Azaindolizines. 7. 7-Azaindolizines, Their Reactivity and Reaction with Dimethyl Acetylenedicarboxylate

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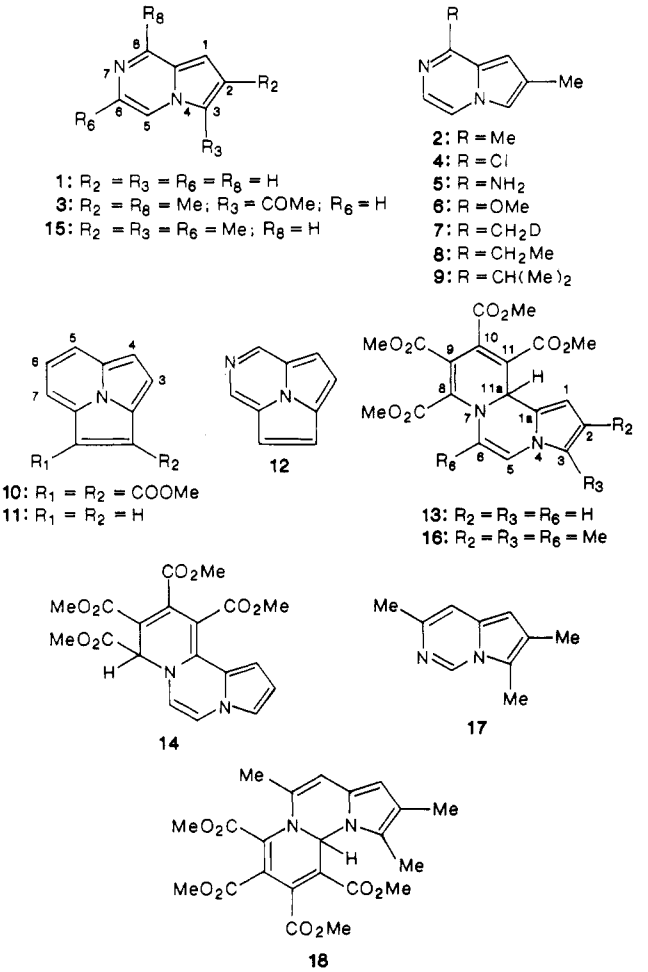
7-Azaindolizine(s) shows a lower propensity to undergo electrophilic substitution than indolizine or other azaindolizines and fails to undergo Vilsmeier formylation, nitrosation, and azo coupling; acetylation is shown to occur preferentially at C-3. Chichibabin amination of 7-azaindolizine (**1**) does not occur but displacement of chloride from 2-methyl-8-chloro-7-azaindolizine with methoxide to give **6** is facile, and with aqueous ammonia at 180 °C the 8-amino-2-methyl-7-azaindolizine (**5**) is obtained. The 8-methyl hydrogens of 2,8-dimethyl-7-azaindolizine are shown to be acidic. In toluene at room temperature the 7-azaindolizines **1** and **15** react with two molecular proportions of dimethyl acetylenedicarboxylate to give the 1:2 adducts **13** and **16** by reaction involving the N-7 nonbridgehead nitrogen and the adjacent electron-deficient C-8 site.

The only reported studies of the reactivity of 7-azaindolizines are those by Paudler and Dunham,[1] who showed the parent system **1** to undergo electrophilic bromination and nitration at the 1- and or 3-positions and when reacted with phenyllithium to give 8-phenyl-7-azaindolizine. These studies are broadly in agreement with theoretical calculations,[1,2] which indicate C-3 and C-1 to be the carbons of greatest electron surplus and C-8 to be the most electron deficient. In this paper we report further studies of the reactivity of 7-azaindolizine(s) and in particular examine the reaction with dimethyl acetylenedicarboxylate.

