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Azaindolizines. 4. Synthesis and Formylation of 8-Azaindolizines

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Received November 12, 1976

The 8-azaindolizines (**1–10**) were synthesized by a Chichibabin reaction between 2-methylpyrimidines and an α-halo ketone. 2-Methylpyrimidine itself gave in low yield 2-carbethoxy- (**2**), 2-methyl- (**3**), 2,3-dimethyl- (**4**), and 2-phenyl-8-azaindolizine (**5**) when reacted with ethyl bromopyruvate, bromoacetone, 3-bromobutanone, and phenacyl bromide; hydrolysis and decarboxylation of **2** gave the parent system (**1**). 2,4-Dimethylpyrimidine similarly gave **6** and **7** with bromoacetone and 3-bromobutanone. 2-Methyl-4-methoxypyrimidine when reacted with phenacyl bromide and bromoacetone gave the expected 7-methoxy-8-azaindolizine structures **8** and **9** along with the 8-methyl-8-azaindolizinones **22, 23,** and **32.** 2-Methyl-4-hydroxypyrimidine with bromoacetone gave **25** and **34.** The structures of the 8-azaindolizines isolated were deduced from their ^1H NMR spectra and the ^1H NMR spectra of their formyl derivatives. Formylation has been shown to occur preferentially at C-3, and 1,3-dipolar addition of dimethyl acetylenedicarboxylate with **6** and **23** occurs to give the corresponding 5-azacycl[3.2.2]azines **37** and **38.**

Substituted 8-azaindolizines have been prepared chiefly by reaction of a 1,3-dicarbonyl compound with a 2-aminopyrrole stabilized by electron-withdrawing groups.[1] An alternative direct synthetic route to 8-azaindolizines would be to employ the Chichibabin reaction[2] between a 2-methylpyrimidine and an α-halo ketone. The simplest and first reported 8-azaindolizine, 5,7-dimethyl-2-phenyl-8-azaindolizine (**11**), was claimed[3] to be obtained by this route using 2,4,6-trimethylpyrimidine and phenacyl bromide; recently we showed[4] that the product of this reaction is the isomeric 5,7-dimethyl-2-phenyl-6-azaindolizine (**14**). In this paper we report the synthesis of the parent 8-azaindolizine (**1**) and several simple derivatives by reaction of a 2-methylpyrimidine with a number of α-halo ketones. The structures of the 8-azaindolizines isolated were determined from their ^1H NMR spectra, shown in Table I, and the ^1H NMR spectra of their formylated derivatives. The assignments of the protons in these structures were made on the basis of their proximity to nitrogen, by the assistance of double irradiation, by deuterium exchange,[5,6] and by a comparative examination of related spectra.

Reaction between 2-methylpyrimidine and ethyl bromopyruvate gave a product whose infrared and ^1H NMR spectra indicated it to be 2-carbethoxy-8-azaindolizine (**2**). The ^1H NMR spectrum showed a 2 H methylene quartet and a 3 H methyl triplet at δ 4.38 and 1.37 assigned to the carbethoxy ethyl group, two lower field 1 H singlets at δ 7.03 and 7.71 assigned to H-1 and H-3, respectively, a 1 H complex signal approximating to a triplet at δ 6.58 assigned to H-6, and a 2 H doublet at δ 8.14 assigned to H-5 and H-7. Alkaline hydrolysis of the ester (**2**) followed by neutralization and decarboxylation gave the parent 8-azaindolizine (**1**) as a yellow oil, stable in vacuo but which decomposed rapidly on exposure to air; the ^1H NMR spectrum of **1** is shown in Figure 1. The 1 H apparent triplet at δ 6.98 is assigned to H-2 since it is coupled with the adjacent H-1 and H-3 protons. The H-1 and H-3 signals are weakly coupled to each other and occurred as differentially exchangeable[7] multiplets at δ 6.64 and 7.19, respectively. The 1 H apparent quartet centered at δ 6.48 is assigned to H-6, its multiplicity arising mainly from coupling with H-5 and H-7. The two lower field overlapping multiplets at δ 8.00–8.24 were assigned to H-5 and H-7. Irradiation at δ 6.48 simplified the multiplet at δ 8.00–8.24 to two broad singlets and to some extent sharpened the H-3 signal at δ 7.19. Support for the above assignments was provided from the ^1H NMR spectrum of its formyl derivative (**17**). The spectrum of **17**, when compared to the spectrum of **1**, showed the absence of the H-3 multiplet, the emergence of a 1 H formyl singlet at δ 9.73, and a marked downfield shift (ca. 170 Hz) of the position of one of the lower field signals; such a shift can only be accounted for by the anisotropic deshielding effect of a 3-formyl group via its peri orientation to H-5. 2-Methylpyrimidine reacted with bromoacetone, bromobutanone, and phenacyl bromide to give 2-methyl- (**3**), 2,3-dimethyl- (**4**), and 2-phenyl-8-azaindolizine (**5**).

Reaction between 2,4-dimethylpyrimidine and phenacyl

Table I. Chemical Shifts (δ) in the 100-MHz ^{1}H NMR Spectra of the 8-Azaindolizines (1–10) in $CDCl_3$[a]

Structure	R_1	R_2	R_3	H-1	H-5	H-6
1	6.98 dd* J = 3.5, 3.0 Hz	7.19 dd* J = 3.0, 1.5 Hz	8.00–8.24 m	6.64 dd* J = 3.5, 1.5 Hz	8.00–8.24 m	6.40–6.56 m
2	1.37 t, 4.38 q J = 7.0 Hz (COOEt)	7.71 d* J = 1.5 Hz	8.14 d* J = 5.5 Hz	7.03 d* J = 1.5 Hz	8.14 d* J = 5.5 Hz	6.58 dd* J = 5.5, 5.5 Hz
3	2.34 (CH_3)	6.99*	7.91–8.15 m	6.44*	7.91–8.15 m	6.33–6.53 m
4	2.32 (CH_3)	2.36 (CH_3)	7.80–8.04 m	6.47	7.84–8.04 m	6.42–6.60 m
5	7.17–7.77 m (Ph)	7.46*	8.00–8.23 m	6.91*	8.00–8.23 m	6.44–6.58 m
6	2.30 (CH_3)	6.87*	2.43 (CH_3)	6.27*	7.90 d J = 7.0 Hz	6.27 d J = 7.0 Hz
7	2.28 (2.31) (CH_3)	2.31 (2.28) (CH_3)	2.45 (CH_3)	6.27	7.76 d J = 7.5 Hz	6.34 d J = 7.5 Hz
8	7.10–7.70 m (Ph)	7.20*	3.94 (OCH_3)	6.54*	7.90 d J = 7.5 Hz	6.08 d J = 7.5 Hz
9	2.26 (CH_3)	6.75*	3.92 (OCH_3)	6.07*	7.85 d J = 7.5 Hz	6.02 d J = 7.5 Hz
10	1.36 t, 4.34 q J = 7.0 Hz (COOEt)	7.49*	3.94 (OCH_3)	6.61*	7.92 d J = 7.5 Hz	6.18 d J = 7.5 Hz

[a] Unless otherwise stated values given refer to singlet absorption: d = doublet, dd = double doublet, t = triplet, q = quartet, and m = complex multiplet absorption. Coupling constants (hertz) are approximate and measured directly from spectra. Signals marked by an asterisk are broadened and/or further split.

