(Na_2SO_4), and evaporated to give 1 g (62%) of **8** which was recrystallized from $CHCl_3$ to give the product, mp 205–207 °C. Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.76; H, 6.98; N, 13.85. Found: C, 70.99; H, 6.89; N, 13.87.

2-Methyl-1,2,3,4-tetrahydro-γ-carboline (9). A mixture of 0.202 g of **8**, 0.2 g of 5% Pd/C, 10 mL of 6 N HCl, and 10 mL of ethanol was hydrogenated at 17 psi for 16 h at room temperature. The product was isolated as described above for **6**. The final residue was triturated with benzene to give 0.123 g (66%) of crystalline **9** with mp 163–165 °C. After recrystallization from acetone/benzene, the compound melted at 172–173 °C (lit.[20] mp 171–172 °C).

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Registry No.—**1a**, 504-02-9; **1b**, 126-81-8; **7**, 66842-79-3; **8**, 66842-80-6; **9**, 5094-12-2; $H_2NCH_2CH(OMe)_2$, 22483-09-6; $PhCH_2NHCH_2CH(OMe)_2$, 54879-88-8; $MeNHCH_2CH(OMe)_2$, 122-07-6; indole, 120-72-9; formaldehyde, 50-00-0.

References and Notes

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(21) The basis of this procedure is that the Schiff base **2** is basic and soluble in dilute HCl, whereas the product **3** is no longer basic and is extracted as it is formed.
(22) Silica gel M was obtained from Herrmann Brothers, Cologne, Ger.

Azaindolizines. 5. Nucleophilic Substitution on Chloro-6- and -8-azaindolizines

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Cyclization of the products of reaction between phenacyl bromide and 4,6-dimethyl-2-pyrimidone and 2-methyl-4-pyrimidone gave the 6- and 8-azaindolizinones **7** and **9**, which on reaction with phosphoryl chloride gave the corresponding 5- and 7-chloro-6- and -8-azaindolizines **2** and **5**, respectively. The substitution of chlorine from **2** and **5** by hydroxide, methoxide, and amide was investigated; displacement of chlorine by all these nucleophiles occurred with the 5-chloro-6-azaindolizine **2**, whereas only methoxylation occurred with the 7-chloro-8-azainolizine **5**. Reaction of **2** with phosphoryl chloride gave the peri condensed structure **13**. Formylation of the product of ammonolysis of **2** gave the 1,7-diazacyclo[3.2.2]azine **16**.

Both 6- and 8-azaindolizines can be formally classified as π-excessive[1] heteroaromatic systems and as such would be expected to show a propensity toward electrophilic rather than nucleophilic substitution processes. Electrophilic substitution of both 6- and 8-azaindolizines has been shown[2,3] to occur preferentially at C-3 and then at C-1, findings which are broadly in agreement with theoretical MO calculations.[4,5] Although the 6- and 8-azaindolizines are π excessive, the MO calculations indicate both systems to have sites of considerable electron deficiency. The sites of minimum electron density, as might be expected, occur within the pyrimidine moiety specifically at C-5 and C-7, the C-5 site being the most deficient for the 6-aza- and the C-7 site for the 8-azaindolizine system.

Although nucleophilic displacement from pyrimide and other π-deficient[1] heteroaromatic systems is common, even hydride ion displacement being possible,[6] no instances of successful nucleophilic displacement from the indolizine nucleus have been reported, and of the seven possible azaindolizines only the 1-azaindolizine system has been shown to undergo nucleophilic displacement of chlorine.[7–9] In this paper we describe the reactivity of the chlorine in 5-chloro-7-methyl-2-phenyl-6-azaindolizine (**2**) and 7-chloro-2-phenyl-8-azaindolizine (**5**). Attempts to effect direct nucleophilic subtitution on 7-methyl-2-phenyl-6-azaindolizine (**1**) by treatment with sodamide or sodium methoxide at temperatures up to 180 °C merely resulted in decomposition or at lower temperatures in the recovery of starting material.

The chloro-6- and 8-azaindolizines **2** and **5** were prepared by heating the corresponding 6- and 8-azaindolizinones **7** and **9** with phosphoryl chloride. 7-Methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (**7**) and 2-phenyl-8-azaindolizine-7(8*H*)-one (**9**) were each obtained by reacting 4,6-dimethyl-2-pyrimidone and 2-methyl-4-pyrimidone, respectively, with phenacyl bromide. In each reaction the minor product was the corresponding azaindolizinone **7** and **9** and the major product the corresponding *N*-phenacylpyrimidones **11** and **12** which were readily cyclized to the 6- and 8-azaindolizinones **7** and **9** by heating at 180 °C. While the reaction of 4,6-dimethyl-2-pyrimidone with phenacyl bromide can only lead, on cyclization, to the 6-azaindolizin-5(6*H*)-one **7**, 2-methyl-4-pyrimidone could give either the 2-phenyl-8-azaindolizin-7(8*H*)-one **9** or

