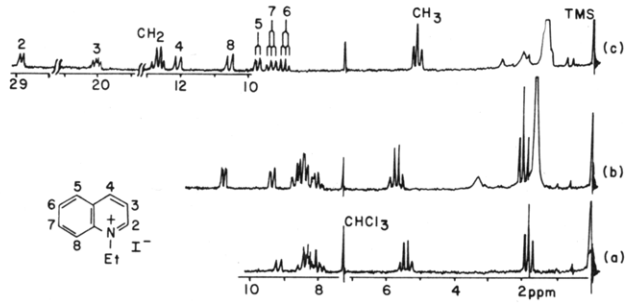


**Figure 1.** Proton NMR spectrum of *N*-ethylquinolinium iodide (0.1 M) in $CDCl_3$ with (a) no shift reagent, (b) 0.05 M $Eu(fod)_3$, and (c) 0.05 M $Eu(fod)_3$ and 0.05 M Ag(fod).

formation of the shift reagent influences the magnitude of the induced shifts.

The spectra reproduced in Figure 1 for *N*-ethylquinolinium iodide demonstrate the shifting ability of $Eu(fod)_4^-$ formed in situ from $Eu(fod)_3$/Ag(fod). The spectrum for the substrate without any shift reagent is shown in Figure 1a. In the unshifted spectrum only one aromatic proton is resolved. Figure 1b is the spectrum obtained for the substrate (0.1 M) with $Eu(fod)_3$ (0.05 M). In this example three of the aromatic protons are resolved. In the presence of $Eu(fod)_4^-$ at a similar concentration, however, the spectrum is completely first order. This spectrum is shown in Figure 1c. The shifts were large enough to perform decoupling experiments and confirm the assignments.

The species $Eu(fod)_4^-$ formed in situ from $Eu(fod)_3$ and Ag(fod) is a powerful organic-soluble NMR shift reagent for organic salts. One reason for the effectiveness is that precipitation of the silver halide enhances the degree of ion pair formation. It is also possible that the geometric term for a cation paired with $Eu(fod)_4^-$ is more favorable than with $Eu(fod)_3X^-$. The geometric term refers to the distance and angle values of the pseudocontact shift equation.[7,8] In addition to ammonium salts, we expect $Eu(fod)_4^-$ to function as an effective NMR shift reagent for sulfonium, oxonium, and phosphonium salts provided the silver complex with the associated anion is insoluble in solvents such as chloroform.

## Experimental Section

The $Eu(fod)_3$[9] (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione) and Ag(fod)[9] were prepared according to procedures reported in the literature. The K(fod) was prepared by a procedure analogous to that used to prepare other potassium $\beta$-diketonate complexes.[10] $Eu(fod)_3$ and Ag(fod) are also available from commercial sources. The substrates were purchased and used as received or prepared by literature methods.[3,11] When recording the NMR spectrum of a substrate in the presence of $Eu(fod)_4^-$, the appropriate amount of $Eu(fod)_3$, Ag(fod), and substrate were weighed into a test tube. The correct amount of chloroform-*d* was added via pipet. The test tube was stoppered, and the mixture was vigorously shaken for 1 min. The silver halide was removed by centrifugation and decantation of the supernatant. Prior to recording the spectrum, the test tube and NMR tube were covered with aluminum foil to exclude light.

**Acknowledgment.** We thank Bates College and Roger C. Schmutz for their support through a College Research Grant.

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# Azaindolizines. 6. The Synthesis of 7-Azaindolizines from Methylpyrazines

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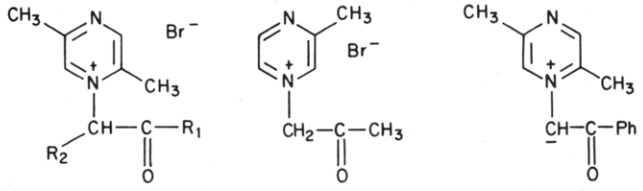
One of the simplest methods of synthesis for 5-, 6-, and 8-azaindolizines has been by the Chichibabin quaternization–cyclization reactions of 3-methylpyridazines and 4-(6)-methyl- and 2-methylpyrimidines with an $\alpha$-halo ketone.[1-4] In contrast the synthesis of 7-azaindolizines has commonly involved a pyrrole precursor onto which a six-membered ring has been grafted.[5-7] There has been no report of the direct successful application of the Chichibabin procedure to the synthesis of 7-azaindolizines from 2-methylpyrazines.

