Azaindolizines. I. Protonation of 5-Azaindolizine

MARTIN FRASER

Department of Chemistry, Robert Gordon's Institute of Technology, Aberdeen, Scotland

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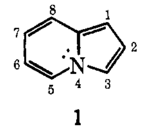
Protonation of azaindolizines generally occurs at the additional nonbridgehead nitrogen. Exceptionally, 5-azaindolizine (**11a**), examined as alkyl and aryl derivatives (**11b–e**) contrary to Huckel MO charge density and cation localization energy predictions, has been shown by pmr studies in trifluoroactic acid to protonate solely at carbon, preferentially at C-3 and then C-1.

Protonation of heterocyclic systems containing a nitrogen center normally occurs at nitrogen rather than carbon. Carbon protonation is not unusual, however, in heteroaromatic systems in which the nitrogen center is located in the ring(s) by three single bonds so that the "unshared pair" on nitrogen contributes toward the total number of π electrons of the ring. Thus, for example, pyrrole,[1] indole,[2] isoindole,[3] pyrrole[2,1-*b*]-thiazole,[4] and indolizine[5–8] all protonate at carbon. On the other hand, N-heteroaromatic systems, in which the nitrogen center is tertiary and is shown in a Lewis structure to be flanked by a single and double bond as in pyridine, invariably appear to coordinate a proton under anhydrous conditions with the accessible sp^2 hybridized "unshared pair" of the nitrogen. Heteroaromatic systems which contain both a pyrrole-type and pyridine-type of nitrogen protonate at the tertiary pyridine nitrogen.[9,10]

Protonation studies on indolizine (**1**) show it to protonate preferentially at C-3 and partially at C-1 in some 3-alkylindolizines.[5–8] Protonation at C-3 and C-1 gives rise to the 3 H and 1 H cations **2** and **3** which show the establishment of the pyridinum sextet in the six-membered ring. Theoretical studies of indolizines are broadly in agreement with these observations.[11–13]



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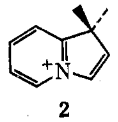

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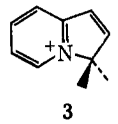

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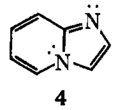

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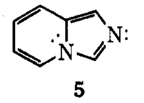

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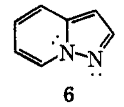

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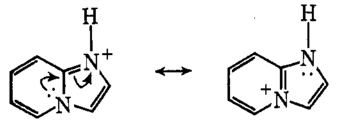

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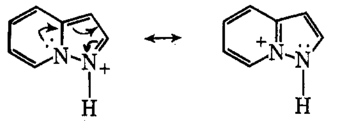

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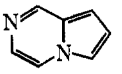

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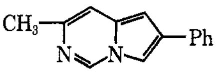

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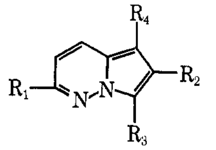

11a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$
c, $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$
d, $R_1 = CH_3$; $R_2 = Ph$; $R_3 = R_4 = H$
e, $R_1 = R_3 = CH_3$; $R_2 = Ph$; $R_4 = H$

The site of protonation of the seven azaindolizines, which may be considered to be derived by replacement of one of the nonbridgehead centers of indolizine by a tertiary pyridine-type nitrogen, may be considered to be governed by either the availability of a pyridine type of nitrogen or possibly by the establishment of an aromatic sextet in the six-membered ring. The former alternative dictates N-protonation and the latter necessitates protonation at ring centers 1 or 3. Both of these alternative factors governing the site of protonation are accommodated in the protonation of 1- and 3-azaindolizines **4** and **6** which yield on protonation the resonance hybrid cations **7** and **8**, resonance being shown to occur between the 6- and 10-π cations. Protonation of the remaining azaindolizines at nitrogen would result in the 10-π cation which precludes the formation of an aromatic sextet in the six-membered ring. Alternatively, protonation at C-1 or C-3 would give rise to the 6-π cation, analogous to the indolizinium cations **2** and **3**.