bromide proved unsuccessful.[3] Reaction with bromoacetone and bromobutanone, however, gave in low yields the 7-methyl-8-azaindolizines **6** and **7**, respectively. The isolation of the 7-methyl-8-azaindolizines **6** and **7** rather than the isomeric 5-methyl-8-azaindolizines **12** and **13** or the 6-azaindolizines **15** and **16** would be expected by attack of the halo ketone at the more accessible nitrogen of 2,4-dimethylpyrimidine, followed by cyclization via the 2-methyl group. That the products of reaction were the 7-methyl-8-azaindolizines **6** and **7** was shown by a comparative examination of their ^{1}H NMR spectra with the ^{1}H NMR spectra of their formylation products **18** and **21**. Thus the spectrum of **6** showed two high-field 3 H singlets at δ 2.30 and 2.43 assigned to the 2- and 7-methyl protons, two deuterium exchangeable[7] lower field aromatic singlets at δ 6.27 and 6.87 assigned to H-1 and H-3, and a pair of spin coupled doublets at δ 7.90 and 6.27 assigned to H-5 and H-6, respectively. Vilsmeier formylation of **6** gave the 3-formyl-2,7-dimethyl-8-azaindolizine (**18**), which showed, relative to the spectrum of **6**, the absence of the lower field H-3 singlet and a large deshielding (179 Hz) of the lower field H-5 doublet due to the peri orientated 3-formyl group whose signal occurred at δ 9.79. Reduction of **18** using lithium aluminum hydride and aluminum chloride gave 2,3,7-trimethyl-8-azaindolizine (**7**) whose ^{1}H NMR spectrum was identical with the spectrum of the product obtained from the reaction between 3-bromobutanone and 2,4-dimethylpyrimidine. Formylation of **7** gave a compound whose ^{1}H NMR spectrum when compared to that of **7** showed the absence of the 1 H singlet at δ 6.27 and the emergence of a 1 H singlet at δ 10.43 assigned to the presence of a 1-formyl proton. The absorption positions of the H-5 and H-6 doublets of 1-formyl-2,3,7-trimethyl-8-azaindolizine (**21**) were only marginally lower than their positions in **7**. Had 2,5-dimethyl-8-azaindolizine (**12**) been isolated from the reaction between bromoacetone and 2,4-dimethylpyrimidine its formylation product could in no way show a peri shift by formylation at C-1 or C-3; had the 6-azaindolizine **15** been isolated formylation would be expected to yield a 5-azacycl[3.2.2]azine structure.[4]

The low yields (0.2–5.6%) obtained for simple 8-azaindolizines compared with the yields (6.0–89%) obtained in the Chichibabin synthesis of 6-azaindolizines from 4-methylpyrimidines[4,8,9] and the preferential formation of 6-azaindolizines from the reaction between 2,4,6-trimethylpyrimidine and bromoacetone or phenacyl bromide[4] suggest that the 2-methyl group is less reactive than the 4-methyl group in methyl substituted pyrimidines.[10] Since a 4-methoxy group would be expected to increase the reactivity of the 2-methyl group, it was hoped that improved yields of 8-azaindolizines would be obtained from the reaction of 4-methoxy-2-methylpyrimidine and an α-halo ketone. Quaternization of 4-methoxy-2-methylpyrimidine with phenacyl bromide at room temperature followed by cyclization gave in fact 7-methoxy-2-phenyl-8-azaindolizine (**8**) in 27% yield. When quaternization was carried out at higher temperatures, however, the main product (58%) was a compound isomeric with **8**, but whose infrared spectrum showed a strong carbonyl band. Further, although the pattern of the ^{1}H NMR spectrum

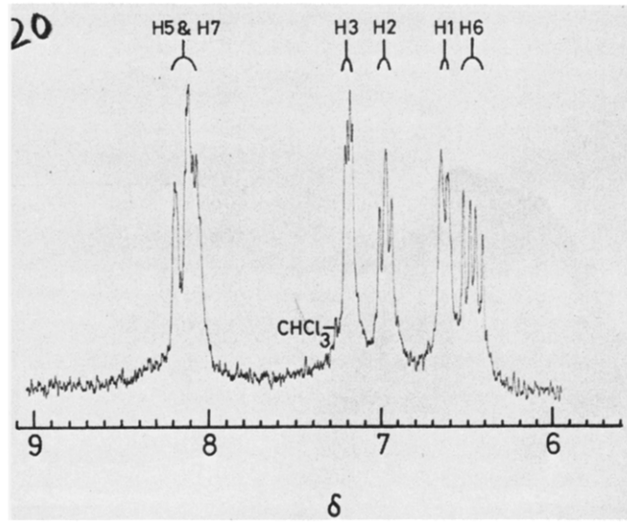


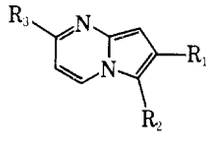
Figure 1. 100 MHz ^{1}H NMR spectrum of 8-azaindolizine in $CDCl_3$.

of this compound was similar to that of the methoxy-2-phenyl-8-azaindolizine (**8**), the chemical shift of the lower field 3 H methyl signal occurred at higher field (δ 3.48). This suggests that the methyl group is attached to nitrogen rather than oxygen and that the main product of reaction between 4-methoxy-2-methylpyrimidine and phenacyl bromide at the higher temperature is 8-methyl-2-phenyl-8-azaindolizin-7(8*H*)-one (**22**). This structure was confirmed by formylation to give **26.** Minor products isolated from this reaction were the *N*-phenacylindolizinones **24** and **31.** The main product (**22**) is possibly formed from an *N*-methylpyrimidone by rearrangement of the methoxypyrimidine,[11,12] and the minor products (**24** and **31**) from 2-methylpyrimidone by demethylation of 4-methoxy-2-methylpyrimidine with hydrogen bromide produced during quaternization.

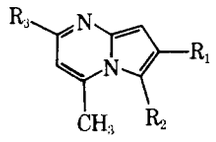
The reaction between 4-methoxy-2-methylpyrimidine and bromoacetone gave the 2,8-dimethyl-8-azaindolizin-7(8*H*)-one (**23**) as the major product (39%) even when quaternization was carried out at room temperature. Only a small amount (1.5%) of the 8-azaindolizine **9** was isolated together with the indolizinones **32** and **34.** Similar products, viz., **10, 28, 29,** and **33,** all in low yields, were obtained when 4-methoxy-2-methylpyrimidine was treated with ethyl bromopyruvate.

Confirmation for the indolizinone structures was obtained by reacting 4-hydroxy 2-methylpyrimidine with bromoacetone. This reaction gave two *N*-acetonylindolizinones presumably resulting from bicarbonate cyclization of the *N,N*-diacetonyl quaternary salt (**36**). One of the products was shown to be 8-acetonyl-2-methyl-8-azaindolizin-7(8*H*)-one (**25**) since on formylation it showed a peri shift (162 Hz) of its lower field doublet signal assigned to H-5. The UV spectrum of this compound closely resembled that of the major product (**23**) of the reaction between 4-methoxy-2-methylpyrimidine and bromoacetone. Formylation studies on the other product from the reaction between 4-hydroxy-2-methylprimidine and bromoacetone indicated it to be 8-acetonyl-2-methyl-8-azaindolizin-5(8*H*)-one (**34**), identical with one of the minor products isolated from the reaction between 4-methoxy-2-methylpyrimidine and bromoacetone.

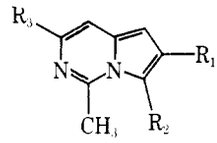
Although formylation was primarily employed to aid in structure elucidation of the products isolated, it also indicates the preferred site of reaction; thus the parent 8-azaindolizine (**1**) formylates at C-3 and 2,7-dimethyl-8-azaindolizine (**6**) preferentially at C-3 and then C-1. Thioformylation of **6** occurs at C-3. These findings correlate well with theoretical MO calculations[13] which predict electrophilic substitution of 8-azaindolizine to occur firstly at C-3 and then C-1. Not sur-



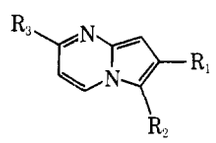
	R_1	R_2	R_3
1	H	H	H
2	COOEt	H	H
3	CH_3	H	H
4	CH_3	CH_3	H
5	Ph	H	H
6	CH_3	H	CH_3
7	CH_3	CH_3	CH_3
8	Ph	H	OCH_3
9	CH_3	H	OCH_3
10	COOEt	H	OCH_3



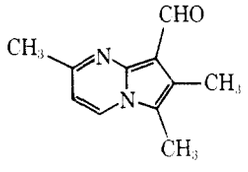
	R_1	R_2	R_3
11	Ph	H	CH_3
12	CH_3	H	H
13	CH_3	CH_3	H