We reported[3] most recently in this series that 7-azaindolizines, in contrast to 5-, 6-, and 8-azaindolizines, protonate solely at the nonbridgehead nitrogen and resist deuterium exchange at C-3 and C-1. Furthermore, with methyl iodide 7-azaindolizine(s) readily quaternize to give the corresponding 7-methyl-7-azaindolizinium iodide salts.[4] This suggests that 7-azaindolizine(s) have surplus π-electron density concentrated more on the nonbridgehead nitrogen at the expense of C-1 and C-3. This inference is substantiated by the resistance of 7-azaindolizine(s) to substitute weaker electrophiles. Most noticeably, 7-azaindolizines failed to undergo Vilsmeier formylation,[5] in contrast to the ready formylation of indolizines[6] and azaindolizines.[7-10] Similarly, while nitroso derivatives of 1-, 3-, 5-, and 6- and azo-coupled products from 1-, 5-, 6-, and 8-azaindolizines have been reported, no nitroso or azo-coupled product was isolated when 7-azaindolizine(s) was reacted with nitrous acid or benzenediazonium chloride.[11,12] However, prolonged reflux of 2,8-dimethyl-7-azaindolizine (**2**) with acetic anhydride gave a low yield of the monoacetyl derivative **3**; the large downfield shift (222 Hz) of the H-5 doublet of **2** on acetylation indicated the preferential introduction of a peri-orientated acetyl group at position 3 (Chart I).

The isolation of 8-phenyl-7-azaindolizine from treatment of 7-azaindolizine with phenyllithium suggests that 7-azaindolizine may similarly emulate pyridine in undergoing Chichibabin amination;[13] however, no 8-amino-7-azaindolizine was isolated when **1** was reacted with powdered sodamide in dimethylaniline at temperatures up to 180 °C.[14] While direct hydride displacement did not occur, the chlorine of 8-chloro-2-methyl-7-azaindolizine (**4**) was successfully substituted by amino and methoxy groups by reacting **4** with aqueous ammonia at 180 °C or with sodium methoxide in methanol to give **5** and **6**, respectively. Thus

Chart I



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7-azaindolizines behave similarly to 6- and 8-azaindolizines in undergoing nucleophilic displacement of chlorine from their most electron deficient sites.[15] The electron deficiency of the 8-position of 7-azaindolizine is also shown by the acidity of the 8-methyl in 2,8-dimethyl-7-azaindolizine (**2**). On treatment with phenyllithium **2** gave a red solution, indicating formation of the intermediate carbanion. This solution when treated with deuterium oxide gave the deuterio compound **7** and when treated with methyl iodide it gave a mixture of the 8-ethyl- and 8-isopropyl-2-methyl-7-azaindolizines (**8** and **9**).

Indolizine has been shown to give 1,2-dicarbomethoxycycl[3.2.2]azine (**10**) in good yield when reacted with dimethyl acetylenedicarboxylate (DMAD) in boiling toluene in the presence of a dehydrogenating catalyst.[16] The reaction is thought to proceed via peri 3,5 bridging to give a 1:1 adduct, which then dehydrogenates; subsequent hydrolysis and decarboxylation of **10** gives the parent cycl-[3.2.2]azine (**11**). Similarly alkyl- and arylindolizines and 1-, 2-, 6-, and 8-azaindolizines have been shown to give the corresponding cycl[3.2.2]azines or azacycl[3.2.2]azines.[17-20] The isolation of 6-azacycl[3.2.2]azine (**12**) from the reaction of 7-azaindolizine with DMAD has been mentioned in a personal communication;[21] however, this observation is at variance with the work of Dunham,[22] who found the reaction between 7-azaindolizine and DMAD in toluene in the presence of palladium on charcoal gave a complex reaction mixture from which no characterizable products could be isolated. We repeated the reaction between 7-azaindolizine and DMAD using identical conditions with those described by Dunham and confirmed his findings. However, when the reaction was carried out at room temperature in the absence of palladium on charcoal a single product was obtained. Elemental analysis and the presence of a molecular ion (*m/e* 402) indicated the molecular formula $C_{19}H_{18}N_2O_8$. Its infrared spectrum showed ester carbonyl bands and its ^1H NMR spectrum showed the presence of four carbomethoxy methyl signals, the disappearance of the lowest field aromatic H-8 signal of the parent 7-azaindolizine (**1**), and the emergence of a 1-H singlet at δ 6.20. These observations suggest two molecules of DMAD to react at sites N-7 and C-8 of **1** to give the pyridopyrrolopyrazine 1:2 adduct **13**; the 1-H singlet at δ 6.20 is ascribed to the angular 11a proton. Mass spectral studies and examination of the ^{13}C NMR spectrum give further evidence for structure **13**. The ^{13}C NMR spectrum showed four methyl carbons, four low-field carbonyl carbons, ten signals between δ 99.6 and 151.9 ascribed to the sp^2-hybridized carbons of the ring system, and an sp^3-hybridized carbon at δ 58.0 ascribed to C-11a. The mass spectrum of **13** showed its base peak at *m/e* 343 and a significant peak at *m/e* 401 (28%); these peaks are interpreted to arise by a preliminary 1,5 hydrogen shift to give compound **14**, followed by a loss of a carbomethoxy group or a hydrogen atom, respectively. These reactions parallel those of pyridine and isoquinoline, which with DMAD give 9a*H*-quinolizine and benzoquinolizine 1:2 adducts that subsequently undergo 1,5 shifts to their 4*H* isomers.[23,24] When 2,3,6-trimethyl-7-azaindolizine (**15**) was similarly reacted with DMAD at room temperature, it gave the corresponding pyridopyrrolopyrazine **16**, which showed spectral characteristics parallel to those of **13**. Significantly, the isomeric 2,3,7-trimethyl-6-azaindolizine (**17**) when treated with DMAD at room temperature in the absence of palladium on charcoal merely gave unchanged **17**: i.e., no corresponding pyridopyrrolopyrimidine **18** was isolated despite the prevention of 3,5-peri bridging. Thus the 7-azaindolizines **1** and **15** unlike other azaindolizines react with DMAD at the nonbridgehead nitrogen and the adjacent electron-deficient 8-position to give angular condensed pyridopyrrolopyrazines rather than a peri-condensed azacycl[3.2.2]azine.