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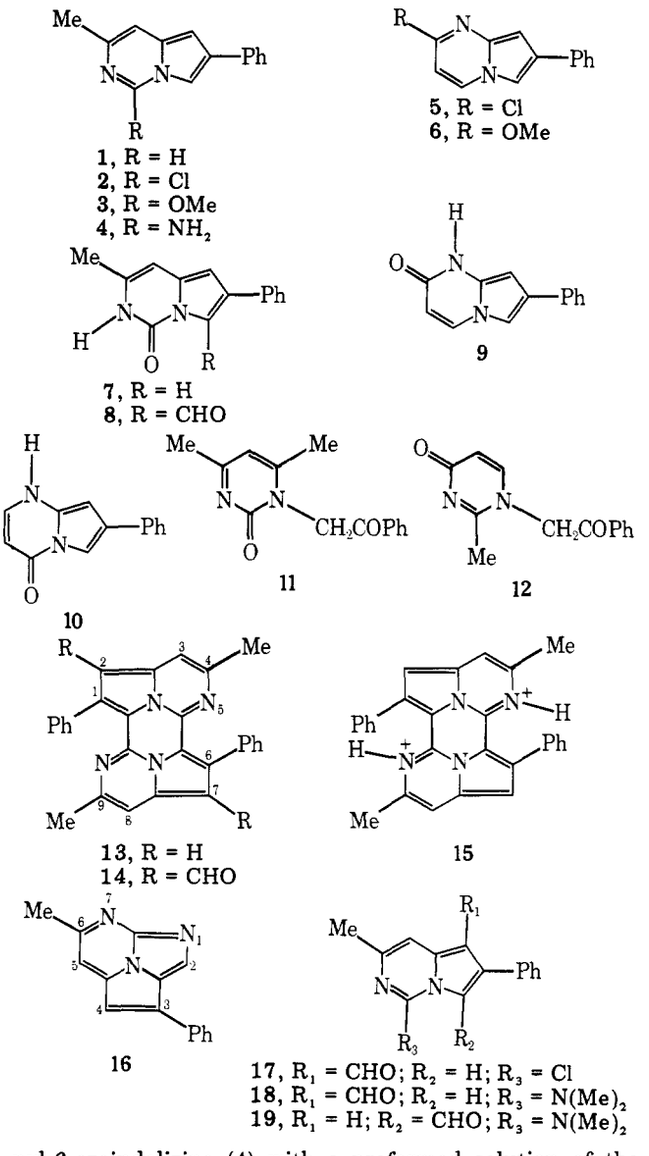
the 8-azaindolizin-5(8*H*)-one **10**. That the former 8-azaindolizin-7(8*H*)-one **9**, the product expected from quaternization at the more accessible nitrogen, was obtained was confirmed by its alternative formation by the demethylation of 7-methoxy-2-phenyl-8-azaindolizine (**6**).[3] The IR and ^{1}H NMR spectra of both the 6- and 8-azaindolizinones **7** and **9** show these compounds to exist in the keto forms. The conversion of the 6- and 8-azaindolizinones **7** and **9** to the corresponding chloroazaindolizines **2** and **5** by treatment with phosphoryl chloride occurred in good yield and presumably substitution occurs in a manner analogous to that postulated for the conversion of pyridones to chloropyridines.[10]

The chloroazaindolizines **2** and **5** were each treated with sodium hydroxide, sodium methoxide, and ammonia or sodamide. Hydrolysis of 5-chloro-7-methyl-2-phenyl-6-azaindolizine (**2**) with aqueous sodium hydroxide was slow and after refluxing for several hours only a 9% yield of the azaindolizinone **7** was obtained. The 7-chloro-2-phenyl-8-azaindolizine **5** when similarly treated with sodium hydroxide gave only unchanged starting material. In contrast methoxylation of either the 5-chloro-6-azaindolizine **2** or the 7-chloro-8-azaindolizine **5** occurred readily by refluxing each with sodium methoxide in boiling methanol to give the corresponding 5- and 7-methoxyazaindolizines **3** and **6** in high yield. Cleavage of the ether linkage of both **3** and **6** with hydrochloric acid gave the 6- and 8-azaindolizinones **7** and **9**. Replacement of chlorine by amino occurred when the 5-chloro-6-azaindolizine **2** was treated with a solution of anhydrous ammonia in ethanol in a sealed tube at 130–150 °C. The IR spectrum of the resulting 5-amino-7-methyl-2-phenyl-6-azaindolizine **4** showed the presence of the amino group by absorptions at 3480, 3340, and 1655 cm^{-1} and the ^{1}H NMR spectrum showed a broad 2 H signal at δ 7.14. No analgous replacement of chlorine by amino occurred when 7-chloro-2-phenyl-8-azaindolizine (**5**) was treated with either ammonia or with sodamide in liquid ammonia.