	R_1	R_2	R_3
14	Ph	H	CH_3
15	CH_3	H	H
16	CH_3	CH_3	H



	R_1	R_2	R_3
17	H	CHO	H
18	CH_3	CHO	CH_3
19	Ph	CHO	OCH_3
20	CH_3	CHS	CH_3



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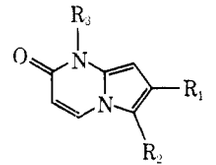
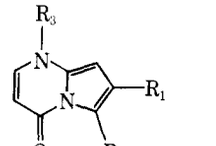
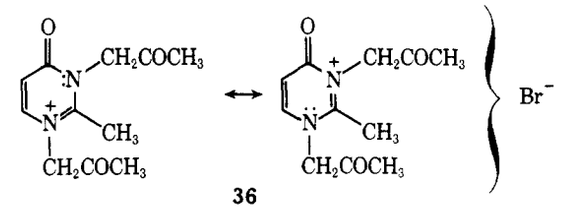


	R_1	R_2	R_3
22	Ph	H	CH_3
23	CH_3	H	CH_3
24	Ph	H	CH_2COPh
25	CH_3	H	CH_2COCH_3
26	Ph	CHO	CH_3
27	CH_3	CHO	CH_3
28	COOEt	H	H
29	COOEt	H	CH_3
30	CH_3	CHO	CH_2COCH_3



	R_1	R_2	R_3
31	Ph	H	CH_2COPh
32	CH_3	H	CH_3
33	COOEt	H	CH_3
34	CH_3	H	CH_2COCH_3
35	CH_3	CHO	CH_2COCH_3



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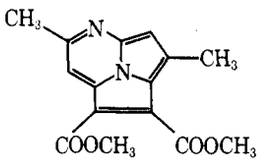

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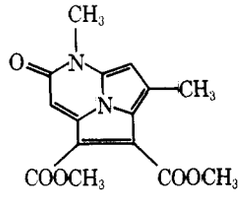

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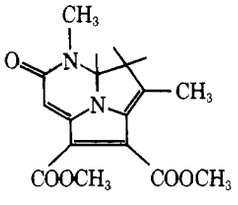

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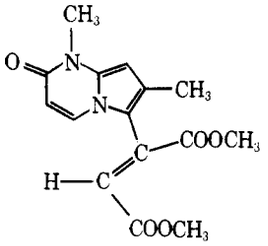

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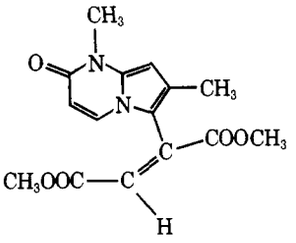

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prisingly, the 8-azaindolizinones **22, 23, 25,** and **34,** which can be considered to be substituted pyrroles, preferably formylate at C-3.

The 8-azaindolizine **6** and the 8-azaindolizinone **23** underwent dipolar addition with dimethyl acetylenedicarboxylate to give the 5-azacycl[3.2.2]azines **37** and **38,** respectively. In addition **23** gave the dihydrocyclazine **39,** and the cis and trans isomeric 8-azaindolizines **40** and **41.** The configuration of the cis and trans stereoisomers was made tentatively on the basis of a comparison of their ^{1}H NMR spectra. The vinyl proton of one stereoisomer absorbs at δ 5.93 whereas the vinyl proton of the other absorbs at δ 7.13. We suggest that the vinyl proton of the trans isomer absorbs at lower field.[14,15]

The dihydro compound **39** was readily dehydrogenated to **38.** The cis and trans isomers were only partially interconverted on heating in toluene with palladium on charcoal; none of the cyclazine **38** was formed. This suggests that the cis and trans isomers are not intermediates en route to the cyclazine **38.**

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed by the analytical laboratories of Aberdeen University. Infrared spectra were measured for Nujol mulls unless otherwise stated with a Unicam SP200 spectrometer. Ultraviolet spectra were measured on a Unicam SP800 spectrometer. Light absorption data refer to solutions in ethanol unless otherwise stated, principal maxima are italicized, and inflections are given in parentheses. ^{1}H NMR spectra were recorded with a Varian HA-100D spectrometer using 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 values and signal assignment are in parentheses. For multiplets d = doublet, dd = double doublet, t = triplet, q = quartet, and m = complex multiplet. Mass spectra (70 eV) were recorded with an AE1 MS30 spectrometer.

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 Kieselgel GF_{254} using benzene–ethyl acetate (3:1) for development and chloroform for band extraction unless otherwise stated. Bands are recorded in the order of their speed of movement, the fastest being given first. Where indicated, spraying with Ehrlich's reagent[16] aided compound identification. Petroleum ether refers to the fraction boiling at 80–100 °C.

The following general procedure was used in the Chichibabin synthesis of the 8-azaindolizines. Deviations are given in individual cases. The α-bromo ketone was added to the pyrimidine and left at room temperature for 1–3 days. Water was added and the aqueous solution extracted with ether or chloroform, then warmed to remove dissolved solvent, before adding an excess of sodium hydrogen carbonate. The resultant was either steam distilled or heated on a boiling water bath for 10–30 min. The steam distillate or the aqueous bicarbonate solution was extracted several times with ether or chloroform, the combined organic extracts dried, and the solvent evaporated to leave a crude residue of the 8-azaindolizine.

2-Methylpyrimidine[17] (5.0 g, 0.053 mol) and ethyl bromopyruvate (10.4 g, 0.053 mol) gave a yellow oil (1 g) which on TLC gave a number of bands. The yellow band, which gave a blue Ehrlich's test on being heated at 100 °C, was extracted and further chromatographed using petroleum ether–ethyl acetate (1:1). The faster moving of the two yellow bands which developed afforded **2-carbethoxy-8-azaindolizine (2),** 94 mg (1.0%), as a yellow oil which gave a waxy, crystalline solid on cooling: mp 48–60 °C; λ_{max} *225,* 235, 242, (249), (258), 282, 292, 303, 370 nm (broad), log ϵ 4.37, 4.35, 4.33, 4.10, 3.95, 3.48, 3.52, 3.37, 3.22; IR (melt) 770, 1198, 1230, 1700 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_{10}H_{10}N_2O_2$: 190.0742. Found: M$^+$ (base peak) 190.0742.

Hydrolysis of the ester **2** (80 mg) with excess ethanolic KOH (3 cm^3) gave the potassium salt of 8-azaindolizine-2-carboxylic acid, 79 mg (94%), as a dark yellow powder which did not melt below 350 °C: λ_{max} (water) *218,* (237), 241, (247), (256), 283, 292, 304, 372 nm (broad), log ϵ 4.33, 4.29, 4.30, 4.02, 3.91, 3.40, 3.47, 3.37, 3.11; IR 770, 1322, 1570 cm^{-1}; ^{1}H NMR (CF_3COOH) δ 7.29 (dd, J = 5.0 and 7.0 Hz, 1 H, H-6), 7.50 (H-1), 8.45 (H-3), 8.75 (d, J = 5.0 Hz, 1 H, H-5 or H-7), 9.17 (d, J = 7.0 Hz, 1 H, H-5 or H-7). Neutralization of a solution of the potassium salt (35 mg, 0.175 mmol in a few drops of water) with 1 M HCl (0.175 cm^3, 0.175 mmol) gave a precipitate of 8-azaindolizine-2-carboxylic acid hydrochloride, 22 mg (63%), as a yellow powder, decomposing >290 °C: λ_{max} *219,* (238), *242,* (247), 282, 292, 303, 374 nm (broad), log ϵ 4.50, 4.45, 4.50, 4.45, 3.61, 3.67, 3.54, 3.37; IR 734, 790, 1250, 1495, 1698, 1880 (broad), 2590 (broad), 2750 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$] 6.77 (m, 2 H, H-1 and H-6), 7.96 (d, J = 2.0 Hz, 1 H, H-3), 8.18 (m, 1 H, H-5 or H-7), 8.68 (d, with additional fine splitting, J = 7.5 Hz, 1 H, H-5 or H-7).