Protonation studies of azaindolizines have previously been restricted to 1-, 2-, and 3-azaindolizines **4**, **5**, and **6**. Using uv spectroscopy these azaindolizines have been shown to protonate solely at the additional nonbridgehead nitrogen located in the five-membered ring.[6] The pmr of **4**, **5**, and **6** in trifluoracetic acid confirm this since they showed only a crop of low-field signals at τ 1.30–2.65, 0.75–3.00, and 1.50–3.10, respectively. No (2 H) methylene signal attributable to carbon protonation was observed. Additionally, neither of the previously synthesized azaindolizines **9**[14] and **10**[15] show a midfield (2 H) methylene signal when their pmr spectra were examined in trifluoracetic acid. The former spectrum showed a crop of low-field signals between τ 0.75 and 2.5. The latter spectrum consisted

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TABLE I

CHEMICAL SHIFTS IN THE 100-MHz ^{1}H NMR SPECTRA OF 5-AZAINDOLIZINES **11b–e** AND THE CORRESPONDING 5-AZAINDOLIZINIUM PERCHLORATES **12a**, **13a**, **12b**, AND **12c** + **13b** (X = ClO_4)[a]

Compd	Solvent	R_1	R_2	R_3	R_4	H_7	H_8
11b	$CDCl_3$	7.58	7.66	2.54	3.76	3.69 (d, 9)	2.53 (d, 9)
	DMSO-d_6	7.62	7.70	2.44	3.71	3.52 (d, 9)	2.30 (d, 9)
	$CDCl_3$, 1 drop of CF_3COOD	7.57	7.66			3.62 (d, 9)	2.43 (d, 9)
	CF_3COOH	7.18	7.51	4.44 [2 H]	3.08	1.92 (d, 8)	1.77 (d, 8)
	CF_3COOD	7.18	7.51			1.92 (d, 8)	1.76 (d, 8)
12a	CF_3COOH	7.18	7.51	4.44 [2 H]	3.09	1.93 (d, 8)	1.76 (d, 8)
11c	$CDCl_3$	7.57	7.77	7.62	3.80	3.83 (d, 9)	2.60 (d, 9)
	CF_3COOH	7.53	7.68	7.13	5.81 [2 H]	1.93 (d, 9)	1.62 (d, 9)
	CF_3COOD	7.53	7.68	7.13		1.93 (d, 9)	1.62 (d, 9)
13a	CF_3COOH	7.49	7.61	7.09	5.71 [2 H]	1.89 (d, 9)	1.57 (d, 9)
11d	$CDCl_3$	7.56	2.30–2.85 (complex)	2.10	3.39	3.70 (d, 9)	2.50 (d, 9)
	CF_3COOH	7.16	2.18–2.50 (complex)	4.00 [2 H]	2.60	1.93 (d, 9)	1.70 (d, 9)
	CF_3COOD	7.16	2.18–2.50 (complex)			1.93 (d, 9)	1.70 (d, 9)
12b	CF_3COOH	7.16	2.18–2.50 (complex)	4.00 [2 H]	2.59	1.93 (d, 9)	1.68 (d, 9)
11e	$CDCl_3$	7.32	2.45–2.82 (complex)	7.53	3.45	3.68 (*J*, 9.5)	2.46 (*J*, 9.5)
12c	CF_3COOH	7.10	2.34	8.0 (d, 7.5) C-3 methine 3.94 (q, 7.5)	2.62	1.85 (*J*, 9)	1.64 (*J*, 9)
	CF_3COOD	7.10	2.34	8.01		1.86 (*J*, 9)	1.65 (*J*, 9)
13b	CF_3COOH	7.0 or 7.20	2.4	7.20 or 7.0	5.32 [2 H]	1.85 (*J*, 9)	1.46 (*J*, 9)
	CF_3COOD	7.0 or 7.20	2.4	7.20 or 7.0		1.86 (*J*, 9)	1.47 (*J*, 9)

[a] Unless otherwise stated values given on the τ scale refer to singlet absorptions, coupling constants (*J*) in centimeters per second (cps) are in parenthesis, square brackets refer to methylene integration, and multiplicity refers to the appearance of spectra on the 100-Hz scale. For multiplets, d = doublet and q = quartet.

