Azaindolizines. 3. Formylation Studies on 6-Azaindolizines

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Received October 22, 1974

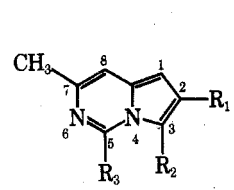
The Chichibabin reaction between an α-halo ketone and 4-methylpyrimidines has been used to synthesise the 6-azaindolizines (**2–5**); 2,4,6-trimethylpyrimidine has been shown to yield the 6-azaindolizine (**4**) rather than the reported isomeric 8-azaindolizine (**14**). The ^{1}H NMR spectra of the 6-azaindolizines (**1–6**) and the formyl-6-azaindolizines (**7–13**) have been elucidated. Vilsmeier formylation was shown to occur at C-3 and C-1; the 5,7-dimethyl-6-azaindolizines **4** and **5** yielded in addition to their formyl derivatives the 4-formyl-5-azacycl[3.2.2]azines **19** and **21**.

The 6-azaindolizines were synthesized by the Chichibabin procedure[1,2] which involved quaternization of 4,6-dimethyl- or 2,4,6-trimethylpyrimidine with phenacyl bromide, bromoacetone, or 3-bromobutanone followed by bicarbonate cyclization. 4,6-Dimethylpyrimidine can only give rise to a 6-azaindolizine whereas 2,4,6-trimethylpyrimidine may give either a 6- or an 8-azaindolizine depending on whether cyclization occurs via the 4- or 2-methyl groups, respectively. The ^{1}H NMR spectra of the azaindolizines are shown in Table I. The assignments of the ring and methyl hydrogen signals were made on the basis of the proximity of the protons to nitrogen, and also with the assistance of double irradiation. The C-1 and C-3 protons were readily identified[3,4] by deuterium exchange.[5]

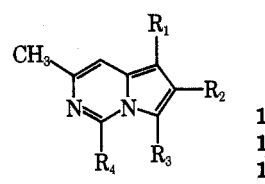
The Chichibabin reaction between 2,4,6-trimethylpyrimidine and phenacyl bromide has been reported by Ochiai[6] to give the 8-azaindolizine (**14**) together with a substituted pyrrole which was thought to be formed by breakdown of the isomeric 6-azaindolizine (**4**), and was assigned the acetonyl pyrrole structure (**15**). We have reinvestigated this reaction and have also obtained an azaindolizine and a small amount of a pyrrole derivative. This pyrrole and its *p*-nitrophenylhydrazone gave melting points consistent with those reported by Ochiai.[6] The pyrrole now has been shown to be 3-acetyl-2-methyl-5-phenylpyrrole (**16**), since its ^{1}H NMR spectrum indicated it to be trisubstituted containing a methyl group (δ 2.43, CH_3), a phenyl group (δ 7.04–7.56, C_6H_5), and an acetyl group (δ 2.59, $COCH_3$), and the position of the groups was established by an alternative Hantzsch synthesis between phenacyl bromide, acetylacetone, and ammonia. Presumably the pyrrole is formed in the Chichibabin reaction by interaction between phenacyl bromide and a degradation product from the pyrimidine or pyrimidinium nucleus.

The azaindolizine isolated by us forms a picrate the melting point of which is identical with that previously recorded.[6] Its ^{1}H NMR spectrum showed a complex multiplet (δ 7.20–7.70) due to the phenyl protons, two 3 H singlets (δ 2.34 and 2.64) both due to methyl protons, and three lower field 1 H singlets at δ 6.52, 6.88, and 7.34. By deuterium exchange[5] H-1 and H-3 were assigned as the 1 H singlets at δ 6.52 and 7.34, respectively; thus the 1 H singlet at δ 6.88 may be assigned to either H-6 of the 8-azaindolizine (**14**) or H-8 of the 6-azaindolizine (**4**). Sharpening of the signal at δ 6.88 only occurred by irradiation at the frequency of the higher field methyl signal at δ 2.34, assigned to the 7-methyl of structure **4**. Since in the 8-azaindolizine (**14**) both methyl groups would be expected to cause a sharpening of the signal at δ 6.88, the 6-azaindolizine structure (**4**) is preferred.

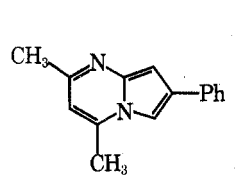
2,4,6-Trimethylpyrimidine has been shown to react analogously with bromoacetone to give a small amount of the acetyl pyrrole (**17**) and the corresponding 6-azaindolizine



	R_1	R_2	R_3
1	Ph	H	H
2	CH_3	H	H
3	CH_3	CH_3	H
4	Ph	H	CH_3
5	CH_3	H	CH_3
6	CH_3	CH_3	CH_3



	R_1	R_2	R_3	R_4
7	H	CH_3	CHO	H
8	H	CH_3	CHS	H
9	CHO	CH_3	CH_3	H
10	H	CH_3	CHO	CH_3
11	CHO	CH_3	CH_3	CH_3
12'	CHO	CH_3	H	CH_3
13	CHO	Ph	H	CH_3