Decarboxylation of the hydrochloride (32 mg) by heating with copper powder[18] in a sealed, evacuated tube (0.01 mm, block temperature 260 °C) gave **8-azaindolizine (1),** 15 mg (79%), as a yellow oil: λ_{max} (234), *239,* 244, (285), 291, 302, 374 nm (broad), log ϵ 4.35, 4.43, 4.37, 3.18, 3.26, 3.08, 3.08; IR 771, 1206, 1257, 1307, 1508, 1612 cm^{-1}; ^{1}H NMR (see Figure 1 and Table I). Calcd mass for $C_7H_6N_2$: 118.0530. Found: M$^+$ (base peak) 118.0529.[19]

2-Methylpyrimidine (0.94 g, 0.01 mol) and bromoacetone (1.31 g, 0.01 mol) gave a few milligrams of a yellow oil which on TLC with benzene–ethyl acetate (10:1) and then with ether gave a yellow band. Ether extraction followed by distillation in a sealed evacuated tube (0.01 mm, 90 °C) gave **2-methyl-8-azaindolizine (3),** 7 mg (0.5%), as a yellow oil which crystallized on cooling: mp 43–45.5 °C; λ_{max} (238), *243,* 250, (291), 301, 313, 347 nm (broad), log ϵ 4.28, 4.35, 4.29, 3.12, 3.27, 3.30, 3.07; IR 747, 773, 799, 1254, 1506, 1615 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_8H_8N_2$: 132.0687. Found: M$^+$ (base peak) 132.0683.

2-Methylpyrimidine (0.94 g, 0.01 mol) and 3-bromo-2-butanone (1.51 g, 0.01 mol) gave a few milligrams of a solid which on TLC with ether gave a yellow band. Ether extraction followed by distillation in a sealed evacuated tube (0.01 mm, 100 °C) gave **2,3-dimethyl-8-azaindolizine (4),** 4 mg (0.3%), as yellow prisms: mp 93–94 °C; λ_{max} (228), 232, *249,* 256, (295), 302, 315, 390 nm (broad), log ϵ 4.25, 4.28, 4.44, 4.37, 3.29, 3.37, 3.37, 3.24; IR 771, 1268, 1502, 1614 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_9H_{10}N_2$: 146.0843. Found: M$^+$ (63% base peak) 146.0841.

2-Methylpyrimidine (0.82 g, 8.7 mmol) and phenacyl bromide (1.73 g, 8.7 mmol) gave a red oil (0.1 g) which on TLC gave a number of bands. The yellow band, which slowly gave a blue Ehrlich's test, on extraction gave **2-phenyl-8-azaindolizine (5),** 9 mg (0.5%), as pale yellow crystals: mp 138–141 °C; λ_{max} *253,* 325, 371 nm (broad), log ϵ 4.54, 3.78, 3.37; IR (KBr) 738, 768, 1198, 1267, 1370, 1510, 1600, 1618 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_{13}H_{10}N_2$: 194.0843. Found: M$^+$ (base peak) 194.0846.

2,4-Dimethylpyrimidine[17] (5.40 g, 0.05 mol) and bromoacetone (6.85 g, 0.05 mol) gave an oil (1.1 g) which on TLC with ether gave a fast-moving yellow band. Ether extraction followed by distillation in a sealed, evacuated tube (0.01 mm, 100 °C) gave **2,7-dimethyl-8-azaindolizine (6),** 0.406 g (6%), as a yellow oil which subsequently crystallized: mp 33–49 °C; λ_{max} (239), *245,* 252, (291), 296, (306), 370 nm (broad), log ϵ 4.33, 4.42, 4.40, 3.54, 3.56, 3.39, 3.06; IR (melt) 780, 1143, 1253, 1521, 1622 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_9H_{10}N_2$: 146.0843. Found: M$^+$ (base peak) 146.0842.

Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89. Found: C, 74.2; H, 7.2.

2,4-Dimethylpyrimidine (5.40 g, 0.05 mol) and 3-bromo-2-butanone (7.60 g, 0.05 mol) were quaternized by heating with a flame for 15 min. Bicarbonate cyclization afforded an oil (0.15 g) which on TLC gave a yellow band. Ether extraction and then distillation in a sealed, evacuated tube (0.01 mm, 100 °C) gave **2,3,7-trimethyl-8-azaindolizine (7),** 18 mg (0.3%), as a yellow oil which subsequently crystallized: mp 65 °C; λ_{max} (237), *250,* (255), 299, 313, 386 nm (broad), log ϵ 4.37, 4.55, 4.50, 3.56, 3.41, 3.26; IR 780, 1268, 1620 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_{10}H_{12}N_2$: 160.1000. Found: M$^+$ (71% base peak) 160.1000.

Reaction between 4-Methoxy-2-methylpyrimidine and Phenacyl Bromide. A. 4-Methoxy-2-methylpyrimidine[20] (0.31 g, 2.5 mmol) and phencyl bromide (0.50 g, 2.5 mmol) gave directly by filtration of the cooled aqueous bicarbonate cyclization solution a buff-colored solid (0.16 g). This was purified by TLC, recrystallized from petroleum ether containing a small amount of benzene, and finally distilled (0.01 mm, 170 °C) to give **7-methoxy-2-phenyl-8-azaindolizine (8),** 150 mg (27%), as pale yellow crystals: mp 147–148 °C; λ_{max} *251,* (255), 301, (310), 347 nm (broad), log ϵ 4.62, 4.61, 3.95, 3.88, 3.31; IR 705, 763, 1015, 1232, 1307, 1627 cm^{-1}; ^{1}H NMR (see Table I); 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, 74.8; H, 5.7; N, 12.2.

B. Quaternization of 4-methoxy-2-methylpyrimidine (0.31 g, 2.5 mmol) with phenacyl bromide (0.50 g, 2.5 mmol) by warming to start the exothermic reaction and then maintaining it at 40 °C for 6 h, gave

directly by filtration of the bicarbonate solution sand-colored crystals (0.36 g). Distillation of these (0.01 mm, 160–170 °C) followed by recrystallization from benzene gave **8-methyl-2-phenyl-8-azaindolizin-7(8*H*)-one (22),** 324 mg (58%), as yellow crystals: mp 158.5–160.5 °C; λ_{max} *243,* (289), 301, (329) nm, log ϵ 4.52, 4.09, 4.12, 3.55; IR 740, 1220, 1548, 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.48 (3 H, CH_3N), 5.92 (H-1), 5.95 (d, J = 7.5 Hz, 1 H, H-6), 6.98 (H-3), 7.10–7.66 (m, 5 H, Ph), 7.66 (d, J = 7.5 Hz, 1 H, H-5); 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, 74.8; H, 5.6; N, 12.3.

The chloroform washing of the quaternary salt solution gave 50 mg of a yellow solid, which on TLC gave a number of bands. The band which gave a green Ehrlich's test and had the same R_f as **22** yielded after recrystallization from ethanol **8-phenacyl-2-phenyl-8-azaindolizin-5(8*H*)-one (31),** 11 mg (1.3%), as needles: mp 244.5–246.5 °C; λ_{max} *247,* (278), (297), 347 nm, log ϵ 4.64, 4.05, 3.85, 3.76; IR 748, 1218, 1590, 1638, 1658, 1688 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$] 5.60 (d, J = 8.0 Hz, 1 H, H-6), 5.78 (2 H, methylene), 6.56 (d, J = 2 Hz, 1 H, H-1), 7.11–8.24 (m, 12 H, H-3, H-7, and Ph). Calcd mass for $C_{21}H_{16}N_2O_2$: 328.1211. Found: M^+ (32% base peak) 328.1213.