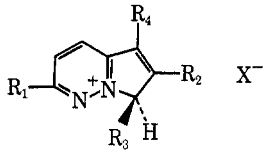
of the following signals: a high-field (3 H) singlet at τ 7.4 assigned to the 7-methyl group and a crop of low-field signals below τ 2.85. The low-field signals included a complex (5 H) signal between τ 2.25 and 2.60 assigned to the 2-phenyl group and four (1 H) singlets at τ 2.84, 2.63, 1.95, and 0.4, tentatively assigned to H-1, H-8, H-3, and H-5, respectively. However, 5-azaindolizine **11a**, examined as alkyl and aryl derivatives **11b**, **11c**, **11d**, and **11e**, is exceptional in that pmr studies discussed herewith and summarized in Table I show it to protonate exclusively at C-3 and or C-1 rather than at the tertiary pyridine-type N-5 site.

The site of protonation of the 5-azaindolizines **11b–e** was determined by comparing the pmr spectra of the 5-azaindolizines with each other and with the spectra of indolizines in trifluoracetic acid. Neither the spectra of the 5-azaindolizines **11b–e** nor of their corresponding perchlorates in trifluoracetic acid showed a broad band or triplet which would arise from a proton bonded to nitrogen. Furthermore, although the ir spectra of the perchlorates of azaindolizines **4**, **5**, **6**, **9**, and **10** showed a strong to medium broad band (3100–3400 cm^{-1}), attributable to protonation at the nonbridgehead nitrogen, the perchlorates of **11b**, **11d**, and **11e** showed no such absorption. The perchlorate of **11c** did show a very weak absorption in the region 3100–3400 cm^{-1}.

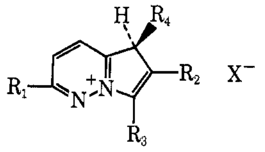
The spectra of 2,3,6-trimethyl-5-azaindolizine (**11c**) in deuteriochloroform show the following signals: three (3 H) singlet peaks at τ 7.77, 7.62, and 7.57 assigned to the three methyl groups, a (1 H) singlet at τ 3.80 assigned to H-1, and two doublets of an AB system (J = 9 cps) τ 3.85 and 2.60 assigned to H-7 and H-8, respectively. The spectrum of **11c** in deuteriotrifluoracetic acid no longer showed the (1 H) singlet at τ 3.80 but the pattern of the three methyl singlets (τ 7.68, 7.53, 7.13) and the H-7, H-8 AB doublet (J = 9 cps) τ 1.93 and 1.62 remains. The spectrum of **11c** in trifluoracetic acid shows, in addition to the signals of the deuteriotrifluoracetic acid spectrum of **11c**, a (2 H) methylene singlet at τ 5.81. This (2 H) methylene singlet and the absence of a (1 H) quartet, along with a corresponding split doublet for any of the methyl signals, indicate **11c** to protonate exclusively at C-1. This conclusion is substantiated by noting that the C-1 methylene of C-1 protonated alkylindolizines occurs around τ 5.9, whereas the C-3 methylene group resulting from C-3 protonation of indolizine and alkylindolizines occurs around τ 4.5.[5-8]