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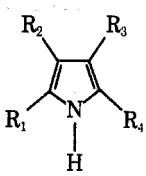
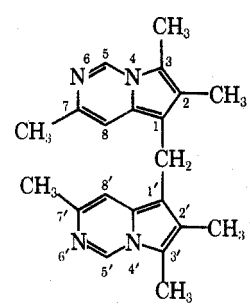


	R_1	R_2	R_3	R_4
15	H	Ph	H	CH_3COCH_2
16	Ph	H	CH_3CO	CH_3
17	CH_3	H	CH_3CO	CH_3



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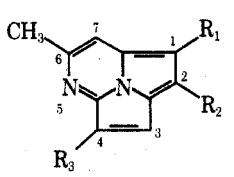
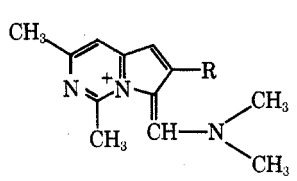
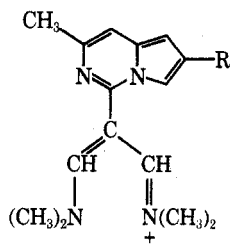


	R_1	R_2	R_3
19	H	Ph	CHO
20	H	Ph	H
21	H	CH_3	CHO
22	H	CH_3	H
23	CHO	Ph	H
24	CHO	CH_3	H



25, R = CH_3 or Ph



26, R = CH_3 or Ph

Table I[a]
Chemical Shifts (δ) in the 100-MHz ^{1}H NMR Spectra of 6-Azaindolizines 1–6 in $CDCl_3$

Structure	R_1	R_2	R_3	7-CH_3	H-1	H-8
1	7.30–7.70 (complex)	7.53	8.70	2.40	6.56	7.00
2	2.25	7.05	8.58	2.29	6.08	6.90
3	2.22	2.36	8.46	2.38	6.07	6.90
4	7.20–7.70 (complex)	7.34	2.64	2.34*	6.52	6.88*
5	2.30	6.94	2.62	2.36	6.13	6.85
6	2.16	2.60	2.86	2.28*	6.00	6.69*

[a] Unless otherwise stated values given refer to singlet absorption, d = doublet, complex = complex multiplet absorption. Coupling constants (hertz) are in parentheses; weakly coupled peaks indicated by double irradiation are marked by an asterisk.

Table II[a]
Chemical Shifts (δ) in the 100-MHz ^{1}H NMR Spectra of Formyl-6-azaindolizines 7–13 in $CDCl_3$

Structure	R_1	R_2	R_3	R_4	7-CH_3	H-8
7	6.23	2.54	9.85 (3-formyl)	10.26	2.60	7.16
8	6.35*	2.51*	10.71 (3-thioformyl)	11.63	2.53	7.24
9	10.6 (1-formyl)	2.43	2.43	8.63	2.51	7.80
10	6.26	2.45	9.97 (3-formyl)	2.98	2.59	7.00
11	10.02 (1-formyl)	2.39	2.66	3.01	2.42	7.73
12	10.06 (1-formyl)	2.51	6.95	2.74	2.49	7.74
13	9.98 (1-formyl)	7.36–7.60 (complex)	7.18	2.81	2.52	8.04

[a] See footnote *a*, Table I.

(**5**), but no identificable products were isolated from the reaction with 3-bromobutanone. Further evidence that a 6- rather than an 8-azaindolizine was isolated from these Chichibabin reactions with 2,4,6-trimethylpyrimidine was obtained from formylation studies.

Vilsmeier formylation of 2,7-dimethyl-6-azaindolizine (**2**) gave either a formyl or thioformyl 2,7-dimethyl-6-azaindolizine depending on whether the reaction mixture was poured into sodium hydroxide or sodium hydrogen sulfide.[7] Comparison of the ^{1}H NMR spectrum of **2** with those of its formylated or thioformylated products indicates that reaction occurs at position 3, since the H-5, *not* the H-8, signals showed large peri shifts (168 and 305 Hz) due to the anisotropic deshielding effect of the 3-formyl and 3-thioformyl groups, respectively. The products must therefore have structures **7** and **8**. Furthermore, reduction of **7** with lithium aluminium hydride–aluminium chloride gave 2,3,7-trimethyl-6-azaindolizine (**3**) which was alternatively synthesized from 4,6-dimethylpyrimidine and 3-bromobutanone. Formylation of **3** gave 1-formyl-2,3,7-trimethyl-6-azaindolizine (**9**), as indicated by comparing the ^{1}H NMR spectrum of **9** with that of its precursor **3** (see Table II). Introduction of the 1-formyl group causes the disappearance of the H-1 singlet (δ 6.07) of **3** and a large downfield shift (90 Hz) in the position of the H-8 signal due to its peri orientation with respect to the formyl group. That C-1 substitution proceeds when the 3 position is blocked is also shown by the formation of the di-6-azaindolizylmethane (**18**) in the reaction of 2,3,7-trimethyl-6-azaindolizine (**3**) with formaldehyde. Compound **18** had no exchangeable hydrogens and its ^{1}H NMR spectrum was similar to that of its precursor (**3**) except that the lowest field aromatic singlet of **3** was no longer present and a new 2 H singlet at δ 3.97 due to the methylene protons appeared. These reactions showing formylation to occur preferentially at C-3[9] and then at C-1 agree in the main with theoretical calculations which point to the 3 and 1 positions as the preferred sites of electrophilic substitution.[10]

Formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine (**4**) gave two aldehydes. The ^{1}H NMR spectrum of one was consistent with it being 1-formyl-5,7-dimethyl-2-phenyl-6-azaindolizine (**13**) showing a considerable peri shift of the H-8 proton (δ 8.04) with respect to the H-8 proton (δ 6.88) of the parent 6-azaindolizine (**4**). The other aldehyde has been shown to be 4-formyl-6-methyl-2-phenyl-5-azacycl[3.2.2]azine (**19**), since the 6-methyl-2-phenyl-5-azacycl[3.2.2]azine (**20**), synthesized by Boekelheide's 1,3-dipolar addition procedure,[2] gave on formylation approximately equal yields of the 1- and 4-formyl derivatives **23** and **19**. The interpretation of the ^{1}H NMR spectra of these cyclazines is shown in Table III. In structure **23** the two aromatic protons at C-3 and C-4 occur as doublets (J = 4.0 Hz) and the C-7 proton, because of its peri orientation to the formyl group and weak coupling to the 6-methyl group, occurs as a lower field broad singlet. Since the ^{1}H NMR spectrum of the other formyl derivative showed only singlets for the 1 H signals it must be either the 3- or 4-formyl-6-methyl-2-phenyl-5-azacycl[3.2.2]azine. As carbon protonation of **20**[2] has been inferred to occur at C-1 and C-4 we suggest that the formyl group is located at position 4. This is supported by the fact that the introduction of the formyl group into **20** does not result in a significant shift of the resonance position of the phenyl protons; and it is consistent with the recent results of Fuentes and Paudler.[11]

Unequivocal proof that a 6-azaindolizine (**5**) is indeed formed in the reaction of 2,4,6-trimethylpyrimidine with bromoacetone was obtained from the following reactions. Formylation of compound **5** gave the two formyl-6-azaindolizines **10** and **12** together with the 5-azacycl[3.2.2]azine **21**, the structures of which can be assigned on the basis of their ^{1}H NMR spectra. Reduction of compound **10** with lithium aluminium hydride–aluminium chloride gave the

Table III[a,b]
Chemical Shifts (δ) in the 100-MHz ^{1}H NMR Spectra of 5-Azacycl[3.2.2]azines 19–24 in $CDCl_3$

Structure	R_1	R_2	R_3	6-CH_3	H-3	H-7
19	7.42	7.30–8.06 (complex)	10.50 (4-formyl)	3.01*	8.37	7.67*
20	7.24	7.34–8.06 (complex)	7.20 (7.91) d, $J \simeq 4.0$Hz	2.93*	7.91 (7.20) d, $J \simeq 4.0$Hz	7.58*
21	6.98*	2.71*	10.49 (4-formyl)	2.99*	8.10	7.57*
22	6.81*	2.70*	7.10 (7.70) d, $J \simeq 4.0$Hz	2.93	7.70 (7.10) d, $J \simeq 4.0$Hz	7.52
23	10.22 (1-formyl)	7.48–7.92 (complex)	7.30 (7.86) d, $J \simeq 4.0$Hz	2.98*	7.86 (7.30) d, $J \simeq 4.0$Hz	8.20*
24	10.29 (1-formyl)	2.96	7.24 (7.82) d, $J \simeq 4.0$Hz	2.96	7.82 (7.24) d, $J \simeq 4.0$Hz	8.02

[a] See footnote *a*, Table I. [b] H-3 and H-4 δ values are tentative and are quoted in parentheses.

tetramethylazaindolizine (**6**) which could be further formylated. This formylazaindolizine showed the expected large peri shift of the one remaining aromatic proton (H-8, 104 Hz) with respect to the lowest field signal (H-8) of **6** and must therefore be 1-formyl-2,3,5,7-tetramethyl-6-azaindolizine (**11**). Finally, compound **10** on heating with solid potassium hydroxide afforded 2,6-dimethyl-5-azacycl[3.2.2]azine (**22**), which was also prepared by reaction of dimethyl acetylenedicarboxylate with 2,7-dimethyl-6-azaindolizine (**2**) followed by hydrolysis and decarboxylation.

There would appear to be two possible routes whereby the 4-formyl-5-azacycl[3.2.2]azine structures **19** and **21** could be formed from the 6-azaindolizines. Cyclization could occur through an intermediate cation such as **25**, formed by attack of the Vilsmeier electrophile[12] on the electron-rich C-3 site of the azaindolizine, followed by formylation of the resulting azacycl[3.2.2]azine. Alternatively attack by the electrophile[12] on the active 5-methyl group[13] of the azaindolizine could give an intermediate such as **26**[14] which on cyclization followed by hydrolysis would yield the 4-formyl-5-azacycl[3.2.2]azine. Presumably the formation of 3-formyl-2,5,7-trimethyl-6-azaindolizine (**10**) from **5** has occurred via cation **25** (R = CH_3), so that the 4-formylazacycl[3.2.2]azine (**21**) could be formed from **5** via this cation. However, formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine (**4**) gave no 3-formyl derivative, suggesting that the access of the Vilsmeier electrophile to the C-3 site is hindered, and yet the 4-formylazacycl[3.2.2]azine **19** was isolated. This infers that the 4-formylazacycl[3.2.2]azines **19** and **21** are more likely to be formed through intermediate **26**. This inference is supported by the fact that formylation of the azacycl[3.2.2]azines **20** and **22** gave approximately equal mixtures of the corresponding 1- and 4-formyl derivatives together with unchanged azacyclazine, whereas formylation of the 6-azaindolizines **4** and **5** gave, inter alia, the 4-formyl-5-azacycl[3.2.2]azines **19** and **21** but no 1-formyl-5-azacycl[3.2.2]azines **23** and **24**; further no unformylated azacyclazines **20** and **22** were isolated.