Refluxing 5-chloro-7-methyl-2-phenyl-6-azaindolizine (**2**) with phosphoryl chloride gave a dark red product whose mass spectrum showed a molecular ion at *m/e* 412 corresponding to the *m/e* value expected for a molecule constructed from two units of the percursor **2** less two molecules of hydrogen chloride. The ^{1}H NMR spectrum of this dark red compound was simple and apart from methyl and phenyl absorptions at δ 1.93 and δ 7.20–7.88 showed only two other singlets at δ 5.96 and 6.08. This suggests the compound to have the centrosymmetric structure **13**. Irradiation at the frequency of the methyl signal resulted in sharpening of the 2 H singlet at δ 6.08; this singlet was therefore assigned to H-3 and H-8 and that at δ 5.96 to H-2 and H-7. The bridging between the two 6-azaindolizine units leading to **13** can be envisaged to occur by the interaction of the electron rich C-3 site of one 6-azaindolizine molecule with the electron deficient C-5 site of another, accompanied by the elimination of hydrogen chloride. Small quantities of **13** were also isolated when the 6-azaindolizin-5(6*H*)-one **7** was treated with phosphoryl chloride, in its conversion to **2**. Formylation and protonation studies on **13**, which has 16 peripheral π electrons, suggest it to behave essentially as two separate 6-azaindolizine units. Thus formylation gave the 2,7-diformyl derivative **14** and the ^{1}H NMR spectrum of **13** in trifluoroacetic acid indicated the formation of the nitrogen protonated dication **15**. The spectrum of the dication was similar in pattern to that of the free base **13** showing no midfield methylene or methine signals. Slow deuterium exchange[12] of the H-2 and H-7 protons was observed when the spectrum of **13** was recorded in deuteriotrifluoroacetic acid.

Previous work on both 5-methyl-6-azaindolizines[2] and aminoindoles[13] suggested that formylation of 5-aminoazaindolizines may serve as a convenient route to diazacycl[3.2.2]-azines. Accordingly treatment of 5-amino-7-methyl-2-phenyl-6-azaindolizine (**4**) with a preformed solution of the Vilsmeier complex[14] at room temperature gave **16** as the sole product of reaction in 31% yield; significantly no 3-formyl derivative of **4** was isolated suggesting the attack of the Vilsmeier electrophile to occur only at the exocyclic 5-amino group.[2] The diazacyclazine **16** did not ring open on treatment with acid[15] nor did it undergo formylation. In contrast to the formylation of the 5-amino-6-azaindolizine **5** the 6-azaindolizin-5(6*H*)-one **7** and the 5-chloro-6-azaindolizine **2** gave formyl products resulting from attack at the electron rich C-3 and/or C-1 sites. Thus **7** gave 3-formyl-7-methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (**8**) whose formyl proton occurred at particularly low field (δ 10.82) due to the anisotropic deshielding effect of the nearby 5-keto group. Formylation of the 5-chloro-6-azaindolizine **2** gave in addition to **8** the three formyl-6-azaindolizines **17**, **18**, and **19**, all in low yield. The H-8 absorption of aldehydes **17** and **18** showed, when compared to the H-8 absorption position of their percursor **2**, peri shifts of 110 and 78 Hz, respectively; such shifts can only arise by formylation at C-1; aldehyde **19** showed no such per shift. Formation of the 5-dimethylamino-6-azaindolizine aldehydes **18** and **19** presumably arises by nucleophilic displacement of the 5-chloro group of **2** by dimethylamino during the course of formylation.



Experimental Section

The instruments used and general procedures are as given in ref 3. ^{1}H NMR signal assignments were made on the basis of the relative

proximity of the protons to nitrogen and by the assistance of double resonance; weakly coupled signals are marked by asterisks.

Attempted Reaction between 7-Methyl-2-phenyl-6-azaindolizine (1) and (a) Sodamide and (b) Sodium methoxide. (a) 7-Methyl-2-phenyl-6-azaindolizine[2] (1) (500 mg, 2.4 mmol) was added to a suspension of $NaNH_2$ (0.5 g, 12.8 mmol) in dry *N,N*-dimethylaniline[16] (20 cm^3) and the mixture was heated at 110 °C for 4 h under N_2. Water was added and the resulting mixture was extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to remove $CHCl_3$ and *N,N*-dimethylaniline. The residual solid was subjected to TLC which gave only starting material (177 mg, 35%). Raising the reaction temperature to 180 °C resulted in complete decomposition of the starting material.

(b) 7-Methyl-2-phenyl-6-azaindolizine (1) (1 g, 4.8 mmol) was added to a solution of NaOMe prepared from MeOH (20 cm^3) and Na (1 g, 43.5 mmol) and the resultant was refluxed for 8 h. The solvent was removed and the residue was treated with water and extracted with $CHCl_3$. The extract gave only unchanged starting material (0.93 g, 93%).

Reaction between 2-Hydroxy-4,6-dimethylpyridine and Phenacyl Bromide. A solution of 2-hydroxy-4,6-dimethylpyrimidine[17] (17.5 g, 0.14 mol) and phenacyl bromide (28.1 g, 0.14 mol) in EtOH (200 cm^3) was refluxed on a water bath for 1.5 h. The solid which separated was filtered from the hot solution, washed with a little boiling EtOH, and dried under vacuum to give **2-hydroxy-4,6-dimethylpyrimidine hydrobromide** (9.1 g, 31%) as a pale orange solid which did not melt below 300 °C: λ_{max} *305* nm (log ϵ 3.79); IR 847, 1627, 1735, 2500–3300 cm^{-1}; NMR [$(CD_3)_2SO$] 2.44 (6 H, Me-4 and Me-6), 6.74 (H-5).

Anal. Calcd for $C_8H_9N_2BrO$: C, 35.14; H, 4.42; N, 13.66; Br, 38.97. Found: C, 35.4; H, 4.5; N, 13.8; Br, 39.0.