C. Quaternization of 4-methoxy-2-methylpyrimidine (0.62 g, 5 mmol) with phenacyl bromide (1.0 g, 5 mmol) by warming for 15 min yielded 0.8 g of a brown oil which on TLC gave a number of bands. The pale yellow band which had an R_f greater than that of **22** and gave a blue-green Ehrlich's test yielded on recrystallization from ethanol **8-phenacyl-2-phenyl-8-azaindolizin-7(8*H*)-one (24),** 19 mg (1.2%), as yellow crystals: mp 209–213 °C; λ_{max} *243,* 300, (331) nm, log ϵ 4.62, 4.12, 3.56; IR 750, 1224, 1554, 1655, 1670 cm^{-1}; ^{1}H NMR 5.40 (2 H, methylene), 5.74 (d, J = 1.5 Hz, 1 H, H-1), 5.97 (d, J = 8.0 Hz, 1 H, H-6), 6.97 (d, J = 1.5 Hz, 1 H, H-3), 7.19–8.19 (m, 10 H, Ph), 7.73 (d, J = 8.0 Hz, 1 H, H-5). Calcd mass for $C_{21}H_{16}N_2O_2$: 328.1211. Found: M^+ (94% base peak) 328.1210.

The band with the same R_f as **22** on extraction gave 0.32 g of yellow crystals. Fractional crystallization from benzene containing a small percentage of ethanol gave **31,** 21 mg (1.3%), with identical melting point and spectral characteristics as the sample obtained previously. The next fraction gave **22,** 213 mg (19%), with identical melting point and spectral characteristics as the sample obtained above.

Reaction between 4-Methoxy-2-methylpyrimidine and Bromoacetone. A. 4-Methoxy-2-methylpyrimidine (0.31 g, 2.5 mmol) and bromoacetone (0.35 g, 2.5 mmol) when mixed at room temperature yielded an oil which was separated by TLC. The fast moving pale yellow band which gave a blue Ehrlich's test was extracted to give a pale yellow chloroform solution. Evaporation of the extract gave **7-methoxy-2-methyl-8-azaindolizine (9),** 6 mg (1.5%), as an oil which crystallized on cooling to a waxy solid: mp gradual up to 54 °C; λ_{max} *242,* 249, 274, 285, 297, 352 nm (broad), log ϵ 4.36, 4.36, 3.37, 3.34, 3.16, 3.04; IR 785, 1025, 1232, 1315, 1635 cm^{-1}; ^{1}H NMR (see Table I). Calcd mass for $C_9H_{10}N_2O$: 162.0793. Found: M^+ (base peak) 162.0794.

The next broad yellow band gave on recrystallization from benzene–petroleum ether **2,8-dimethyl-8-azaindolizin-7(8*H*)-one (23),** 159 mg (39%), as yellow needles: mp 122–124 °C; λ_{max} *239,* 287, 335 nm (broad), log ϵ 4.18, 3.85, 3.02; IR 740, 1502, 1558, 1628, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.16 (3 H, CH_3-2), 3.40 (3 H, CH_3N), 5.47 (H-1), 5.84 (d, J = 8.0 Hz, 1 H, H-6), 6.47 (H-3), 7.56 (d, J = 8.0 Hz, 1 H, H-5); mass spectrum *m/e* 162 (M^+, base peak).

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.64; H, 6.22; N, 17.27. Found: C, 66.4; H, 6.5; N, 17.0.

The following band with a blue fluorescence under UV light gave a few milligrams of an oil which on distillation (0.01 mm, 110 °C) gave **2,8-dimethyl-8-azaindolizin-5(8*H*)-one (32),** 3 mg (0.7%), as a waxy solid: mp 78–83.5 °C; λ_{max} *226,* (255), 345 nm, log ϵ 4.36, 3.68, 3.63; IR (mulled under dry N_2) 732, 782, 1600, 1658 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.24 (3 H, CH_3-2), 3.58 (3 H, CH_3N), 5.54 (d, J = 1.5 Hz, 1 H, H-1), 7.15 (d, J = 7.5 Hz, 1 H, H-7), 7.26 (d, J = 1.5 Hz, 1 H, H-3). Calcd mass for $C_9H_{10}N_2O$: 162.0793. Found: M^+ (base peak) 162.0794.

B. Quaternization of 4-methoxy-2-methylpyrimidine (1.00 g, 8.1 mmol) with bromoacetone (1.11 g, 8.1 mmol) at 40 °C for 2 days gave in addition to **23** (22%) and **32** (0.5%) a slower moving band with a turquoise fluorescence under UV light. This band gave **8-acetonyl-2-methyl-8-azaindolizin-5(8*H*)-one (34),** 12 mg (0.7%), as needles: mp 170.5–174.5 °C; λ_{max} *225,* (255), 347 nm (broad), log ϵ 4.39, 3.74, 3.58; IR 782, 1598, 1660, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.19 (3 H, CH_3-2 or CH_3 of acetonyl), 2.20 (3 H, CH_3-2 or CH_3 of acetonyl), 4.54 (2 H, methylene), 5.53 (H-1), 5.62 (d, J = 8.0 Hz, 1 H, H-6), 7.09 (d, J = 8.0 Hz, 1 H, H-7), 7.22 (H-3); mass spectrum *m/e* 204 (M^+, 50% base peak).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92. Found: C, 64.6; H, 6.2.

Reaction between 4-Methoxy-2-methylpyrimidine and Ethyl Bromopyruvate. A. 4-Methoxy-2-methylpyrimidine (0.62 g, 5 mmol) and ethyl bromopyruvate (0.98 g, 5 mmol) when mixed at room temperature yielded an oil which was subjected to TLC. The fast moving band, which gave a blue Ehrlich's test, yielded after recrystallization from petroleum ether **2-carbethoxy-7-methoxy-8-azaindolizine (10),** 19 mg (1.7%), as yellow needles in clusters: mp 117.5–119 °C; λ_{max} *231,* 239, 256, 264, (277), (287), 343 nm (broad), log ϵ 4.58, 4.51, 4.04, 4.02, 3.66, 3.45, 3.11; IR 1020, 1220, 1640, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.36 (t, J = 7.0 Hz, 3 H, CH_3 of carbethoxy), 3.94 (3 H, CH_3O), 4.34 (q, J = 7.0 Hz, 2 H, CH_2 of carbethoxy), 6.18 (d, J = 7.5 Hz, 1 H, H-6), 6.61 (H-1), 7.49 (d, J = 1.5 Hz, 1 H, H-3), 7.92 (d, J = 7.5 Hz, 1 H, H-6). Calcd mass for $C_{11}H_{12}N_2O_3$: 220.0847. Found: M^+ (base peak) 220.0844.

B. Quaternization of 4-methoxy-2-methylpyrimidine (0.62 g, 5 mmol) and ethyl bromopyruvate (0.98 g, 5 mmol) at 50 °C for 6 h gave only a trace of **10.** However, the ether washing of the quaternary salt solution gave 0.6 g of a brown oil which on TLC gave four bands. The fast moving band, which gave a blue Ehrlich's test, gave **10,** 4 mg (0.4%). The next band, which gave a purple Ehrlich's test, gave after recrystallization from benzene–petroleum ether **2-carbethoxy-8-methyl-8-azaindolizin-7(8*H*)-one (29),** 14 mg (1.3%), as pale yellow crystals: mp 207–207.5 °C; λ_{max} *226,* (232), (271), 275, 286, 328 nm (broad), log ϵ 4.51, 4.42, 4.05, 4.10, 3.98, 3.18; IR 1213, 1658, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.36 (t, J = 7.0 Hz, 3 H, CH_3 of carbethoxy), 3.45 (3 H, CH_3-N), 4.34 (q, J = 7.0 Hz, 2 H, CH_2 of carbethoxy), 6.05 (H-1), 6.06 (d, J = 7.5 Hz, 1 H, H-6), 7.31 (d, J = 2 Hz, 1 H, H-3), 7.68 (d, J = 7.5 Hz, 1 H, H-5). Calcd mass for $C_{11}H_{12}N_2O_3$: 220.0847. Found: M^+ (base peak) 220.0844.