Experimental Section

Melting points were determined by the capillary method and are uncorrected. Elemental analyses were performed by the analytical laboratories of Aberdeen University. Infrared spectra were measured for Nujol mulls with a Unicam SP200 spectrometer. Ultraviolet spectra were measured with a Unicam SP800 spectrometer. Light absorption data refer to solutions in ethanol, principal maxima are italicized, br = broad, infl = inflection. ^{1}H NMR 100-MHz 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, coupling constants in hertz, and integration values and signal assignment are in parentheses. For multiplets d = doublet, m = complex multiplet. Mass spectra were measured with an AEI MS30 spectrometer.

Procedures. Solutions were dried over anhydrous magnesium sulfate and solvents evaporated at reduced pressure on a rotary film evaporator. Column chromatography was carried out with Woelm neutral alumina. Thin layer chromatography was carried out on Merck Kieselgel GF_{254} using benzene–ethyl acetate (3:1) as eluent unless otherwise stated. Petroleum ether refers to the fraction bp 80–100° except when otherwise indicated.

The synthesis of 7-methyl-2-phenyl-6-azaindolizine (**1**) has been previously reported.[2] The following general procedure was used in the Chichibabin synthesis of **2,7-dimethyl- (2), 2,3,7-trimethyl- (3), 2,5,7-trimethyl- (5), and 5,7-dimethyl-2-phenyl-6-azaindolizine (4).** Deviations are given in individual cases. The α-bromo ketone was added to the pyrimidine in a small volume of ethanol. The solution was left overnight and if required the quaternization reaction completed by evaporating off the ethanol. Water was added to the resulting viscous oil. This was extracted several times with ether and warmed to remove the dissolved ether, before adding an excess of sodium hydrogen carbonate. After the effervescence had ceased, the resulting solution was steam distilled. The steam distillate was extracted several times with ether, the combined ether extracts were washed with water and dried, and the ether was evaporated to leave a crude residue of the 6-azaindolizine.

4,6-Dimethylpyrimidine (16.2 g, 0.15 mol) and bromoacetone (12.6 ml, 0.15 mol) gave **2,7-dimethyl-6-azaindolizine (2)** as a brown oil. This was taken up in petroleum ether and chromatographed on a short column (5 cm). Elution and evaporation gave a light brown solid which vacuum distilled at 160° (20 mm) to give 2,7-dimethyl-6-azaindolizine (**2**) as a cream, waxy solid (2.7 g, 10%), mp 63–65°, which darkened on standing: λ_{max} 291, 280 (br), 270 (infl), *239* nm (log ε 3.61, 3.57, 3.44, 4.31, respectively); ir 780, 860, 1240, 1615 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2$: C, 73.9; H, 6.9; N, 19.2. Found: C, 73.8; H, 7.2; N, 19.0.

4,6-Dimethylpyrimidine (21.6 g, 0.2 mol) and 3-bromo-2-butanone (21.4 ml, 0.2 mol) gave **2,3,7-trimethyl-6-azaindolizine (3,** 4.17 g, 15%) as a brown oil which solidified on cooling. Distillation at 100° (12 mm) gave **3** as yellow, waxy needles, mp 55–57°, which darkened slowly on standing: λ_{max} 293, 282, 272 (infl), *240* nm (log ε 3.76, 3.74, 3.73, 4.42, respectively); ir 760, 880, 1190, 1250, 1355, 1420, 1635 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 75.0; H, 7.6; N, 17.5. Found: C, 74.7; H, 7.7; N, 17.2.

2,4,6-Trimethylpyrimidine (12.2 g, 0.1 mol) and bromoacetone (8.4 ml, 0.1 mol) gave the crude 2,5,7-trimethyl-6-azaindolizine (**5**) as a golden-brown oil. Distillation of this oil (20 mm) gave as the first fraction unreacted 2,4,6-trimethylpyrimidine (3.0 g). **2,5,7-Trimethyl-6-azaindolizine (5)** was then collected at 110° (2 mm) as a pale yellow oil (0.86 g, 6%) which slowly turned blue green on standing; λ_{max} 350 (br), 290, 279, 250 (infl), *235* nm (log ε 3.26, 3.92, 3.89, 3.97, 4.59, respectively); ir 770, 930, 1165, 1295, 1535, 1625 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 75.0; H, 7.6; N, 17.5. Found: C, 74.8; H, 7.6; N, 17.3.