The ethanolic solution was refluxed for a further 1.5 h and the EtOH was removed. The brown solid obtained was dissolved in water (400 cm^3) and the solution was extracted with ether (4 × 100 cm^3). $NaHCO_3$ (25 g) was added to the aqueous part and the solution was heated for 15 min on a boiling water bath. The solid (4.4 g) which separated was collected and dried. The UV and NMR spectra of this solid indicated it to be a 1:4 mixture of 7-methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (7) and 4,6-dimethyl-1-phenacylpyrimid-2(1*H*)-one (11).

The residual aqueous bicarbonate phase was extracted with $CHCl_3$ (5 × 200 cm^3) and the $CHCl_3$ extract was dried and evaporated to give a pale yellow solid which was recrystallized from $CHCl_3$ to give **4,6-dimethyl-1-phenacylpyrimid-2(1*H*)-one** (11) (1.17 g, 3%) as needles: mp 166.5 °C; λ_{max} *243*, 305 nm (log ϵ 4.17, 3.89); IR 760, 1225, 1608, 1655, 1690 cm^{-1}; NMR ($CDCl_3$) 2.11 (3 H, Me), 2.35 (3 H, Me), 5.51 (2 H, methylene), 6.16 (H-5), 7.33–8.13 (m, 5 H, Ph); mass spectrum *m/e* 242 (M^+, 40% base peak).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.83; N, 11.56. Found: C, 69.2; H, 5.7; N, 11.8.

7-Methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (7). The pyrimidone 11 (50 mg) was heated at 180 °C under vacuum (10 mm) for 15 min to give 7 (44 mg, 96%) as a buff colored solid: mp 275 °C dec; λ_{max} *253*, (277), (305) nm (log ϵ 4.69; 4.09; 3.72); IR 832, 1200, 1410, 1640, 1693, 3100, 3210, cm^{-1}; NMR [$(CD_3)_2SO$] 2.13* (3 H, Me-7), 6.23* (H-8), 6.58 (H-1), 7.20–7.78 (m, 5 H, Ph), 7.83 (H-3), 10.88 (broad, NH); mass spectrum *m/e* 224 (M^+, base peak).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.1; H, 5.3; N, 12.8.

2-Methyl-1-phenacylpyrimid-4(1*H*)-one (12). 4-Hydroxy-2-methylpyrimidine[18] (5.5 g, 50 mmol) and phenacyl bromide (10 g, 50 mmol) were heated together at 60 °C for 8 h in dimethylformamide (10 cm^3). The dark red product was dissolved in water (150 cm^3) and washed with $CHCl_3$ (3 × 100 cm^3). $NaHCO_3$ (5 g) was added to the aqueous part and the needles which separated were collected, washed with a little water, and dried at 50 °C (0.01 mm) to give hydrated **12** (3.2 g, 27%): λ_{max} *248* (log ϵ 4.47); IR 750, 1210, 1520, 1590, 1639, 1690, 3430 (broad) cm^{-1}; NMR [$(CD_3)_2SO$] 2.22 (3 H, Me), 5.72 (2 H, methylene), 5.97 (d, J = 7.5 Hz, H-5), 7.40–8.20 (m, 5 H, Ph), 7.59 (d, J = 7.5 Hz, H-6).

Anal. Calcd for $C_{13}H_{12}N_2O_2 \cdot \frac{1}{2}H_2O$: C, 65.81; H, 5.62. Found: C, 65.7; H, 5.6. Heating the hydrated pyrimidone **12** at 110 °C (0.01 mm) for 30 min gave the anhydrous pyrimidone; mp 172–182 °C, followed by the formation of new crystals at 184 °C which decomposed at 270 °C; λ_{max} *248* nm (log ϵ 4.48); IR 759, 1228, 1528, 1627, 1643, 1692 cm^{-1}; NMR ($CDCl_3$) 2.25 (3 H, Me), 5.50 (2 H, methylene), 6.05 (d, J = 7.5 Hz), 7.32 (d, J = 7.5 Hz, H-6), 7.40–8.17 (m, 5 H, Ph), the NMR spectrum in $(CD_3)_2SO$ was identical to that of the above hydrated derivative; mass spectrum *m/e* 228 (M^+, 1% base peak), 210 (M^+ − 18, base peak).

Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found C, 68.1; H, 5.4; N, 12.3.

2-Phenyl-8-azaindolizin-7(8*H*)-one (9). (a) A solution of 7-methoxy-2-phenyl-8-azaindolizine[3] (6) (100 mg) in concentrated hydrochloric acid (20 cm^3) was heated on a boiling water bath for 30 min and evaporated to dryness. The solid obtained was dissolved in water (20 cm^3) and the solution was made basic by the addition of $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried and evaporated and the residue was sublimed at 200 °C (0.01 mm) to give **9** (80 mg, 85%) as a pale yellow solid which decomposed at 270 °C: λ_{max} *243*, (249) 290, 299, (329) nm (log ϵ 4.50, 4.47, 4.12, 4.13, 3.54); IR 728, 760, 811, 968, 1219, 1440, 1680, 2800, 3140 cm^{-1}; NMR [$(CD_3)_2SO$] 5.78 (d, J = 8.0 Hz, H-6), 5.89 (d, J = 1.5 Hz, H-1), 7.06–7.70 (m, 5 H, Ph), 7.36 (H-3), 8.17 (d, J = 8.0 Hz, H-5), 11.52 (broad, NH, disappears on addition of D_2O); mass spectrum *m/e* 210 (M^+, base peak).

Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found; C, 74.0; H, 5.0; N, 13.3.

(b) The pyrimidone **12** (100 mg) was heated at 180 °C under vacuum (15 mm) for 30 min and the product sublimed at 200 °C (0.01 mm) to give **9** (90 mg, 98%) with identical spectral characteristics to the sample obtained above.

Reaction between 7-Methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (7) and Phosphoryl Chloride. A solution of the 6-azaindolizinone **7** (300 mg) in $POCl_3$ (45 cm^3) was refluxed for 4 h and the bulk of the $POCl_3$ was then removed at 60 °C (10 mm). The dark colored residue was poured onto crushed ice (30 g), basified by the addition of 2 M NaOH, and extracted with $CHCl_3$ (4 × 50 cm^3). The $CHCl_3$ extract was dried and evaporated and the gum obtained was subjected to TLC with benzene. Two main bands developed. The material from the fast moving orange colored band was extracted with $CHCl_3$ and the extract concentrated to approximately 5 cm^3 and cooled in ice. **4,9-Dimethyl-1,6-diphenyldi(6-azaindolizino)-[3,4,5-*af*:3′,4′,5′-*dc*]pyrazine (13)** (8 mg, 3.1%) separated as dark red prisms: mp 262.5–265 °C dec; λ_{max} (CH_2Cl_2) *268*, (288), (410), (438), 460, 486 nm (log ϵ 4.80, 4.55, 3.47, 3.87, 4.09, 4.17); IR 698, 760, 839, 1387, 1541, 1615 cm^{-1}; NMR ($CDCl_3$) 1.93* (6 H, Me-4 and Me-9), 5.96 (2 H, H-2 and H-7), 6.08* (2 H, H-3 and H-8), 7.20–7.88 (m, 10 H, Ph-1 and Ph-6); NMR (CF_3COOH) 2.20* (6 H, Me-4 and Me-9), 6.69* (2 H, H-3 and H-8), 6.78 (2 H, H-2 and H-7), 7.70 (10 H, Ph-1 and Ph-6); mass spectrum *m/e* 412 (M^+, base peak).

Anal. Calcd for $C_{28}H_{20}N_4$: C, 81.53; H, 4.89; N, 13.58. Found C, 81.7; H, 4.7; N, 13.8.

The material from the slower moving band which gave a green Ehrlich's test was extracted and recrystallized from petroleum ether to give **5-chloro-7-methyl-2-phenyl-6-azaindolizine (2)** (243 mg, 75%) as white flakes: mp 144.5–145 °C; λ_{max} *254*, (256), (283), (300), 358 (broad) nm (log ϵ 4.71, 4.71, 3.95, 3.57, 3.45); IR 728, 768, 1245, 1407, 1620 cm^{-1}; NMR ($CDCl_3$) 2.39* (3 H, Me-7), 6.70 (H-1), 7.00* (h-8), 7.10–7.75 (m, 5 H, Ph), 7.70 (H-3); mass spectrum (^{35}Cl) *m/e* 242 (M^+, base peak).

Anal. Calcd for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.3; H, 4.3; N, 11.5; Cl, 14.9.

7-Chloro-2-phenyl-8-azaindolizine (5). A solution of the 8-azaindolizinone 9 (100 mg) in $POCl_3$ (10 cm^3) was gently refluxed for 4 h and the product was worked up as in the reaction between the 6-azaindolizinone **7** and $POCl_3$. TLC with benzene/ethyl acetate (20:1) gave a fast-moving yellow band. The material from this band was extracted and recrystallized from benzene to give **5** (82 mg, 75%): mp 212 °C dec; λ_{max} *254*, 325, 370 (broad) nm (log ϵ 4.60, 3.88, 3.47); IR 737, 770, 1090, 1132, 1510, 1609 cm^{-1}; NMR ($CDCl_3$) 6.50 (d, J = 7.0 Hz, H-6), 6.84 (H-1), 7.26 (H-3), 7.30–7.76 (m, 5 H, Ph), 8.07 (d, J = 7.0 Hz, H-5); mass spectrum (^{35}Cl) *m/e* 228 (M^+, base peak).

Anal. Calcd for $C_{13}H_9N_2Cl$: C, 68.28; H, 3.97; N, 12.25; Cl, 15.50. Found: C, 68.5; H, 4.1; N, 12.0; Cl, 15.4.

Reaction between 5-Chloro-7-methyl-2-phenyl-6-azaindolizine (2) and (a) Hydroxide ion, (b) Methoxide, and (c) Ammonia. (a) A suspension of **2** (20 mg) in aqueous $NaHCO_3$ was heated on a boiling water bath for 30 min, cooled, and extracted with $CHCl_3$. The extract was dried and evaporated and the residue was subjected to TLC with benzene and then with benzene/ethyl acetate (4:1). The fast-moving band gave unchanged **2** (12 mg, 60%). TLC indicated the crude hydrolysis product to contain only traces of the azaindolizinone **7**.