Experimental Section

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ultraviolet absorption data refers to solutions in ethanol unless otherwise stated and were measured on a Perkin-Elmer 552 spectrometer; principal maxima are italicized and inflections are given in parentheses. Infrared spectra were recorded with a Perkin-Elmer 781 spectrometer and are for Nujol mulls unless otherwise stated. ^1H and ^{13}C NMR spectra refer to solutions in deuteriochloroform unless otherwise stated and were recorded on Perkin-Elmer R12B, Varian FT-80A, or JOEL FX90 Q spectrometers with tetramethylsilane as an internal standard. Unless otherwise stated, values given on the δ scale refer to singlet absorption, approximate coupling constants are in hertz, and integration and signal assignment are in parentheses. For multiplets d = doublet, dd = double doublet, t = triplet, q = quartet, and m = complex multiplet. Signals marked with an asterisk are broadened and or weakly split. Mass spectroscopy data was obtained from a VG 70-250 SE spectrometer. Elemental analysis and much of the spectroscopic analysis was by courtesy of the analytical laboratories of ICI Pharmaceuticals Division.

Procedures. Solutions were dried over anhydrous magnesium sulfate and solvents evaporated at reduced pressure on a rotary film evaporator. Thin layer chromatography (TLC) was carried out on Merck Kiesegel GF_{254} using toluene–ethyl acetate (3:1) for development and chloroform for band extractions unless otherwise stated.

7-Azaindolizine (**1**),[25] 2,8-dimethyl- and 2,3,6-trimethyl-7-azaindolizine (**2** and **15**)[3], and 2,3,7-trimethyl-6-azaindolizine (**17**)[9] were prepared by procedures described in the references cited. The methiodide salts of **1** and **2** were obtained by warming a solution of the 7-azaindolizine with excess methyl iodide; the resulting yellow precipitate was recrystallized from ethanol, 7-azaindolizine methiodide: mp 108–109 °C; IR 784, 1150, 1560, 1660, 3080 cm^{-1}; ^1H NMR (CF_3COOH) 4.37 (3 H, Me-7), 7.30* (1 H, H-1), 7.35 m (1 H, H-2), 7.65 d (1 H, J = 5.5 Hz, H-6), 8.12* (1 H, H-3), 8.35 d (1 H, J = 5.5 Hz, H-5), 8.88* (1 H, H-8). 2,8-Dimethyl-7-azaindolizine methiodide: mp 227–228 °C; IR 805, 1160, 1305, 1505, 1605 cm^{-1}; ^1H NMR (CF_3COOH) 2.48 (3 H, Me-2), 2.95 (3 H, Me-8), 4.08 (3 H, M-7), 7.25 d (1 H, J = 5.5 Hz, H-6), 7.42* (1 H, H-1), 7.88* (1 H, H-3), 8.15 d (1 H, J = 5.5 Hz, H-5).