The spectrum of 2,6-dimethyl-5-azaindolizine (**11b**) in deuteriochloroform shows the following signals. Two high-field (3 H) singlets at τ 7.66 and 7.58 are assigned to the 2- and 6-methyl groups. Two doublets of an AB system (J = 9 cps) occur at τ 3.69 and 2.53 and are assigned to H-7 and H-8, respectively. The two (1 H) singlets at τ 2.54 and 3.76 are respectively assigned to H-3 and H-1 on the bases of the H-1 assignment of **11c**, together with the fact that H-3 is adjacent to N-4 and would consequently be the lower field singlet. The environment of H-1 approximates that of H-7 and this singlet at τ 3.76 is partly obscured by the higher field signal of the H-7 doublet at τ 3.69. The H-1 and H-3 assignments are confirmed by the disappearance of the singlets at τ 3.76 and 2.54 by deuterium exchange when the deuteriochloroform solution of **11b** is treated with 1 drop of deuteriotrifluoroacetic acid;[7] the resulting spectrum then clearly shows the AB system of the two doublets assigned to H-7 and H-8. The spectrum of **11b** in deuterated dimethyl sulfoxide is also useful in that it shows H-1, H-3, H-7, and H-8 as distinct nonoverlapping signals at slightly different τ values [3.71, 2.44, 3.52, 2.30 (J = 9 cps), respectively]. The spectrum of **11b** in trifluoracetic acid shows two high-field (3 H) singlets at τ 7.51 and 7.18 and a lower (1 H) singlet at 3.08, assigned to the 2- and 6-methyl groups and H-1, respectively. The (2 H) singlet at τ 4.44 is assigned to a C-3 methylene group arising from C-3 protonation. This assignment and conclusion are supported by (a) a comparison of this (2 H) singlet at τ 4.44 with the C-3 methylene signal of C-3 protonated indolizines and the C-1 methylene singlet at τ 5.81 of the spectrum of **11c** in trifluoracetic acid, and (b) by the absence due to deuterium exchange of the (2 H) singlet at τ 4.44 and the 1 H singlet at 3.08 in the spectrum of **11b** in deuteriotrifluoracetic acid.

Similarly, by using the same comparative procedure 6-methyl-2-phenyl-5-azaindolizine (**11d**) and 3,6-dimethyl-2-phenyl-5-azaindolizine (**11e**), whose spectra in deuteriochloroform, deuteriotrifluoracetic acid, and trifluoracetic acid are summarized in Table I, are concluded to protonate at C-3 and at C-1 and C-3, respectively. Protonation of **11d** in trifluoracetic acid gives rise to a (2 H) methylene singlet at τ 4.00. The trifluoracetic and deuteriotrifluoracetic acid solutions of **11d** give rise to identical spectra apart from the absence of the (2 H) methylene singlet at τ 4.00 and a (1 H) singlet at τ 2.60, assigned to the exchangeable H-1 proton. In trifluoracetic acid, **11e** gives rise to the superposed spectra of cations **12c** and **13b** whose respective C-3 (1 H) methine quartet (J = 7.5 cps) and C-1 (2 H) methylene singlet signals occur at τ 3.94 and 5.32. The methine quartet of **12c** is coupled to the 3-methyl (3 H) doublet (J = 7.5 cps) at τ 8.00. The methine and methylene signals of **12c** and **13b** together with the exchangeable H-1 singlet at τ 2.62 of **12c** are absent from the deuteriotrifluoracetic acid spectrum of **11e**, which also shows the 3-methyl doublet (J = 7.5 cps) to have collapsed to a singlet at τ 8.02. The ratio of the two cations **12c** and **13b** did not alter significantly with time, their approximate concentrations being in the ratio 1:4.



12a, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$
b, $R_1 = CH_3$; $R_2 = Ph$; $R_3 = R_4 = H$
c, $R_1 = R_3 = CH_3$; $R_2 = Ph$; $R_4 = H$



13a, $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$
b, $R_1 = R_3 = CH_3$; $R_2 = Ph$; $R_4 = H$

Solutions of the 5-azaindolizines **11b–e** in deuteriotrifluoracetic acid behave like similarly structured indolizines and readily exchange hydrogens with deuterium at the unsubstituted 1 and 3 positions.[7] The pmr spectra of the perchlorates of **11b–d** in trifluoracetic acid are identical in pattern with the spectra of the corresponding 5-azaindolizines in trifluoracetic acid. The spectrum of **11e** in trifluoracetic acid, however, initially showed a greater proponderance of the 1 H cation **13b**, approximately 30:1, suggesting that either protonation of **11e** with perchloric acid in ethyl acetate gives a greater concentration of the 1 H cation or that the 1 H cation **13b** is less soluble than the 3 H cation **12c** in ethyl acetate. Unlike the perchlorates of the indolizine series, the protons attached to C-1 and C-3 of the perchlorates of **11b–e** exchange with the solvent, since the intensity of the C-1 and C-3 proton signals of these 5-azaindolizinium perchlorates are reduced when deuteriotrifluoracetic acid is used in place of trifluoroacetic acid as solvent. In deuterated dimethyl sulfoxide the spectra of the perchlorates from **11b–e** were identical in pattern with the spectra of the corresponding 5-azaindolizines thus showing that in a more basic solvent these 5-azaindolizinium perchlorates readily lose a proton.