2,4,6-Trimethylpyrimidine (12.2 g, 0.1 mol) and phenacyl bromide (19.9 g, 0.1 mol) gave on evaporation of the ether extract from the aqueous bicarbonate solution a dark-colored liquid residue. This residue was distilled at 130° (5 mm) to give as the first fraction unreacted 2,4,6-trimethylpyrimidine (2.2 g). Distillation at 180–200° (1 mm) then gave **5,7-dimethyl-2-phenyl-6-azaindolizine (4)** as a yellow oil which solidified to a hard, compact

mass (1.5 g, 7%): mp 89–92° dec; λ_{max} 290 (infl), *257*, 212.5 nm (log ϵ 3.81, 4.61, 4.19, respectively); ir 690, 730, 770, 860, 1200, 1410, 1540, 1625 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.2; H, 6.3; N, 12.6. Found: C, 81.5; H, 6.0; N, 12.3.

3-Acetyl-2,5-dimethyl- (17) and 3-acetyl-2-methyl-5-phenylpyrrole (16) were isolated from the reaction of 2,4,6-trimethylpyrimidine with bromoacetone or phenacyl bromide, respectively. The ether extracts of the aqueous solutions of the quaternary salts resulting from the reaction between 2,4,6-trimethylpyrimidine and the bromo ketone were evaporated to leave brown oils which, by TLC, gave the pyrrole which was finally recrystallized from petroleum ether.

3-Acetyl-2,5-dimethylpyrrole (17, 0.092 g) was obtained as white needles: mp 93–94°;[15,16] λ_{max} 294, *246* nm (log ϵ 3.77, 3.96, respectively); ir 950, 1225, 1360, 1531, 1630, 1639, 3175, 3240 cm^{-1}; ^1H NMR ($CDCl_3$) 2.19 (3 H, 5-Me), 2.35 (3 H, 2-Me), 2.48 (3 H, 3-acetyl-Me), 6.15 (1 H, H-4), 8.60 (1 H, NH).

Anal. Calcd for $C_8H_{11}NO$: C, 70.0; H, 8.1. Found: C, 69.9; H, 8.4.

3-Acetyl-2-methyl-5-phenylpyrrole (16, 0.028 g) was obtained as pale green needles: mp 179–181°;[17] λ_{max} 310, 288, *242*, 236 (infl), 229 (infl) (log ϵ 4.06, 4.31, 4.34, 4.31, 4.22, respectively); ir 775, 812, 930, 952, 1238, 1561, 1600, 1629, 3220 cm^{-1}; ^1H NMR ($CDCl_3$) 2.43 (3 H, 2-Me), 2.59 (3 H, 3-acetyl-Me), 6.77 (1 H, H-4), 7.04–7.56 (5 H, 5-Ph), 8.78 (1 H, NH).

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.4; H, 6.6; N, 7.0. Found: C, 78.4; H, 6.5; N, 6.7.

The *p*-nitrophenylhydrazone derivative of **16** gave mp 235–237°.[6] Calcd mass for $C_{19}H_{18}N_4O_2$: 334.1429. Found: M^+ (35% base peak) 334.1429.

3-Acetyl-2-methyl-5-phenylpyrrole was synthesized by the Hantzsch procedure[18] as follows. To a mixture of phenacyl bromide (1.99 g, 0.01 mol) and acetylacetone (1.00 g, 0.01 mol) was added slowly excess aqueous ammonia (20 ml, sp gr 0.88) and the mixture gently warmed before refluxing for 15 min. The reaction mixture was evaporated to dryness, the residue extracted with chloroform, and the chloroform extract evaporated to leave a red gum which after TLC gave the pyrrole **16** (0.084 g, 4.2%) with identical melting point and spectral characteristics as cited above.

6-Methyl-2-phenyl-5-azacycl[3.2.2]azine (**20**) was synthesized according to Boekelheide's procedure.[2]

2,6-Dimethyl-5-azacycl[3.2.2]azine (22). 2,7-Dimethyl-6-azaindolizine (**2,** 1.00 g) in nitrobenzene[19] (20 ml) was added to dimethyl acetylenedicarboxylate (3 g) in nitrobenzene (20 ml). The resultant red solution was refluxed (1 hr) and the solvent evaporated. The resulting black tar gave after TLC a slow-moving bright yellow band which after extraction and distillation (160–180°, ~0.1 mm) followed by recrystallization (ethyl acetate) gave **3,4-dicarbomethoxy-2,6-dimethyl-5-azacycl[3.2.2]azine** (0.208 g, 11%) as orange prisms: mp 143–145°; λ_{max} 438, 315, 263, *239* nm (log ϵ 3.93, 4.07, 4.36, 4.51, respectively); ir 792, 1060, 1131, 1153, 1190, 1229, 1261, 1700, 1726 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.9; H, 4.9; N, 9.8. Found: C, 62.8; H, 5.1; N, 10.0.