Vilsmeier formylation of 2,8-dimethyl-7-azaindolizine (**2**; 0.5 g, 3.42×10^{-3} mol) was carried out by using the procedure cited in a previous paper;[8] chloroform extraction of the sodium hydroxide basified Vilsmeier solution gave a dark green oil, which on distillation gave 2,8-dimethyl-7-azaindolizine (**2**; 0.3 g).

Acetylation of 2,8-Dimethyl-7-azaindolizine (2). A solution of **2** (0.5 g, 3×10^{-3} mol) in acetic anhydride (25 mL) was refluxed for 24 h. The excess acetic anhydride was evaporated to leave a red oil, which was poured into cooled sodium hydroxide (50 mL, 2 M), and the resulting solution was extracted with $CHCl_3$ (4 × 15 cm^3). Evaporation of the dried $CHCl_3$ extract gave a brown residue, which on preparative TLC gave starting material (**2**; 0.2 g, 40%) and *3-acetyl-2,8-dimethyl-7-azaindolizine* (**3**; 0.1 g, 16%) as pale yellow needles: mp 138 °C; IR 790, 815, 975, 1290, 1410, 1630 cm^{-1}; ^1H NMR 2.59 (3 H, COMe-3), 2.65 (3 H, M-2), 2.70

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(3 H, Me-8), 6.62 (1 H, H-1), 7.72 d (1 H, J = 5.3 Hz, H-6), 9.54 d (1 H, J = 5.3 Hz, H-5).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found: C, 69.9; H, 6.5; N, 14.4.

2-Methyl-7-azaindolizin-8(7*H*)-one[26] (0.143 g, 1×10^{-3} mol) was refluxed with $POCl_3$ (25 mL) for 3 h. After evaporation of the excess $POCl_3$ and basefication with aqueous Na_2CO_3, the resulting solution was extracted with $CHCl_3$ (3 × 25 mL). The $CHCl_3$ extract was dried and evaporated to give a red oil, which on vacuum sublimation (18 mm, 70 °C) gave *8-chloro-2-methyl-7-azaindolizine* (**4**; 0.15 g, 93%) as colorless crystals: mp 28 °C; λ_{max} (216.5), 226.5, (238), (244.5), 290, 300, (335) nm (log ϵ 4.43, 4.47, 4.31, 4.19, 3.57, 3.64, 3.47); ^{1}H NMR 2.31 (3 H, Me-2), 6.66 (1 H, H-1), 7.02 (1 H, H-3), 7.20 d (1 H, J = 4.5 Hz, H-5), 7.63 d (1 H, J = 4.5 Hz, H-6); mass spectrum calcd for $C_8H_7N_2Cl$ 166, found m/e 166 (base peak).

Anal. Calcd for $C_8H_7N_2Cl$: C, 57.7; H, 4.2; N, 16.8. Found: C, 58.1; H, 4.2; N, 17.1.

Reaction of 8-Chloro-2-methyl-7-azaindolizine (4) with (a) Sodium Methoxide and (b) with Ammonia. (a) A suspension of 4 (0.30 g, 1.8×10^{-4} mol) in a methanolic solution of NaOMe obtained from MeOH (20 mL) and Na (0.3 g) was refluxed for 10 h. The excess MeOH was evaporated and water (20 mL) added, and the resulting solution was extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ gave a yellow oil, which was vacuum distilled to give *8-methoxy-2-methyl-7-azaindolizine* (**6**; 0.02 g, 68%) as a colorless oil: IR 760, 1100, 1160, 1330, 1370, 1620, 3100; ^{1}H NMR 2.26 (Me-2), 4.00 (MeO-8), 6.65* (1 H, H-1), 7.07* (1 H, H-3), 7.00 d (1 H, J = 4.6 Hz, H-5), 7.35 d (1 H, J = 4.6 Hz, H-6).

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.6; H, 6.2; N, 17.3. Found: C, 66.3; H, 6.3; N, 16.9.