A suspension of **2** (35 mg) in 2 M aqueous NaOH was heated on a boiling water bath for 6 h and the hydrolysis product was worked up as in the attempted hydrolysis using $NaHCO_3$. The fast-moving band gave unchanged **2** (15 mg, 43%). The slower-moving band gave (7), (3 mg, 9%).

(b) A suspension of **2** (40 mg, 0.16 mmol) in a methanolic solution of NaOMe obtained from MeOH (20 cm^3) and Na (0.3 g) was refluxed for 30 min. The MeOH was evaporated and the residue was dissolved

in water, dried, and evaporated and the residue obtained was subjected to TLC with benzene. Only one band developed; the material from this band was recrystallized from petroleum ether to give **5-methoxy-7-methyl-2-phenyl-6-azaindolizine (3)** (32 mg, 81%) as pale green needles: mp 87 °C; λ_{max} *253*, (276), (289), 322 nm (log ϵ 4.67, 4.02, 3.78, 3.46); IR 700, 758, 1570, 1630 cm^{-1}; NMR ($CDCl_3$) 2.30* (3 H, Me-7), 4.13 (3 H, OMe), 6.47 (H-1), 6.65* (H-8), 7.20–7.80 (m, 5 H, Ph), 7.55 (H-3).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.8; H, 5.8; N, 11.8.

Demethylation of **3** (10 mg) with hydrochloric acid gave **7** in quantitative yield.

(c) The 6-azaindolizine **2** (100 mg) was heated at 140 °C for 4 h in a sealed glass tube containing EtOH (10 cm^3) saturated with anhydrous NH_3 at 0 °C. After cooling the tube was opened and the solvent was evaporated. The residue was subjected to TLC with benzene/ethyl acetate (2:1) and gave one main band. The material from this band was recrystallized from benzene containing a small percentage of EtOH to give **5-amino-7-methyl-2-phenyl-6-azaindolizine (4)** (65 mg, 71%) as small white crystals which decomposed at temperatures greater than 215 °C: λ_{max} *257*, 301, 331 (broad) nm (log ϵ 4.61, 3.82, 3.49; IR 699, 765, 1540, 1610, 1655, 3050, 3340, 3450 cm^{-1}; NMR [$(CD_3)_2SO$] 2.17* (3 H, Me), 6.50 (2 H, H-1 and H-8), 7.14 (2 H, broad, NH_2), 7.20–7.78 (m, 5 H, Ph), 7.89 (H-3); NMR ($CDCl_3$) 2.32 (3 H, Me), 6.52 (H-1), 6.65* (H-8), 7.12–7.74 (m, 5 H, Ph), 7.22 (H-3); mass spectrum *m/e* 223 (M^+, base peak).

Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.3; H, 5.9; N, 18.6.

Attempted Reaction between 7-Chloro-2-phenyl-8-azaindolizine (5) and (a) Hydroxide Ion, (b) Amide Ion, and (c) Ammonia. (a) A suspension of **5** (10 mg) in 2 M aqueous NaOH (5 cm^3) was heated on a boiling water bath for 6 h, cooled, and extracted with $CHCl_3$. The extract was dried and evaporated to give unchanged **5** in quantitative yield.

The same procedure was repeated with the suspension contained in a sealed tube at a reaction temperature of 130 °C. The crude product was subjected to TLC using benzene and benzene/ethanol (10:1); this gave only unchanged **5** (6.3 mg, 63%).

(b) The azaindolizine **5** (20 mg, 0.08 mmol) was added to a stirred suspension of $NaNH_2$ (100 mg, 2.6 mmol) in liquid NH_3 (10 cm^3) at −33 °C. The suspension gradually darkened and after 30 min the NH_3 was allowed to evaporate and the residue was treated with water and extracted with $CHCl_3$. The extract was evaporated to give a brown amorphous solid from which no crystalline material could be obtained.

(c) The azaindolizine **5** (30 mg) was heated at 140 °C and also at 200 °C for 4 h in a sealed glass tube containing EtOH (10 cm^3) which had been saturated with anhydrous NH_3 at 0 °C. In each case only unchanged **5** was recovered.

Reaction between 7-Chloro-2-phenyl-8-azaindolizine (5) and Methoxide Ion. The chloro-8-azaindolizine **5** (14 mg, 0.06 mmol) in MeOH (2 cm^3) was added to a solution of NaOMe, obtained from MeOH (4 cm^3) and Na (50 mg, 2.2 mmol), and refluxed for 2 h. The solvent was removed, water (25 cm^3) was added, and the mixture was extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to yield **6** (13 mg, 97%) as a yellow crystalline solid, mp 139–143 °C, with spectral characteristics identical with those previously reported.[3]

4,9-Dimethyl-1,6-diphenyldi(6-azaindolizino)[3,4,5-*af*:3′,4′,5′-*dc*]pyrazine (13). A solution of the chloro-6-azaindolizine **2** (5 mg) in $POCl_3$ (10 cm^3) was refluxed for 4 h. The excess $POCl_3$ was removed at 60 °C (10 mm) and ice (5 g) was added to the residue which was then basified with 2 M NaOH. Extraction with $CHCl_3$ and evaporation of the solvent gave **13** (3 mg, 70%) with identical mp and IR spectrum to that of the sample obtained from **7** with $POCl_3$.