To the diester (0.10 g) in warm methanol (2 ml) was added a solution of potassium hydroxide (5.2 g) in methanol (13 ml). A fine precipitate formed and the reaction mixture was warmed (50°) for 1 hr to ensure complete hydrolysis. The precipitate was collected, dissolved in water, and acidified with 6 *M* hydrochloric acid. The crude diacid (0.064 g, 71%) was collected, dried, and refluxed with copper powder (0.25 g) and aniline (50 ml) for 2 hr. The copper powder was filtered and the filtrate evaporated to remove the bulk of the aniline. The residue after TLC [benzene–ethyl acetate (25:1) and then petroleum ether (60–80°)–ethyl acetate (10:1)] gave a bright yellow band which afforded **2,6-dimethyl-5-azacycl[3.2.2]azine (22,** 0.008, 19%) as yellow crystals: mp 40–43°; λ_{max} 433, 306, 291, *249* nm (log ϵ 3.54, 3.54, 3.75, 4.62, respectively); ir 710, 719, 741, 1332, 1515, 1525, 1590 cm^{-1}.

Calcd mass for $C_{11}H_{10}N_2$: 170.0843. Found: M^+ (base peak) 170.0843.

General Formylation Procedure. Formylation was carried out by treatment of the 6-azaindolizine or azacycl[3.2.2]azine with dimethylformamide and phosphoryl chloride at room temperature by a procedure similar to that reported in a previous paper.[20]

2,7-Dimethyl-6-azaindolizine (1.46 g) gave **3-formyl-2,7-dimethyl-6-azaindolizine (7,** 1.08 g, 62%) as yellow needles: mp 109–110°; λ_{max} 367, 360 (infl), 264, 253 (infl), 247, *228* nm (log ϵ 4.22, 4.17, 3.97, 4.01, 4.07, 4.27, respectively); ir 720, 780, 960, 1130, 1260, 1625, 1675 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 69.0; H, 5.8. Found: C, 69.2; H, 6.1.

2,3,7-Trimethyl-6-azaindolizine (**3,** 1.6 g) gave **1-formyl-2,3,7-trimethyl-6-azaindolizine (9,** 1.28 g, 68%) as straw-colored needles: mp 143–146°; λ_{max} 340, 274 (infl) 264 (infl), *240* nm (log ϵ 4.10, 3.37, 3.71, 4.41, respectively); ir 780, 870, 1045, 1250, 1360, 1510, 1615, 1660 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.3; H, 6.4. Found: C, 70.2; H, 6.7.

2,3,5,7-Tetramethyl-6-azaindolizine (**6,** 0.032 g) gave **1-formyl-2,3,5,7-tetramethyl-6-azaindolizine (11,** 0.002 g, 5%) as white needles from petroleum ether: mp 166°; λ_{max} 349, 279 (infl), 267 (infl), *239* nm (log ϵ 4.14, 3.30, 3.60, 4.40, respectively); ir 965, 1438, 1519, 1610, 1647 cm^{-1}. Calcd mass for $C_{12}H_{14}N_2O$: 202.1106. Found: M^+ (base peak) 202.1104.

5,7-Dimethyl-2-phenyl-6-azaindolizine (**4,** 0.22 g) gave after TLC two bands. The faster moving band afforded **1-formyl-5,7-dimethyl-2-phenyl-6-azaindolizine (13,** 0.01 g, 4.0%) as small needles from petroleum ether: mp 167–169°; λ_{max} 348, 282 (infl), *242* nm (log ϵ 4.19, 3.79, 4.50, respectively); ir 719, 1490, 1508, 1610, 1641 cm^{-1}. Calcd mass for $C_{16}H_{14}N_2O$: 250.1106. Found: M^+ (base peak) 250.1107.

The slower moving yellow band afforded **4-formyl-6-methyl-2-phenyl-5-azacycl[3.2.2]azine (19,** 0.005 g, 1.9%) as orange needles from petroleum ether–benzene: mp 178–179°; λ_{max} 454, 342, 283, 253 (infl), *245*, 230 nm (infl) (log ϵ 3.98, 4.36, 4.22, 4.52, 4.59, 4.46, respectively); ir 685, 770, 1150, 1410, 1505, 1528, 1591, 1659 cm^{-1}. Calcd mass for $C_{17}H_{12}N_2O$: 260.0949. Found: M^+ (base peak) 260.0946.

2,5,7-Trimethyl-6-azaindolizine (**5,** 1.0 g) gave after TLC three main bands. The fastest moving band gave unchanged starting material (0.17 g, 17%). The middle band afforded **3-formyl-2,5,7-trimethyl-6-azaindolizine (10,** 0.19 g, 20%) as prisms from petroleum ether: mp 100–101°; λ_{max} *365*, 355 (infl), 260 (infl), 253 (infl), 246, 228 nm (log ϵ 4.29, 4.23, 3.99, 4.03, 4.06, 4.26, respectively); ir 790, 850, 1263, 1319, 1410, 1518, 1630 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found: C, 70.1; H, 6.5; N, 15.2.

The slowest moving band gave orange crystals (0.127 g) which on fractional crystallization (petroleum ether–benzene, 10:1) gave **4-formyl-2,6-dimethyl-5-azacycl[3.2.2]azine (21,** 0.072 g, 7%) as long yellow needles: mp 202.5°; λ_{max} 435 (infl), 428, 315, 309, 281, *249*, 224 nm (log ϵ 3.98, 3.99, 4.01, 4.01, 4.20, 4.47, 4.33, respectively); ir 870, 1139, 1410, 1534, 1592, 1664 cm^{-1}.

Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.7; H, 5.1; N, 14.1. Found: C, 72.9; H, 5.0; N, 14.3.

The mother liquors from the fractional crystallization were evaporated and the residue after TLC [acetone–petroleum ether (60–80°), 5:2] gave two overlapping bands. The lower portion of the slower moving component afforded **1-formyl-2,5,7-trimethyl-6-azaindolizine (12,** 0.022 g, 2.2%) as prisms from petroleum ether: mp 127–129°; λ_{max} 338, 261 (infl), *232* nm (log ϵ 4.16, 3.60, 4.39, respectively); ir 961, 1278, 1441, 1523, 1610, 1649 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4. Found: C, 70.4; H, 6.5. Calcd mass: 188.049. Found: M^+ (base peak) 188.049.

Formylation of 6-methyl-2-phenyl-5-azacycl[3.2.2]azine (**20,** 0.016 g) gave after TLC (benzene–ethyl acetate, 50:3) three well-separated bands, the fastest moving one being starting material (0.003 g, 20%). The middle band gave **1-formyl-6-methyl-2-phenyl-5-azacycl[3.2.2]azine (23,** 0.004 g, 29%) as orange needles from petroleum ether: mp 163–164°; λ_{max} 438, 315 (infl), *297*, 284 (infl), 233 (infl), 255 nm (log ϵ 3.97, 4.27, 4.46, 4.42, 4.33, 4.40, respectively); ir 709, 760, 794, 1362, 1529, 1588, 1643 cm^{-1}. Calcd mass for $C_{17}H_{12}N_2O$: 260.0949. Found: M^+ (84% base peak) 260.0946.

The slowest moving band gave **4-formyl-6-methyl-2-phenyl-5-azacycl[3.2.2]azine (19,** 0.004 g, 28%). It showed identical melting point and spectral characteristics with the sample obtained from the formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine (**4**).

Formylation of 2,6-dimethyl-5-azacycl[3.2.2]azine (**22,** 0.017 g) gave after TLC (benzene–ethyl acetate, 50:3) three well-separated bands, the fastest moving band being starting material (0.004 g, 24%). The middle band gave **1-formyl-2,6-dimethyl-5-azacycl[3.2.2]azine (24,** 0.003 g, 20%) as small yellow crystals from petroleum ether: mp 152–160°; λ_{max} 424, 312, 286 (infl), 267 (infl), *258*, 227 nm (log ϵ 3.92, 4.00, 4.03, 4.33, 4.45, 4.38, respectively); ir 720, 781, 1324, 1365, 1422, 1518, 1533, 1590, 1640 cm^{-1}. Calcd mass for $C_{12}H_{10}N_2O$: 198.0793. Found: M^+ (75% base peak) 198.0791.

The slowest moving band gave **4-formyl-2,6-dimethyl-5-aza-**

cycl[3.2.2]azine (**21**, 0.004 g, 27%) showing identical melting point and spectral characteristics with those of sample obtained from the formylation of 2,5,7-trimethyl-6-azaindolizine (**5**).

Thioformylation of 2,7-dimethyl-6-azaindolizine (**2**, 0.250 g) was carried out by treatment of **2** with dimethylformamide (2 ml) and phosphoryl chloride (0.35 g) at room temperature. The reaction mixture was poured into a 2 *M* aqueous sodium hydrogen sulfide[7] solution (30 ml) and extracted with chloroform. Evaporation of the chloroform followed by column chromatography using benzene and recrystallization from benzene–cyclohexane (1:5) gave **2,7-dimethyl-3-thioformyl-6-azaindolizine** (**8**, 0.190 g, 58%) as red needles: mp 175–176°; λ_{max} *439*, 433 (infl), 420 (infl), 370, 308, 300 (infl), 253 (infl), 238 (infl), *227* nm (log ϵ 4.20, 4.15, 3.98, 3.65, 3.76, 3.72, 3.91, 4.02, 4.20, respectively); ir 870, 980, 1135, 1258, 1318, 1510, 1610 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_2S$: C, 63.1; H, 5.3; N, 14.7. Found: C, 63.4; H, 5.4; N, 15.0.

Reduction of aldehydes **7** and **10** to give, respectively, **2,3,7-trimethyl-6-azaindolizine** (**3**) and **2,3,5,7-tetramethyl-6-azaindolizine** (**6**) was carried out with lithium aluminum hydride–aluminum chloride in ether by a procedure similar to that reported in a previous paper.[20] 3-Formyl-2,7-dimethyl-6-azaindolizine (**7**, 0.5 g) gave a brown oil (0.21 g). This oil after TLC afforded as the main band 2,3,7-trimethyl-6-azaindolizine (**3**, 0.01 g, 2%) which showed identical spectral characteristics with the sample obtained from the Chichibabin reaction between 4,6-dimethylpyrimidine and 3-bromo-2-butanone.