Thus, the protonation of the 5-azaindolizine structures **11b** and **11d** has been shown to occur in trifluoracetic acid at position C-3 to yield the 6-π 3*H*-5-azaindolizinium cations **12a** and **12b**. Protonation of **11c** occurs at C-1 to give the 6-π 1*H*-5-azaindolizinium cation **13a**, and **11e** protonates at both C-1 and C-3 to give a mixture of the 1 H and 3 H 6-π cations **12c** and **13b**. The equilibrium concentration of cations resulting from protonation at N-5 or other carbon centers, if formed, must be below the limits of measurement by proton magnetic resonance spectroscopy. These results conflict with the predictions of the Hückel charge density and cation localization energy calculations of the parent 5-azaindolizine **11a** (cited in Table II[16])

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[16] By courtesy of Dr. J. Binks (Aberdeen University), unpublished data.

TABLE II

HMO CHARGE DENSITY AND CATION LOCALIZATION ENERGIES FOR 5-AZAINDOLIZINE

Position	Charge density	Cation localization energy
1	1.172	1.940
2	1.092	2.356
3	1.108	1.872
4	1.507	
5	1.193	1.525
6	0.928	2.358
7	1.031	2.229
8	0.947	2.179
9	1.023	

which suggest that protonation should occur preferentially at N-5 with the formation of the 10 π-cation.

Experimental Section

Melting points were determined by the capillary method and are uncorrected. Elemental analyses were performed by the analytical laboratories of Aberdeen University. Pmr 100-MHz spectra were recorded at *ca.* 29° with a Varian HA-100B spectrometer. Infrared spectra were measured with a Unicam SP200 spectrometer and absorption peaks werere corded in wavenumbers (cm^{-1}). Ultraviolet spectra were measured with a Unicam SP800 spectrometer. Light absorption data refer to solutions in ethanol; principal maxima are underlined; sh = shoulder, br = broad, infl = inflection. Mass spectra were measured with an AEI MS9 spectrometer;

Procedures.—Solutions were dried over anhydrous magnesium sulfate, and solvents were evaporated at reduced pressure with a rotary film evaporator. Column chromatography was carried out with Woelm neutral alumina. Perchloric acid refers to 70% w/w "analar" perchloric acid. Petroleum ether was of boiling point range 40–60°.

2,6-Dimethyl-5-azaindolizine (11b).—A solution of 3,6-dimethylpyridazine[17] (20.16 g, 0.20 mol) and bromoacetone (16.7 ml, 0.20 mol) in acetone (10 ml) was gently refluxed until the exothermic reaction commenced. The mixture was gently refluxed for a further 10 min whereupon a white crystalline solid precipitated. The solid was collected (37.1 g, 76%) and washed with acetone and then with ether, and a portion was recrystallized from ethanol to give 1-acetonyl-3,6-dimethylpyridazinium bromide, mp 218–219° dec.

Anal. Calcd for $C_9H_{13}BrN_2O$: C, 44.1; H, 5.3; N, 11.4. Found: C, 44.2; H, 5.2; N, 11.5.

A solution of the bromide salt (24.5 g, 0.10 mol) and sodium hydrogen carbonate (30 g) in water (200 ml) was heated to boiling and then steam distilled. The steam distillate was extracted several times with ether and the ether extract, which had a distinct blue fluorescence, was washed with water, dried, and evaporated to leave a light brown oil of the crude **11b** (7.8 g, 53.5%). Chromatography on a short column of alumina, with benzene for absorption and elution, gave a light yellow-brown oil which was vacuum distilled, and the fraction distilling between 98 and 102° (8 mm) was collected: λ_{max} 370 (br), 310 (br), 250, *242*, 235 nm (sh) (log ε 3.23, 3.01, 4.24, 4.25, 4.12, respectively); ir (thin film) 800, 1110, 1290, 1545, 1660 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2$: C, 73.9; H, 6.90; mass, 146.0844. Found: C, 74.2; H, 7.2; mass, 146.0846.