Formylation of 4,9-Dimethyl-1,6-diphenyldi(6-azaindolizino)[3,4,5-*af*:3′,4′,5′-*dc*]pyrazine (13). Formylation[2] of **13** (20 mg) gave a product which was subjected to TLC with benzene/ethyl acetate (10:1). The material from the slow moving orange band was extracted to give **2,7-diformyl-4,9-dimethyl-1,6-diphenyldi(6-azaindolizino)[3,4,5-*af*:3′,4′,5′-*dc*]pyrazine (14)** (22 mg, 97%): mp >350 °C; λ_{max} (CH_2Cl_2) *274*, 370, (452), 467 nm (log ϵ 4.72, 4.12, 4.19, 4.28); IR 702, 830, 1200, 1500, 1545, 1608, 1645 cm^{-1}; NMR (CF_3COOH) 2.28* (6 H, Me-4 and Me-9), 7.58* (2 H, H-3 and H-8), 7.72 (10 H, Ph-1 and Ph-6), 9.72 (2 H, CHO-2 and CHO-7). Calcd mass for $C_{30}H_{20}N_4O_2$: 468.1586. Found M^+ (base beak): 468.1585.

6-Methyl-3-phenyl-1,7-diazacyclo[3.2.2]azine (16). Formylation[2] of the amino-6-azaindolizine **4** (50 mg) yielded a product which after TLC with petroleum ether/ethyl acetate (1:1) gave two bands. The material from the faster moving band gave unchanged **4** (6 mg). The material from the following yellow band on extraction and recrystallization from benzene/petroleum ether gave **16** (16 mg, 31%) as yellow needles: mp 155–157 °C; λ_{max} (238), *247*, 332, 404, 416 nm (log ϵ 4.34, 4.43, 4.30, 3.72, 3.69); IR 700, 778, 1133, 1540, 1595 cm^{-1}; NMR ($CDCl_3$) 3.00* (3 H, Me), 7.33–8.11 (m, 5 H, Ph), 7.40 (H-1), 7.65* (H-7), 8.83 (H-3). Calcd mass for $C_{15}H_{11}N_3$: 233.0952. Found M^+ (base peak): 233.0952.

An attempted formylation[2] of **16** (5 mg, 0.02 mmol) gave only unchanged starting material (3 mg).

Attempted Ring Opening of 6-Methyl-3-phenyl-1,7-diazacyclo[3.2.2]azine (16). A solution of **16** (5 mg) in MeOH (2 cm^3) containing concentrated hydrochloric acid (0.2 cm^3) was left at room temperature for 24 h. The solution was concentrated under reduced pressure, basified with 2 M aqueous sodium hydroxide, and extracted with ether. The extract gave unchanged **16** (5 mg).

3-Formyl-7-methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (8). Formylation[2] of the azaindolizin-5(6*H*)-one **7** (100 mg) gave **8** (58 mg, 52%) as yellow crystals from $CHCl_3$: mp 258 °C dec; λ_{max} 225, *272*, (293), 365 nm (log ϵ 4.12, 4.28, 3.86, 4.19); IR 791, 838, 1360, 1638, 1690, 3110, 3250 cm^{-1}; NMR [$(CD_3)_2SO$] 2.22* (3 H, Me), 6.46* (H-8), 6.49 (H-1), 7.28–7.74 (m, 5 H, Ph), 10.82 (CHO); mass spectrum *m/e* 252 (M^+, base peak).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79. Found: C, 71.3; H, 4.9.

Formylation of 5-Chloro-7-methyl-2-phenyl-6-azaindolizine (2). Formylation[2] of **2** (58 mg) gave four products which were separated by TLC using benzene–ethyl acetate (3:1). The material from the fastest moving band gave **5-chloro-1-formyl-7-methyl-2-phenyl-6-azaindolizine (17)** (2 mg, 3%): mp 169.5–170 °C: λ_{max} (243), *249*, (276), 339 nm (log ϵ 4.27, 4.29, 3.71, 3.92); IR 700, 728, 1220, 1420, 1609, 1650 cm^{-1}; NMR ($CDCl_3$) 2.55* (3 H, Me), 7.47 (H-3), 7.50 (5 H, Ph), 8.10* (H-8), 10.04 (CHO). Calcd mass for $C_{15}H_{11}{}^{35}ClN_2O$: 270.0559. Found M^+ (79% base peak): 270.0555.

The next band gave a product which crystallized from benzene/petroleum ether to give **5-(*N*,*N*-dimethylamino)-1-formyl-7-methyl-2-phenyl-6-azaindolizine (18)** (4 mg, 6.0%) as needles: mp 208.5 °C; λ_{max} *240*, 367 nm (log ϵ 4.54, 424);IR 757, 850, 1410, 1510, 1648 cm^{-1}; NMR ($CDCl_3$) 2.47* (3 H, Me-7), 3.07 (6 H, NMe_2), 7.22 (H-3), 7.32–7.64 (m, 5 H, Ph), 7.78* (H-8), 9.98 (CHO). Calcd mass for $C_{17}H_{17}N_3O$: 279.1371. Found M^+ (base peak): 279.1369.