3-Formyl-2,5,7-trimethyl-6-azaindolizine (**10**, 0.20 g) after TLC gave 2,3,5,7-tetramethyl-6-azaindolizine (**6**, 0.05, 27%) as needles: mp 64–67°; λ_{max} 358 (br), 295, 284, 277 (infl), *240* nm (log ϵ 3.15, 3.82, 3.83, 3.71, 4.39, respectively); ir 868, 1287, 1363, 1436, 1530, 1630 cm^{-1}. Calcd mass for $C_{11}H_{14}N_2$: 174.1156. Found: M^+ (base peak) 174.1157.

2,6-Dimethyl-5-azacycl[3.2.2]azine (22) from 3-Formyl-2,7-dimethyl-6-azaindolizine (**10**). A mixture of 3-formyl-2,7-dimethyl-6-azaindolizine (**10**, 0.05 g) and potassium hydroxide (2.0 g) were quickly fused in a sealed, evacuated tube. Immediately a yellow vapor formed and droplets of a yellow-brown liquid condensed. After cooling, the contents of the tube were extracted with ether, the ether evaporated, and the residue after TLC gave as an intense yellow band 2,6-dimethyl-5-azacycl[3.2.2]azine (**22**, 0.012 g, 27%) which showed identical melting point and spectral characteristics with those of the sample obtained after hydrolysis and decarboxylation of the product from the 1,3-dipolar addition reaction between 2,7-dimethyl-6-azaindolizine and dimethyl acetylenedicarboxylate.

Methylene-1,1′-(2,2′,3,3′,7,7′-hexamethyl)di-6-azaindolizine (**18**). Addition of 40% aqueous formaldehyde (2.0 ml) to a solution of 2,3,7-trimethyl-6-azaindolizine (**3**, 0.8 g, 5 mmol) in ethanol (3 ml) gave on gentle reflux for 15 min a cloudy solution from which yellow needles of the symmetrical di-6-azaindolizylmethane (**18**, 0.73 g, 88%) precipitated. Recrystallization from ethyl acetate gave the compound **18**: mp 238–240° dec; λ_{max} 376, 299, 287, 277 (infl), *243* nm (log ϵ 3.22, 3.91, 3.91, 3.83, 4.53, respectively); ir 850, 1120, 1175, 1240, 1350, 1420, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (6 H, 2- and 2′-Me), 2.32 (6 H, 3- and 3′-Me), 2.39 (6 H, 7- and 7′-Me), 3.97 (2 H, bridge methylene), 6.68 (2 H, H-8 and H-8′), 8.44 (2 H, H-5 and H-5′).

Anal. Calcd for $C_{21}H_{24}N_4$: C, 75.9; H, 7.3; N, 16.8. Found: C, 76.0; H, 7.5; N, 17.1.

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

Registry No.—**1**, 57139-15-8; **2**, 57108-98-2; **3**, 57108-99-3; **4**, 57109-00-9; **5**, 57109-01-0; **6**, 57109-02-1; **7**, 57109-03-2; **8**, 57109-04-3; **9**, 57109-05-4; **10**, 57109-06-5; **11**, 57109-07-6; **12**, 57109-08-7; **13**, 57109-09-8; **16**, 13219-97-1; **16** *p*-nitrophenylhydrazone, 57109-10-1; **17**, 1500-94-3; **18**, 57109-11-2; **19**, 57109-12-3; **20**, 57109-13-4; **21**, 57109-14-5; **22**, 57109-15-6; **23**, 57109-16-7; **24**, 57109-17-8; 4,6-dimethylpyrimidine, 1558-17-4; bromoacetone, 598-31-2; 3-bromo-2-butanone, 814-75-5; 2,4,6-trimethylpyrimidine, 22114-27-8; phenacyl bromide, 70-11-1; acetylacetone, 123-54-6; 3,4-dicarbomethoxy-2,6-dimethyl-5-azacycl[3.2.2]azine, 57109-18-9.

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Stereospecific Epoxidation of Dihydrophthalates

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Received June 16, 1975

Carboxylate groups exert specific syn-directing effects on the epoxidation of adjacent double bonds in the absence of steric or conformational effects. Peracid epoxidation of dimethyl *trans*-1,2-dihydrophthalate is stereospecific and gives a 90:9.5:0.5 mixture of diepoxides **2**, **3**, and **4** in 95–98% yields. Epoxidation converts monoepoxide **5** to diepoxide **2** in 100% selectivity, and dimethyl 1,4-dihydrophthalate to a 75:25 mixture of the cis and trans monoepoxides. Cis diepoxide **4** is obtained by thermal rearrangement of endo peroxide **11**. Irradiation of **11** in cyclohexane gives a mixture of **4** and unsaturated diol **12**. Both catalytic hydrogenation and lithium aluminum hydride reduction of diepoxide **2** are regiospecific and give alcohols **13** and **14**.

Epoxidation[1] and photooxygenation[2] are valuable for stereospecific introduction of oxygen into olefins. The stereochemistry of epoxidations and of ring opening reactions of epoxides has been extensively studied.[3] There is considerable interest in syntheses and reactions of cyclohexadiene diepoxides[4–6] and in 1,4-endo peroxides (1,4-epidioxide compounds)[7] as precursors to cis diepoxides by thermal[8] or photochemical rearrangements.[9] Recently, iso-