The following band, which gave a turquoise Ehrlich's test, gave after recrystallization from benzene–petroleum ether **2-carbethoxy-8-methyl-8-azaindolizin-5(8*H*)-one (33),** 5 mg (0.5%), as needles: mp 178.5–179.5 °C; λ_{max} *231,* (239), (256), (277), 347 nm, log ϵ 4.48, 4.37, 3.52, 3.12, 3.74; IR 1190, 1208, 1660, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.36 (t, J = 7.0 Hz, 3 H, CH_3 of carbethoxy), 3.64 (3 H, CH_3N), 4.34 (q, J = 7.0 Hz, 2 H, CH_2 of carbethoxy), 5.60 (d, J = 7.5 Hz, 1 H, H-6), 6.30 (d, J = 2.0 Hz, 1 H, H-1), 7.26 (d, J = 7.5 Hz, 1 H, H-7), 8.02 (d, J = 2.0 Hz, 1 H, H-3). Calcd mass for $C_{11}H_{12}N_2O_3$: 220.0847. Found: M^+ (base peak) 220.0844.

The slowest band, which gave a blue Ehrlich's test, gave after recrystallization from benzene–ethanol **2-carbethoxy-8-azaindolizin-7(8*H*)-one (28),** 16 mg (1.6%), as a pale yellow solid: mp 260 °C dec; λ_{max} *226,* (233), (272), 276, 286, 328 nm (broad), log ϵ 4.49, 4.37, 4.08, 4.12, 3.97, 3.09; IR 1228, 1424, 1700, 2740 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$] 1.26 (t, J = 7.0 Hz, 3 H, CH_3 of carbethoxy), 4.20 (q, J = 7.0 Hz, 2 H, CH_2 of carbethoxy), 5.76 (d, J = 1.5 Hz, 1 H, H-1), 5.91 (d, J = 8.0 Hz, 1 H, H-6), 7.54 (d, J = 1.5 Hz, 1 H, H-3), 8.21 (d, J = 8.0 Hz, 1 H, H-5), 11.5 (broad, exchangeable on addition of D_2O, 1 H, HN). Calcd mass for $C_{10}H_{10}N_2O_3$: 206.0691. Found: M^+ (base peak) 206.0688.

Reaction between 4-Hydroxy-2-methylpyrimidine and Bromoacetone. 4-Hydroxy-2-methylpyrimidine[21] (3.0 g, 27 mmol) and bromoacetone were heated in dimethylformamide (30 cm^3) at 60 °C for 8 h. The bulk of the solvent was removed and the dark colored residue extracted into water and worked up in the usual manner to give a small volume of a brown liquid. TLC gave two main bands. The faster band, which gave a violet Ehrlich's test, gave **8-acetonyl-2-methyl-8-azaindolizin-7(8*H*)-one (25),** 84 mg (1.5%), as a yellow oil which subsequently crystallized: mp 100 °C; λ_{max} *238,* 287, 340 nm (broad), log ϵ 4.29, 3.80, 2.84; IR 768, 1169, 1351, 1549, 1641, 1660, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.10 (3 H, CH_3-2), 2.17 (3 H, CH_3 of acetonyl), 4.64 (2 H, methylene), 5.30 (H-1), 5.86 (d, J = 8.0 Hz, 1 H, H-6), 6.48 (H-3), 7.62 (d, J = 8.0 Hz, 1 H, H-5); mass spectrum *m/e* 204 (M^+, 89% base peak).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.09; H, 5.92. Found: C, 64.4; H, 6.0.

The slower band, which gave a blue Ehrlich's test and had a turquoise fluorescence under UV light, gave 8-acetonyl-2-methyl-8-azaindolizin-5(8*H*)-one (**34**), 63 mg (1.0%), with identical melting point and spectral characteristics as the sample obtained previously from 4-methoxy-2-methylpyrimidine and bromoacetone.

General Formylation Procedure. To a stirred solution of the azaindolizine in dimethylformamide (DMF) (1 cm^3) was added a 10% molar excess of phosphoryl chloride in DMF (1 cm^3). After 2–4 h the resultant solution was poured into 2 M NaOH (30 cm^3), or 2 M NaSH[22] in the case of thioformylation, and extracted with chloroform or ether. Evaporation of the ether or chloroform extract and any residual DMF gave the crude aldehyde, which was purified by TLC.

8-Azaindolizine (**1**), 15 mg, gave **3-formyl-8-azaindolizine (17),** 8 mg (43%), as pale yellow needles from petroleum ether: mp 121–122

°C; λ_{max} 222, (267), *270*, 343 nm, log ϵ 4.17, 4.43, 4.44, 4.03; IR 786, 1408, 1604, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) 6.75 (d, J = 5.0 Hz, 1 H, H-1), 6.93 (dd, J = 4.0 and 7.0 Hz, 1 H, H-6), 7.63 (d, J = 5.0 Hz, 1 H, H-2), 8.47 (dd, J = 2.0 and 4.0 Hz, 1 H, H-7), 9.73 (CHO), 9.82 (dd, J = 2.0 and 7.0 Hz, 1 H, H-5); mass spectrum m/e 146 (M^+, base peak).

Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14. Found: C, 65.7; H, 4.2.

2,7-Dimethyl-8-azaindolizine (**6**), 40 mg, gave **3-formyl-2,7-dimethyl-8-azaindolizine (18)**, 22 mg (46%), as pale yellow needles from petroleum ether: mp 110 °C; λ_{max} (227), 230, (266), (276), *282*, 352 nm, log ϵ 4.21, 4.22, 4.22, 4.36, 4.43, 4.11; IR 720, 1438, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) 2.57 (6 H, CH_3-2 and CH_3-7), 6.35 (H-1), 6.73 (d, J = 7.0 Hz, 1 H, H-6), 9.69 (d, J = 7.0 Hz, 1 H, H-5), 9.79 (CHO). Calcd mass for $C_{10}H_{10}N_2O$: 174.0793. Found: M^+ (base peak) 174.0792. Similarly, by pouring the intermediate Vilsmeier salt solution into 2 M aqueous sodium hydrogen sulfide, **6** gave **3-thioformyl-2,7-dimethyl-8-azaindolizine (20)**, 26 mg (50%), as red needles in clusters from benzene–petroleum ether: mp 168.5–169 °C; λ_{max} *227*, 275, (310), 317, 418, *429* nm, log ϵ 4.38, 4.01, 3.95, 4.06, 4.47, 4.50; IR 977, 1422, 1500, 1530, 1607 cm^{-1}; ^1H NMR ($CDCl_3$) 2.54 (3 H, CH_3-2), 2.61 (3 H, CH_3-7), 6.48 (H-1), 6.90 (d, J = 7.0 Hz, 1 H, H-6), 10.65 (CHS), 11.26 (d, J = 7.0 Hz, 1 H, H-5). Calcd mass for $C_{10}H_{10}N_2S$: 190.0563. Found: M^+ (67% base peak) 190.0561.

Anal. Calcd for $C_{10}H_{10}N_2S$, C, 63.13; H, 5.30. Found: C, 63.4; H, 5.2.

7-Methoxy-2-phenyl-8-azaindolizine (**8**), 31 mg, gave **3-formyl-7-methoxy-2-phenyl-8-azaindolizine (19)**, 22 mg (63%), as needles from petroleum ether: mp 143–143.5 °C; λ_{max} 230, 249, *277*, 350 nm, log ϵ 4.24, 4.10, 4.43, 4.13; IR 810, 1240, 1410, 1625, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) 4.04 (3 H, CH_3O), 6.45 (H-1), 6.45 (d, J = 7.0 Hz, 1 H, H-6), 7.32–7.72 (m, 5 H, Ph), 9.64 (CHO), 9.73 (d, J = 7.0 Hz, 1 H, H-5); mass spectrum m/e 252 (M^+, base peak).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.1; H, 5.1; N, 11.1.

2,3,7-Trimethyl-8-azaindolizine (**7**), 12 mg, gave **1-formyl-2,3,7-trimethyl-8-azaindolizine (21)**, 4 mg (28%), as pale yellow needles from benzene–petroleum ether: mp 140 °C; λ_{max} *235*, 242, 255, 280, 289, 324, 360 nm, log ϵ 4.14, 4.13, 3.92, 3.80, 3.80, 3.79, 3.24; IR 786, 1278, 1535, 1643 cm^{-1}; ^1H NMR ($CDCl_3$) 2.32 (3 H, CH_3-3), 2.51 (3 H, CH_3-7), 2.58 (3 H, CH_3-2), 6.70 (d, J = 7.0 Hz, 1 H, H-6), 7.91 (d, J = 7.0 Hz, 1 H, H-5), 10.43 (CHO). Calcd mass for $C_{11}H_{12}N_2O$: 188.0949. Found: M^+ (base peak) 188.0946.