Boekelheide et al.[8] attempted to synthesize 6-methyl-2-phenyl-7-azaindolizine (**1**) (Table I) by reacting 2,5-dimethylpyrazine with phenacyl bromide, the resulting quaternary salt **2**, however, did not cyclize when treated




**2**, $R_1$ = Ph; $R_2$ = H
**4**, $R_1$ = $CH_3$; $R_2$ = H
**5**, $R_1$ = $CH_3$; $R_2$ = $CH_3$

**6** **3**

with bicarbonate but was interpreted to give the zwitterion **3**. We repeated this reaction between 2,5-dimethylpyrazine and phenacyl bromide and found that the resulting salt on treatment with bicarbonate gave 2,5-dimethylpyrazine but none of the 7-azaindolizine **1**. It is suggested that the salt **2** on reaction with base besides giving the zwitterion **3** undergoes nucleophilic displacement with loss of the 2,5-dimethylpyrazine as the leaving group. The expected abstraction of a proton from the 2-methyl group of **2** followed by cyclization is evidently not favored. Similarly 2,5-dimethylpyrazine was obtained when the salt **4** formed between 2,5-dimethylpyrazine and bromoacetone was treated with base. However, on using 3-bromobutan-2-one as the quaternizing $\alpha$-halo ketone the resulting salt **5** on reaction with base gave the 2,3,6-trimethyl-7-azaindolizine (**7**) in low yield. In this case it would appear that the methyl branching reduces the acidity of the methine hydrogen and also suppresses substitution sufficiently to allow some cyclization to occur.

Reaction of 2-methylpyrazine with bromoacetone gave a single quaternary salt which when treated with base regenerated the 2-methylpyrazine. It is likely that 2-methylpyrazine preferentially quaternizes at the more accessible nitrogen N-4 to give **6** from which 2-methyl-

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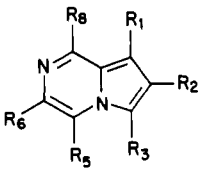
0022-3263/85/1950-1324$01.50/0 

Table I



| compd | $R_1$ | $R_2$ | $R_3$ | $R_5$ | $R_6$ | $R_8$ | % yield | mp °C |
|---|---|---|---|---|---|---|---|---|
| 1 | H | Ph | H | H | $CH_3$ | H | | |
| 7 | H | $CH_3$ | $CH_3$ | H | $CH_3$ | H | 2 | 99–102 |
| 8 | H | $CH_3$ | H | H | H | $CH_3$ | 41 | 205–208 |
| 9 | H | Ph | H | H | H | $CH_3$ | 21 | 133–135 |
| 10 | H | $CH_3$ | $CH_3$ | H | H | $CH_3$ | 63 | 60–61 |
| 11 | H | $CH_3$ | H | H | $CH_3$ | $CH_3$ | 31 | yellow oil |
| 12 | H | $CH_3$ | $CH_3$ | H | $CH_3$ | $CH_3$ | 31 | 83–85 |
| 13 | H | Ph | H | H | $CH_3$ | $CH_3$ | 9 | 110–111 |
| 14 | H | $CH_3$ | H | $CH_3$ | $CH_3$ | $CH_3$ | 44 | 49–50 |
| 15 | H | $CH_3$ | H | H | $CH_3$ | $OCH_3$ | 12 | yellow oil |
| 16 | H | Ph | H | H | $CH_3$ | $OCH_3$ | 25 | 133–134 |
| 17 | H | $CH_3$ | H | H | $CH_3$ | Cl | 6 | 68–70 |
| 18 | H | $CH_3$ | H | | | $CH_3$ | 1 | 78–79 |

pyrazine is displaced by base.

In contrast to these reactions involving 2-methyl- and 2,5-dimethylpyrazine, 3-substituted 2-methylpyrazines when subjected to Chichibabin quaternization and treatment with bicarbonate tended to favor the formation of the 7-azaindolizine. Thus 2,3-di-, 2,3,5-tri-, and 2,3,5,6-tetramethylpyrazine gave the corresponding 7-azaindolizines **8–14** in yields generally between 10% and 60%. Analogously, 2,3-dimethylquinoxaline reacted with bromoacetone to give after treatment with sodium bicarbonate the 2,8-dimethyl-5,6-benzo-7-azaindolizine (**18**). The 3-methoxy and 3-chloro derivatives of 2,5-dimethylpyrazine when quaternized with bromoacetone or phenacyl bromide also successfully cyclized to the corresponding 7-azaindolizines **15–17**. Why cyclization should be preferred with these 3-substituted 2-methylpyrazines is difficult to account for; in the absence of any obvious electronic explanation it may be that the steric repulsion of an adjacent substituent to the methyl group involved in the cyclization helps in the bonding to the carbonyl carbon.