(b) A solution of concentrated ammonia (10 mL) was added to 4 (0.4 g, 2.4×10^{-4} mol) and the mixture heated in an autoclave at 180 °C for 48 h. After cooling, a few KOH pellets were added and the mixture was extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ gave 8-amino-2-methyl-7-azaindolizine (**5**; 0.02 g, 57%) as white needle crystals: mp 135 °C; λ_{max} 206, (213), 227, 285, (304) nm (log ϵ 4.33, 4.25, 4.37, 3.78, 3.64); IR 760, 1630, 1650, 3300, 3440 cm^{-1}; ^{1}H NMR 2.29 (3 H, Me-2), 4.49 (2 H, NH_2-8), 6.27 (1 H, H-1), 6.99 d (1 H, J = 4.9 Hz, H-5), 7.08 (1 H, H-3), 7.28 d (1 H, J = 4.9 Hz, H-6); mass spectrum, mass calcd for $C_8H_9N_3$ 147, found M (base peak) 147, 146 (M − 1, 38), 119 (M − 28, 25).

Anal. Calcd for $C_8H_9N_3$: C, 65.3; H, 6.1; N, 28.5. Found: C, 65.0; H, 6.0; N, 28.7.

Lithiation. 2,8-Dimethyl-7-azaindolizine (**2**; 1.0 g, 6.85×10^{-3} mol) was dissolved in dry diethyl ether (15 mL), the solution was cooled, and a solution of methyllithium (1.3 M) in dry ether (15 mL) was added dropwise, resulting in a deep red solution. This solution was then added to (a) deuterium oxide and (b) methyl iodide.

(a) Introduction of D_2O (1.0 mL) caused the disappearance of the red color. The resulting solution was extracted with $CHCl_3$, and evaporation of the dried $CHCl_3$ extract afforded the deuterated 2,8-dimethyl-7-azaindolizine (**7**; 0.8 g, 79%): ^{1}H NMR 2.35 (3 H, Me-2), 2.52 (2 H, CH_2D-8), 6.55* (1 H, H-1), 7.14* (1 H, H-3), 7.35 d (1 H, J = 5.5 Hz, H-5), 7.55 d (1 H, J = 5.5 Hz, H-6).

(b) Addition of methyl iodide (2.4 mL) afforded a green solution, which was stirred for 1 h at room temperature and then added to water (25 mL). The resulting solution was extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ extract afforded a black oil (2.68 g), which showed two bands on TLC. The faster moving band gave *8-ethyl-2-methyl-7-azaindolizine* (**8**; 1.6 g, 63%) as a colorless oil, which darkened on standing: λ_{max} (213), 226, 234, (241), 286, 298, 332 nm (log ϵ 4.26, 4.39, 4.37, 4.18, 3.54, 3.54, 3.42); IR (thin film) 795, 1310, 1475, 1545, 2940, 2980 cm^{-1}; ^{1}H NMR 1.35 t (3 H, Et-8), 2.32 (3 H, Me-2), 2.90 q (2 H, Et-8), 6.60 (1 H, H-1), 7.14 (1 H, H-3), 7.35 d (1 H, J = 5.5 Hz, H-5), 7.55 d (1 H, J = 5.5 Hz, H-6).

Anal. Calcd for $C_{10}H_{12}N_2$: C, 75.0; H, 7.5; N, 17.5. Found: C, 74.8; H, 7.4; N, 17.8.

The slower moving band gave *8-isopropyl-2-methyl-7-azaindolizine* (**9**; 1.0 g, 34%) as a colorless oil, which darkened on standing: λ_{max} (214), 225, 240, (244), 285, 296, 334 nm (log ϵ 4.20, 4.23, 4.21, 4.14, 3.63, 3.63, 3.41); IR 780, 1100, 1300, 1610 cm^{-1}; ^{1}H NMR 1.35 d (6 H, isopropyl-8), 2.30 (3 H, Me-2), 3.30 m (1 H, isopropyl-8), 6.58 (1 H, H-1), 7.12 (1 H, H-3), 7.35 d (1 H, J = 5.5 Hz, H-5), 7.53 d (1 H, J = 5.5 Hz, H-6).

Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.9; H, 8.0; N, 16.1. Found: C, 75.6; H, 7.8; N, 16.2.

