1 H, J = 8.8 Hz, C7-H), 7.38 (s, 1 H, J = 1.7 Hz, C6-H), 3.99 (s, 3 H, CO_2CH_3); IR (KBr) ν_{max} 3232, 3152, 2958, 1718, 1540, 1504, 1440, 1352, 1310, 1260, 1234, 1208, 1096, 998, 830, 782, 754, 670 cm^{-1}; EIMS, m/e (relative intensity) 216 (M^+, 77), 184 (base), 156 (41), 130 (19), 101 (27), 75 (30), 50 (22); CIMS (2-methylpropane), m/e 217 (M^+ + H, base); HRMS, m/e 216.0536 ($C_{11}H_8N_2O_3$ requires 216.0535).

In addition, methyl 2-(hydroxymethyl)pyrrolo[2,3-*e*]benzoxazole-5-carboxylate (6%) was isolated from the reaction mixture.

Methyl 2-(1-Hydroxyethyl)pyrrolo[2,3-*e*]benzoxazole-5-carboxylate (6h). Reaction conditions: 25 °C, 4 h, mp 171 °C dec (EtOAc–hexane); ^1H NMR (DMSO-d_6, 300 MHz) δ 12.63 (br s, 1 H, NH), 7.63 (d, 1 H, J = 8.7 Hz, C8-H), 7.44 (d, 1 H, J = 8.7 Hz, C7-H), 7.33 (d, 1 H, J = 1.6 Hz, C6-H), 4.94 (t, 2 H, J = 5.4 Hz, OH), 3.91 (q, 2 H, J = 6.0 Hz, $ArCH_2CH_2OH$), 3.86 (s, 3 H, CO_2CH_3), 3.13 (t, 2 H, J = 6.4 Hz, $ArCH_2CH_2OH$); IR (KBr) ν_{max} 3176, 2950, 1718, 1574, 1536, 1436, 1344, 1296, 1262, 1232, 1200, 1110, 1058, 1000, 782, 666 cm^{-1}; EIMS, m/e (relative intensity) 260 (M^+, base), 228 (42), 210 (7), 198 (79), 170 (20), 156 (4), 141 (8), 129 (5), 114 (12), 101 (22), 75 (17); CIMS (2-methylpropane), m/e 261 (M^+ + H, base); HRMS, m/e 260.0800 ($C_{13}H_{12}N_2O_4$ requires 260.0797).

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Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.62; N, 10.77. Found: C, 60.20; H, 4.45; N, 10.55.

Methyl Pyrrolo[2,3-*f*]quinoxaline-6-carboxylate (7). Reaction conditions: 25 °C, 1.5 h, mp 186-187 °C dec (EtOAc-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.40 (br s, 1 H, NH), 8.88 and 8.79 (two d, 1 H, J = 1.8 Hz, C2-H and C3-H), 7.99 (d, 1 H, J = 8.9 Hz, C9-H), 7.76 (d, 1 H, J = 8.9 Hz, C8-H), 7.39 (d, 1 H, J = 2.1 Hz, C7-H), 4.00 (s, 3 H, CO_2CH_3); IR (KBr) ν_{max} 3307, 2952, 1713, 1514, 1440, 1372, 1334, 1272, 1250, 1202, 1108, 1058, 998, 862, 830, 758, 700 cm^{-1}; EIMS, m/e (relative intensity) 227 (M^+, base), 195 (94), 167 (46), 141 (25), 114 (17), 87 (16), 76 (8), 62 (14), 52 (10); CIMS (2-methylpropane), m/e 228 (M^+ + H, base); HRMS, m/e 227.0690 ($C_{12}H_9N_3O_2$ requires 227.0695).

In addition, methyl pyrrolo[2,3-*e*]benzoxazole-5-carboxylate (**6g**, 12%) was isolated from the reaction mixture.