8-Methyl-2-phenyl-8-azaindolizin-7(8*H*)-one (**22**), 31 mg, gave **3-formyl-8-methyl-2-phenyl-8-azaindolizin-7(8*H*)-one (26)**, 28 mg (80%), as needles from benzene: mp 218.5 °C; λ_{max} 226, 239, *295*, 340 nm, log ϵ 4.21, 4.23, 4.39, 4.05; IR 840, 1542, 1618, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) 3.57 (3 H, CH_3N), 5.95 (H-1), 6.17 (d, J = 7.5 Hz, 1 H, H-6), 7.48 (5 H, Ph), 9.32 (d, J = 7.5 Hz, 1 H, H-5), 9.57 (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; N, 11.10. Found: C, 71.1; H, 4.9; N, 11.2.

2,8-Dimethyl-8-azaindolizin-7(8*H*)-one (**23**), 280 mg, gave **2,8-dimethyl-3-formyl-8-azaindolizin-7(8*H*)-one (27)**, 228 mg (69%), as sand-colored prisms from benzene containing a small amount of petroleum ether: mp 212 °C; λ_{max} (220), (229), (226), *283*, (287), 312, 336 nm, log ϵ 3.92, 3.76, 3.95, 4.19, 4.16, 4.09, 4.06; ir 890, 1288, 1501, 1620, 1637, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) 2.45 (3 H, CH_3-2), 3.48 (3 H, CH_3-N), 5.68 (H-1), 6.06 (d, J = 8.0 Hz, 1 H, H-6), 9.15 (d, J = 8.0 Hz, 1 H, H-5), 9.61 (CHO); mass spectrum m/e 190 (M^+, base peak).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.2; H, 5.4; N, 14.8.

8-Acetonyl-2-methyl-8-azaindolizin-7(8*H*)-one (**25**), 25 mg, gave **8-acetonyl-3-formyl-2-methyl-8-azaindolizin-7(8*H*)-one (30)**, 18 mg (63%), as glassy needles from benzene: mp 196–197 °C; λ_{max} (220), (229), (267), *283*, 288, 311, 335 nm, log ϵ 3.97, 3.76, 3.98, 4.22, 4.20, 4.12, 4.07; IR 818, 1642, 1665, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) 2.27 (3 H, CH_3 of acetonyl), 2.42 (3 H, CH_3-2), 4.77 (2 H, methylene), 5.48 (H-1), 6.11 (d, J = 8.0 Hz, 1 H, H-6), 9.24 (d, J = 8.0 Hz, 1 H, H-5), 9.66 (CHO); mass spectrum m/e 232 (M^+, 75% base peak).

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21. Found: C, 62.2; H, 5.5.

8-Acetonyl-2-methyl-8-azaindolizin-5(8*H*)-one (**34**), 15 mg, gave **8-acetonyl-3-formyl-2-methyl-8-azaindolizin-5(8*H*)-one (35)**, 11 mg (64%), as needle clusters from benzene–ethanol and then chloroform: mp 201–202 °C; λ_{max} *225*, 247, 337, 343 nm, log ϵ 4.38, 4.05, 4.28, 4.28; IR 803, 1500, 1580, 1632, 1671, 1722 cm^{-1}; ^1H NMR 2.29 (3 H, CH_3 of acetonyl), 2.52 (3 H, CH_3-2), 4.66 (2 H, methylene), 5.64 (H-1), 5.85 (d, J = 8.0 Hz, 1 H, H-6), 7.13 (d, J = 8.0 Hz, 1 H, H-7), 10.95 (CHO). Calcd mass for $C_{12}H_{12}N_2O_3$: 232.0847. Found: M^+ (40% base peak) 232.0846.

1,3-Dipolar Addition. Reactions with dimethyl acetylenedicarboxylate (DAD) were carried out by a procedure similar to that reported by Boekelheide.[8]

2,7-Dimethyl-8-azaindolizine (**6**), 100 mg (0.68 mmol,) and DAD, 150 mg (1.06 mmol), gave after recrystallization from ethanol **1,2-dicarbmethoxy-3,6-dimethyl-5-azacycl[3.2.2]azine (37)**, 129 mg (66%), as yellow crystals which had a green fluorescence in solution: mp 137 °C; λ_{max} *250*, (280), (294), (317), 434 nm, log ϵ 4.39, 4.03, 3.93, 3.68, 3.80; IR 1120, 1195, 1310, 1598, 1700, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) 2.71 (3 H, CH_3-3), 2.93 (3 H, CH_3-6), 3.99 (3 H, CH_3 of ester), 4.07 (3 H, CH_3 of ester), 7.04 (H-4), 7.99 (H-7); mass spectrum m/e 286 (M^+, 84% base peak).

Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78. Found: C, 63.2; H, 5.2; N, 9.5.

2,8-Dimethyl-8-azaindolizin-7(8*H*)-one (**23**), 110 mg (0.68 mmol), and DAD, 145 mg (1.02 mmol), gave via TLC four colored bands. The fast-moving, yellow band gave an oil which crystallized to give **4,4a-dihydro-1,2-dicarbmethoxy-3,5-dimethyl-5-azacycl-[3.2.2]azin-6(5*H*)-one (39)**, 8 mg (3.9%), as orange crystals: mp 128–131 °C; λ_{max} 240 (broad), 280 (broad), *420* nm, log ϵ 4.00, 3.71, 4.02; IR 805, 1130, 1280, 1680, 1733 cm^{-1}; ^1H NMR ($CDCl_3$) 2.11 (d, J = 1.5 Hz, 3 H, CH_3-3), 2.47 (dd, J = 14.5 and 15.5 Hz, 1 H, H of methylene), 3.12 (dd, J = 5.5 and 15.5 Hz, 1 H, H of methylene), 3.25 (3 H, CH_3-N), 3.75 (3 H, CH_3O), 3.96 (3 H, CH_3O), 4.77–5.03 (m, 1 H, methine), 5.63 (H-7) (irradiation at δ 4.90 causes the signals at 2.47 and 3.12 to become broad doublets, $J \simeq$ 15 Hz, and the signal at 2.11 to become a broad singlet); mass spectrum m/e 304 (M^+, 63% base peak).

Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.4; H, 5.1; N, 9.2.

The next yellow band gave **3-(*cis*-dicarbomethoxyethenyl)-2,8-dimethyl-8-azaindolizin-7(8*H*)-one (40)**, 28 mg (13.6%), as an oil which crystallized slowly: mp 116–118 °C; λ_{max} *240*, 285, 370 nm, log ϵ 4.13, 3.78, 4.03; IR 1240, 1650, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) 2.20 (3 H, CH_3-2), 3.43 (3 H, CH_3N), 3.78 (3 H, CH_3O), 3.88 (3 H, CH_3O), 5.65 (H-1), 5.93 (vinyl H), 5.96 (d, J = 8.0 Hz, 1 H, H-6), 7.96 (d, J = 8.0 Hz, 1 H, H-5). Calcd mass for $C_{15}H_{16}N_2O_5$: 304.1059. Found: M^+ (71% base peak) 304.1056.

The following orange band gave **3-(*trans*-dicarbomethoxyethenyl)-2,8-dimethyl-8-azaindolizin-7(8*H*)-one (41)**, 37 mg (18%), as an oil which crystallized slowly: mp 106–110 °C; λ_{max} *240*, 284, 420 nm (broad), log ϵ 4.38, 3.83, 3.48; IR 1240, 1660, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) 2.01 (3 H, CH_3-2), 3.44 (3 H, CH_3N), 3.68 (3 H, CH_3O), 3.82 (3 H, CH_3O), 5.63 (H-1), 5.89 (d, J = 8.0 Hz, 1 H, H-6), 7.13 (vinyl H), 7.33 (d, J = 8.0 Hz, 1 H, H-5). Calcd mass for $C_{15}H_{16}N_2O_5$: 304.1059. Found: M^+ (79% base peak) 304.1056.