The material from the next yellow band was extracted and recrystallized from benzene/petroleum ether to give **5-(*N*,*N*-dimethylamino)-3-formyl-7-methyl-2-phenyl-6-azaindolizine (19)** (17 mg, 25%) as yellow crystals: mp 178 °C; λ_{max} *246*, 272, 330 (broad), 407 nm (log ϵ 4.48, 4.16, 3.70, 4.05); IR 702, 795, 1170, 1352, 1530, 1610, 1645 cm^{-1}; NMR ($CDCl_3$) 2.38* (Me-7), 3.05 (6 H, NMe_2), 6.37 (H-1), 6.68* (H-8), 7.30–7.72 (m, 5 H, Ph), 9.80 (CHO). Calcd mass for $C_{17}H_{17}N_3O$: 279.1371. Found M^+ (35% base peak): 279.1369. The slowest moving band gave **8** (17 mg, 28%).

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Use of (Thio)Acetal Esters as Reagents for the Protection of Alcohols. Synthesis of 2-Tetrahydrothienyl Ethers[1]

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Primary and secondary alcohols can be converted in high yields into their 2-tetrahydrothienyl (THT) ethers by an acid-catalyzed exchange reaction with 2-tetrahydrothienyl diphenylacetate. The characteristics of the THT group as a protecting group for alcohols are discussed. Conditions for quantitative removal under neutral conditions are described. This acetal exchange reaction also provides an excellent method for the preparation of other mixed acetals, in particular THP and THF ethers.

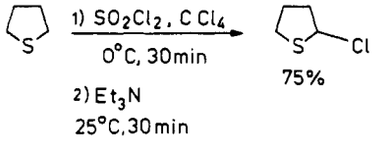
The protection of hydroxyl groups, often as mixed acetals, is an extensively used technique in the synthesis of polyfunctional compounds.[2] Recently, several new protecting groups have been introduced, which can be removed with a highly specific reagent.[3]

The methylthiomethyl (MTM) group has been recommended in this respect because of its stability toward both basic and mildly acidic conditions and its easy cleavage under neutral conditions with certain metal ions.[3b,4,5] In the acetal series, protecting groups with a cyclic structure, in particular 2-tetrahydropyranyl (THP) ethers, have been employed frequently. We have focused our attention on the synthesis of 2-tetrahydrothienyl (THT) ethers. Previously, two THT ethers have been prepared in moderate yield by reaction of alcohols with 2,3-dihydrothiophene,[5] but this procedure is not suitable for the introduction of a THT protecting group. In this study we describe an efficient method for the protection of primary and secondary alcohols with a THT group. This method appears to be also very suitable for the introduction of THP and THF groups. The possibility of selective cleavage of THT ethers in the presence of THF ethers and vice versa is discussed.

Results and Discussion

Synthesis of 2-Chlorotetrahydrothiophene (2-Cl-THT). In view of the favorable results obtained with the reaction of 2-chlorotetrahydrofuran with alcohols,[3d] our initial objective was to use 2-Cl-THT as a reagent for introducing the THT group. Various reports in the literature deal with the chlorination of THT.[6,7] 2-Cl-THT has not been isolated in a pure state because of its lack of stability.[6b]

Conversion of THT into 2-Cl-THT could be accomplished in apolar solvents [*N*-chlorosuccinimide in benzene at 25 °C (50% conversion)[6b] or chlorine in carbon tetrachloride at 40 °C (80% conversion)[6c]]. By contrast, sulfuryl chloride in refluxing pentane was reported to cause extensive polymerization.[6a] Because of the successful application of sulfuryl chloride to the chlorination of tetrahydrofuran[3d] and 1,3-dithiane,[8] we have reexamined its reaction with THT. It appeared that THT could be converted into 2-Cl-THT in 75% yield by a simple and fast procedure.[9]



Polymerization was effectively retarded by addition of triethylamine. In more polar solvents, mixtures of 2-Cl-THT and 2,3-diCl-THT were formed and the yield of chlorinated products decreased (see Table I). The reaction exhibits the same characteristics as the reaction with chlorine which was studied by Wilson and Albert.[7]

It is generally accepted[10] that upon reaction of sulfides with chlorinating agents, sulfonium salts are formed in the first step. In general, two structures are possible.[11] To our knowledge no spectroscopic data are available on sulfonium salts formed with chlorine or sulfuryl chloride.[12] Upon addition of sulfuryl chloride to a solution of THT in $CDCl_3$, the signals of the original NMR spectrum shifted downfield appreciably (α protons, 1.4 ppm; β protons, 0.8 ppm).[13] Interestingly, exactly the same spectrum was obtained when *thionyl chloride* (1.0 equiv) was added at −65 °C to a $CDCl_3$ solution of *THT sulfoxide*.[10e] When $CDCl_3$ solutions of THT and chlorine (1.0 equiv each) were mixed at −75 °C, the NMR spectrum revealed the presence of both THT and the chlorosulfonium chloride **2** (δ 4.2 and 2.7) in about equal quantities. Comparison with data obtained for the 1:1 adduct of THT and bromine (**2a**) (α and β protons shifted 0.8 and 0.3 ppm)[12] leads to the conclusion that the charge separation in the adduct with chlorine is more pronounced, and therefore structure **2** seems most likely. Also, these data indicate that chlorosulfonium salts **1** and **2** have the same cation since their spectra are identical and a different anion. Only **2** is in equilibrium with its components because of the better nucleophilicity of chloride ion.

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