The deuterochloroform $^1H$ NMR spectra of the prepared 7-azaindolizines **7–18** were recorded; their interpretation and signal assignments were based on a comparative examination of related spectra and on the proximity of methyl substituents and ring hydrogens to nitrogen, occasionally double irradiation helped to resolve ambiguous assignments. The ring proton absorptions were generally found to occur at a chemical shift corresponding to that reported for the parent 7-azaindolizine[9] occurring at progressively higher field in the order H-8, $\delta \simeq 8.6$, H-5, $\delta \simeq 7.4$, H-6, $\delta \simeq 7.3$, H-3, $\delta \simeq 7.1$, and H-1, $\delta \simeq 6.6$. The trifluoracetic and deuterotrifluoracetic acid spectra of the prepared 7-azaindolizines showed the absence of a methylene signal and were found to be virtually identical in pattern and chemical shift. A comparison of the deuterochloroform and trifluoracetic acid spectra shows H-6 to experience the smallest downfield shift on conversion of the 7-azaindolizine to its corresponding conjugate acid cation.[10] Such an observation implies protonation at N-7 by analogy with the chemical shifts of pyridine which on protonation at its nitrogen shows large shifts of its $\beta$- and $\gamma$-protons (1.07 and 1.22 ppm)[11,12] and only a relatively small shift of its $\alpha$-protons (0.25 ppm). It is thus concluded that the 7-azaindolizines examined invariably protonate at N-7 and resist deuterium exchange. This contrasts with the behavior of 5-, 6-, and 8-azaindolizines which generally show partial C-3 protonation and exchange of their H-3 and to a lesser extent H-1 protons.[1,2,13]

## Experimental Section

The instruments and procedures are as given in ref 4. The following general procedure was used in the Chichibabin synthesis of the 7-azaindolizines. The $\alpha$-bromoketone was added to the methylpyrazine and left 3–28 days at 35–60 °C (the tri- and tetramethylpyrazines were given longer times and higher temperatures for quaternization). Generally the purified quaternary salt was not isolated—water was added to the crude salt and the aqueous solution extracted with ether or chloroform to remove unchanged reactant. The aqueous solution was then warmed to remove dissolved solvent, before adding an excess of sodium bicarbonate. The bicarbonate solution was refluxed (approximately 30 min) and then extracted several times with chloroform. The combined chloroform extracts were dried and the chloroform was evaporated to leave a crude residue of the 7-azaindolizine which was generally purified by vacuum distillation or sublimation or occasionally by recrystallization. The infrared spectra of the 7-azaindolizines showed characteristic absorption around 1620, 1550, 1300, and a group of strong bands around 800 $cm^{-1}$. Satisfactory elemental analysis of all the compounds prepared was obtained, compounds **8** and **15** being analyzed as their perchlorates.

**Registry No.** **7**, 95407-80-0; **8**, 95407-81-1; **9**, 95407-88-8; **10**, 95407-82-2; **11**, 95407-83-3; **12**, 95407-84-4; **13**, 95407-85-5; **14**, 95407-86-6; **15**, 95407-89-9; **16**, 95420-15-8; **17**, 95407-87-7; **18**, 1831-73-8; phenacyl bromide, 70-11-1; bromoacetone, 598-31-2; 3-bromobutan-2-one, 814-75-5; 2,5-dimethylpyrazine, 123-32-0; 2,3-dimethylpyrazine, 5910-89-4; 2,3,5-trimethylpyrazine, 14667-55-1; 2,3,5,6-tetramethylpyrazine, 1124-11-4; 2,3-dimethylquinoxaline, 2379-55-7; 3-methoxy-2,5-dimethylpyrazine, 19846-22-1; 3-chloro-2,5-dimethylpyrazine, 95-89-6.

**Supplementary Material Available:** Tables giving $^1H$ NMR spectra of the 7-azaindolizines **7–18** in deuteriochloroform and of compounds **8**, **10–12**, **14**, and **18** in trifluoroacetic acid (2 pages). Ordering information is given on any current masthead page.

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(10) The order of increasing magnitude of the downfield shift on conversion of the 7-azaindolizine to it's conjugate acid cation was observed to be H-6 < H-5 < H-3 < H-1. The downfield shift in H-1 was of the order of 1.00 ppm whereas that of the H-6 proton was of the order of 0.1 ppm.

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