The slow-moving red band gave after recrystallization from ethyl acetate **1,2-dicarbomethoxy-3,5-dimethyl-5-azacycl[3.2.2]azin-6(5*H*)-one (38)**, 121 mg (59%), as dark red needle clusters with a strong fluorescence in solution: mp 179.5–180 °C; λ_{max} *231*, (240), 278, (287), (298), 362, (498), 526, (552) nm, log ϵ 4.32, 4.27, 4.18, 4.13, 3.60, 3.66, 3.81, 3.99, 3.66; IR 1083, 1290, 1658, 1689, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) 2.49 (3 H, CH_3-3), 3.78 (3 H, CH_3N), 3.91 (3 H, CH_3O), 4.04 (3 H, CH_3O), 6.20 (H-4), 7.02 (H-7) (double resonance shows signals at δ 2.49 and 6.20 to be weakly coupled); mass spectrum m/e 302 (M^+, base peak).

Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.4; H, 4.5; N, 9.5.

Dehydration of 4,4a-Dihydro-1,2-dicarbomethoxy-3,5-dimethyl-5-azacycl[3.2.2]azin-6(5*H*)-one (39). The dihydro derivative (**39**), 30 mg, in toluene (15 cm^3) and 5% Pd on charcoal (25 mg) were refluxed for 20 h under a stream of nitrogen. The solution was filtered, concentrated, and subjected to TLC. The slow-moving red band gave 1,2-dicarbomethoxy-3,5-dimethyl-5-azacycl[3.2.2]azin-6(5*H*)-one (**38**), 13 mg (43%), as dark red crystals, with identical spectral characteristics with the sample obtained previously.

Attempted Cyclization of 3-(*cis*-Dicarbomethoxyethenyl)-2,8-dimethyl-8-azaindolizin-7(8*H*)-one (40). The cis isomer (**40**), 12 mg, in toluene (15 cm^3) and 5% Pd on charcoal (20 mg) were refluxed under a stream of nitrogen for 4 h. The catalyst was removed and the resulting orange solution was concentrated and subjected to TLC. The first yellow band gave unchanged starting material, 10 mg. The following orange band gave 3-(*trans*-dicarbomethoxyethenyl)-2,8-dimethyl-8-azaindolizin-7(8*H*)-one (**41**), 2 mg (17%). No red band corresponding to the cyclized derivative (**38**) was observed.

Similarly the trans isomer (**41**), 20 mg, when subjected to the same treatment gave unchanged starting material, 15 mg, and the cis isomer (**40**), 3 mg.

Acknowledgment. The authors wish to thank Dr. Murray and Dr. Youngson for helpful suggestions, Mr. N. Faulkes for the ^1H NMR spectra, and the S. R. C. for a research studentship to C.S.

Registry No.—1, 274-66-8; 2, 61900-67-2; 3, 61900-68-3; 4, 61900-69-4; 5, 61900-70-7; 6, 61900-71-8; 7, 61900-72-9; 8, 61900-73-0; 9, 61900-74-1; 10, 61900-75-2; 17, 61900-76-3; 18, 61900-77-4; 19, 61900-78-5; 20, 61900-79-6; 21, 61915-57-9; 22, 61900-80-9; 23, 61900-81-0; 24, 61900-82-1; 25, 61900-83-2; 26, 61900-84-3; 27, 61900-85-4; 28, 61900-86-5; 29, 61900-87-6; 30, 61900-88-7; 31, 61900-89-8; 32, 61900-90-1; 33, 61900-57-0; 34, 61900-58-1; 35, 61900-59-2; 37, 61900-60-5; 38, 61900-61-6; 39, 61900-62-7; 40, 61900-63-8; 41, 61900-64-9; 2-methylpyrimidine, 5053-43-0; ethyl bromopyruvate, 70-23-5; 8-azaindolizine-2-carboxylic acid K, 61900-65-0; 8-azaindolizine-2-carboxylic acid HCl, 61900-66-1; bromoacetone, 598-31-2; 3-bromo-2-butanone, 814-75-5; phenacyl bromide, 70-11-1; 2,4-dimethylpyrimidine, 14331-54-5; 4-methoxy-2-methylpyrimidine, 7314-65-0; 4-hydroxy-2-methylpyrimidine, 19875-04-8; DAD, 762-42-5.

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Reactions of Aryl Diazonium Salts and Arylazo Alkyl Ethers in Basic Alcoholic Solvents.[1] Steric and Mechanistic Studies

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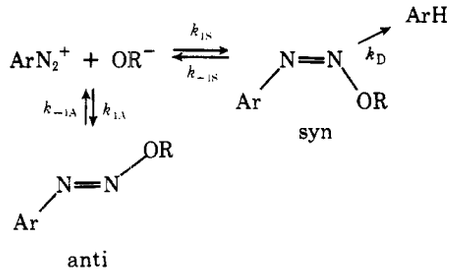
Received November 22, 1976

Kinetic studies of the rate of ionization of halo-substituted *anti*-arylazo alkyl ethers show that the enhanced reactivity of the 2-halo substituted compounds is a function of the size of the halogen atom concerned. It is concluded that this effect is a steric effect. Comparison of the effects of *o*- and *p*-nitro groups on the rates of ionization of *syn*- and *anti*-arylazo alkyl ethers leads to the conclusion that the transition state for ionization of the syn ether is later than the transition state for ionization of the anti ether. This interpretation is consistent with the observed solvent and substituent effects on the two processes. Solvent and substituent effects on the initial partitioning of the diazonium salt are also explained on the basis of this interpretation. For carbanionic dediazoniation of the 2-chloro and 3-chloro compounds the species undergoing dediazoniation is shown to be the *syn*-arylazo alkyl ether.

Dediazoniation of aryldiazonium salts in basic methanolic solution can occur by either a free-radical or a carbanionic mechanism.[2] The mechanism depends on the base concentration[2] and on the substituent on the aromatic ring.[2] As the electron-withdrawing power of the substituent on the aromatic ring is increased (4-CH_3O → 2,4-Cl_2) the amount of anionic reaction increases, but a further increase in the electron-withdrawing power of the substituent (4-NO_2) causes a complete reversion to the radical mechanism.[2] In the case of the 4-nitro substituted compound it has been shown[1] that the processes occurring on dissolving the diazonium salt in basic methanol are as in Scheme I.

Scheme I



These reactions occur in three distinct stages. Phase 1 involves partitioning of the diazonium ion between the *syn*- and *anti*-arylazo alkyl ethers. This occurs extremely rapidly and Ritchie[3] has estimated a rate constant for production of the syn ether at 23 °C in methanol ($k_{1S} = 3 \times 10^8\ M^{-1}\ s^{-1}$), and also an equilibrium constant ($K = k_{1S}/k_{-1S} = 5.6 \times 10^7\ M^{-1}$). A small fraction of *anti*-arylazo alkyl ether is also produced[1] and the rate constant, $k_{1A} = 2.5 \times 10^6\ M^{-1}\ s^{-1}$. Thus the ratio $k_{1S}/k_{1A} = 120$.

Phase 2 involves a slower partitioning of the syn ether between decomposition and protection. Protection involves conversion of the syn ether into the anti ether via the free diazonium ion.

$$k_p = (\text{syn} \rightarrow \text{anti})$$

$$k_p = k_{-1S}\frac{k_{1A}}{k_{1A} + k_{1S}} \quad (1)$$

In the case of the *p*-nitro compound, which decomposes via a free-radical mechanism, it is the syn ether that actually undergoes decomposition, not the free diazonium ion[1] (k_D = syn → ArH).

Phase 3 involves the slow dediazoniation of the anti ether via the free diazonium ion and the syn ether. The rate of this process (k_ψ, i.e., anti → ArH) is defined as follows.