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Registry No. **5** (R = CH_2Ph), 103781-89-1; **5** (R = H), 116350-38-0; **6a**, 116350-39-1; **6b**, 116350-40-4; **6c**, 116350-41-5; **6d**, 116350-42-6; **6e**, 116350-43-7; **6f**, 116350-44-8; **6g** (R = H), 116350-45-9; **6g** (R = CH_2OH), 116350-46-0; **6h**, 116350-47-1; **7**, 116350-48-2; $H_2N(CH_2)_3CH_3$, 109-73-9; $H_2NCH_2CH{=}CH_2$, 107-11-9; $H_2N(CH_2)_3SMe$, 4104-45-4; $H_2NCH_2CO_2Me$, 616-34-2; *n*-$C_7H_{15}CH_2NH_2$, 111-86-4; $H_2N(CH_2)_2OH$, 141-43-5; $H_2N(CH_2)_3OH$, 156-87-6; $H_2N(CH_2)_2NH_2$, 107-15-3; 4-(benzyloxy)benzaldehyde, 4397-53-9; methyl α-azidoacetate, 1816-92-8; methyl α-azide-4-(benzyloxy)cinnamate, 115663-17-7; benzylamine, 100-46-9; 7- or 8-(*n*-octylamino)-2-*n*-heptylpyrrolo[2,3-*e*]benzoxazole-5-carboxylate, 116350-49-3.

Control of Product Distribution in Mixing-Controlled Reactions

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Introduction

The product distribution from fast reactions is often influenced by the way in which reagents are mixed. The concentration gradients present during the mixing of miscible reagent solutions determine the local absolute and relative rates of individual reactions. Qualitative understanding of this situation has been available since 1926,[1] when the relative rates of bromination of some organic substrates were found to differ less than the differences in reactivity. Similar results have been obtained in the competitive single-phase nitration of benzene and toluene.[2] The competitive method of determining relative reactivities will fail when the rate of reaction is similar to, or greater than, the rate of mixing, although it is not widely known that the mixing rate can now be predicted.

Fast competitive-consecutive reactions, typified by

$$A + B \xrightarrow{k_1} R \quad (1)$$

$$R + B \xrightarrow{k_2} S \quad (2)$$

exhibit lower yields of R and higher yields of S when mixing is insuffiently rapid to homogenize the reagents. Reactions falling in this category include diamines with isocyanates,[3] nitration of durene,[4] iodination of *l*-tyrosine,[5] coupling of 1-naphthol with diazotized sulfanilic acid,[6,7] and acylation of diamines.[8] Mixing effects in nitration have been extensively described.[9] More complex reactions are known to be mixing-sensitive.[10,11] In some cases hydrogen ions, which are products of rapid reactions, influence the ionic preequilibria of the reagents and the product distribution, e.g., bromination of resorcinol,[12] coupling of 1-hydroxynaphthalene-6-sulfonic acid with benzenediazonium ion,[13] and coupling of 6-amino-4-hydroxy-2-naphthalenesulfonic acid with 3-(trifluoromethyl)-benzenediazonium ion.[14]

Measures to improve yields in mixing-controlled reactions comprise changing factors that determine the reaction kinetics and the mixing rate. Kinetic factors considered in the literature already cited are concentration (increasing the dilution often improves the yield) and stoichiometric ratio (e.g., a large excess of A relative to B raises the yield of R in eq 1 and 2). Mixing-rate factors are stirrer speed and type of mixer. It is intended here to show that these results are fully consistent with the theory of mixing. This theory also identifies other options available to the synthetic chemist for increasing yield.

Principles of Mixing

Mixing in a reaction vessel occurs on different scales. Macromixing refers to mixing on a scale much coarser than the molecular. It brings about homogeneity in the vessel by bulk transport of materials. Micromixing refers to mixing on the molecular scale. Molecular diffusion, which brings about encounters between the different species, is an important micromixing mechanism. Detailed consideration of macromixing will be avoided here by concentrating on the slow addition of one reagent (B) solution to the other (A). The rate at which A is transported by the general circulation in the vessel to the point of addition of B will greatly exceed the rate of feeding in fresh B. The concentration of A (and of any other substances present in the vessel) entering the mixing zone will then be the average value for the vessel. Micromixing will be the controlling step in the whole mixing process and has a half-life t_D[15] given by

$$t_D \simeq 2(\nu/\epsilon)^{1/2} \text{ arc sinh } (0.05\nu/D) \quad (3)$$

where ν is the kinematic viscosity of the solution, D is the diffusivity of the solute, and ϵ is the rate of energy dissipation per unit mass of solution. Parameter ϵ, whose units are watts per kilogram, is a measure of the rate of stirring, and t_D is the time at which the molecular mixing process, which occurs by diffusion and fine-scale fluid deformation, is 50% complete. Comparing t_D with t_R, the half-life of the chemical reaction, three possibilities arise.

(i) $t_D \ll t_R$. Reaction is so slow that mixing on a mo-

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