Reaction between 7-Azaindolizine (1) and DMAD. To a solution of 1 (0.5 g, 4.23×10^{-3} mol) in toluene (25 mL) was added DMAD (1.26 g, 8.8×10^{-3} mol) dropwise. This resulted in an exothermic reaction and formation of an intense dark red solution. After 3 h at room temperature TLC examination of this reaction mixture showed only one spot with a different R_f value to that of the starting material. Evaporation of the solvent afforded a dark red oil, which on tituration with methanol gave a yellow precipitate (0.5 g) that on recrystallization from acetone yielded *tetramethyl 11aH-pyrido[2,1-c]pyrrolo[1,2-a]pyrazine-8,9,10,11-tetracarboxylate* (**13**; 0.4 g, 14%) as yellow crystals: mp 176 °C; IR 730, 1165, 1535, 1620, 1700, 1730, 3095, 3150 cm^{-1}; ^{1}H NMR 3.62 (3 H, COOMe), 3.68 (3 H, COOMe), 3.85 (6 H, COOMe × 2), 5.80–6.80 (5 H, complex multiplet, H-1, H-2, H-3, H-6), 6.20 (1 H, H-11a); ^{13}C NMR 55.88, 55.99, 56.34, 57.15 (four carbmethoxy methyls COOMe attached to C-8, C-9, C-10, C-11), 58.80 (C-11a), 99.42, 114.96, 129.56, 142.47, 151.91 (five quaternary carbons at C-8, C-9, C-10, C-11, C-1a), 112.12, 113.64, 116.29, 121.13, 123.66 (five methine carbons at C-1, C-2, C-3, C-5, C-6), 171.13, 168.28, 167.51, 166.69 (four carbonyl carbons of carbomethoxy groups at C-8, C-9, C-10, C-11); mass spectrum, mass calcd for $C_{19}H_{18}N_2O_8$ 402, found 402 ($M^{\bullet+}$, 2), 40 (M − 1, 28), 343 (M − 59, 100).

Anal. Calcd for $C_{19}H_{18}N_2O_8$: C, 56.7; H, 4.5; N, 7.0. Found: C, 56.0; H, 4.5; N, 6.6.

Reaction between 2,3,6-Trimethyl-7-azaindolizine (15) and DMAD. To a solution of **15** (0.1 g, 6.25×10^{-4} mol) in toluene (15 mL) was added DMAD (0.18 g, 1.25×10^{-3} mol). This resulted in an exothermic reaction and formation of a dark orange solution. Evaporation of the solvent gave after separation by preparative TLC *tetramethyl 11aH-2,3,6-trimethylpyrrido[2,1-c]pyrrolo-[1,2-a]pyrazine-8,9,10,11-tetracarboxylate* (**16**; 0.01 g, 4%) as yellow crystals: mp 130–131 °C; IR 705, 1020, 1240, 1510, 1620, 1715, 1750 cm^{-1}; ^{1}H NMR 1.95 (6 H, Me-2, Me-3), 2.12 (3 H, Me-6), 3.60 (3 H, COOMe-11), 3.72 (3 H, COOMe-10), 3.80 (3 H, COOMe-9), 3.90 (3 H, COOMe-8), 5.50 (1 H, H-11a), 5.70 (1 H, H-1), 6.65 (1 H, H-5); mass spectrum, mass calcd for $C_{22}H_{24}N_2O_8$ 444, found 444 ($M^{\bullet+}$, 47), 429 (M − 15, 65), 413 (M − 31, 14), 397 (M − 47, 14), 385 (M − 59, 100).

Anal. Calcd for $C_{22}H_{24}N_2O_8$: C, 59.5; H, 5.4; N, 6.3. Found: C, 59.9; H, 5.8; N, 6.2.

Registry No. 1, 274-45-3; 1·MeI, 118355-93-4; 2, 95407-81-1; 2·MeI, 118355-94-5; 3, 118355-95-6; 4, 118355-96-7; 5, 118355-97-8; 6, 118355-98-9; 7, 118355-99-0; 8, 118356-00-6; 9, 118356-01-7; 13, 118356-02-8; 15, 95407-80-0; 16, 118356-03-9; DMAD, 762-42-5; 2-methyl-7-azaindolizine-8(7*H*)-one, 118356-04-0.

(26) 2-Methyl-7-azaindolizin-8(7*H*)-one was synthesized from 2-methyl-3-methoxypyrazine by Chichibabin quaternization–cyclization with bromoacetone in a manner analogous to that reported (ref 15) in the synthesis of 6- and 8-azaindolizinones.