2,6-Dimethyl-5-azaindolizinium Perchlorate (12a, X = ClO_4).—Perchloric acid (1.5 ml, 37% excess) was added to a solution of **11b** (0.146 g, 1 mmol) in ethanol (2 ml) at room temperature. The perchlorate which crystallized out from the cooled red brown solution on titration with ether was filtered off, washed with ether–ethanol (10:1) (5 ml), and dried at reduced pressure. The 2,6-dimethyl-5-azaindolizinium perchlorate (0.194 g, 79%), white needles, mp 159–160°, is hygroscopic and starts to darken 2–3 days after preparation: ir (Nujol) 860, 920, 1100 (ClO_4), 1600 cm^{-1}.

Anal. Calcd for $C_9H_{11}ClN_2O_4$: C, 43.8; H, 4.5; N, 13.6; Cl, 14.4. Found: C, 43.7; H, 4.3; N, 13.7; Cl, 14.7.

2,3,6-Trimethyl-5-azaindolizine (11c).—A solution of 3,6-dimethylpyridazine (10.8 g, 0.1 mol) and 3-bromo-2-butanone (10.7 ml, 0.1 mol) in acetone (10 ml) was gently warmed and left overnight. The resulting brown crystalline mass of the quaternary bromide salt was taken up in water (200 ml), the aqueous solution extracted with ether, and sodium hydrogen carbonate (25 g) added to the aqueous layer. The resulting aqueous solution was then steam distilled. The steam distillate was extracted several times with ether and the ether extract was washed with water (50 ml), dried, and evaporated to leave the crude 2,3,6-trimethyl-5-azaindolizine (**11c**) as a brown-yellow oil (7.2 g, 45%). The crude product was taken up in petroleum ether and chromatographed on a short column of alumina (5 cm). The fast-moving bright yellow band was eluted and evaporation of the petroleum solvent gave **11c** as a golden yellow oil which was vacuum distilled: bp 116–118° (12 mm); λ_{max} 386 (br), 310 (br), 255, *248*, 234 nm (log ε 3.18, 2.90, 4.09, 4.11, 4.07, respectively); ir (thin film) 795, 1100, 1290, 1545, 1660 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 75.0; H, 7.8; N, 17.5; mass, 159.0922. Found: C, 74.7; H, 7.8; N, 17.2; mass, 159.0922.

2,3,6-Trimethyl-5-azaindolizinium Perchlorate (13a, X = ClO_4).—Perchloric acid (3.0 ml, 37% excess) was added to a solution of **11c** (0.32 g, 2 mmol) in ethanol (2 ml). This solution on thorough cooling and trituration with ether gave **13a** (X = ClO_4) as yellow highly hygroscopic needles (0.28 g, 54%): mp 70–73°; ir (Nujol) 840, 1100 (ClO_4), 1585 cm^{-1}.

Anal. Calcd for $C_{10}H_{13}ClN_2O_4$: C, 46.1; H, 5.0 N, 10.8; Cl, 13.6. Found: C, 46.0; H, 5.0; N, 11.0; Cl, 13.6.

6-Methyl-2-phenyl-5-azaindolizine (11d).—A solution of 3,6-dimethylpyridazine (21.6 g, 0.2 mol) and phenacyl bromide (39.8 g, 0.2 mol) in acetone (10 ml) was gently warmed until a vigorous exothermic reaction occurred with the precipitation of a white solid. The solid was collected and recrystallized from ethanol to give 3,6-dimethyl-1-phenacylpyridazinium bromide (18.95 g, 62%) as white needles, mp 218–219° dec.

Anal. Calcd for $C_{14}H_{15}BrN_2O$: C, 54.7; H, 4.9; N, 9.1. Found: C, 54.8; H, 5.1; N, 9.4.

A solution of the bromide salt (12.28 g, 0.04 mol) and sodium hydrogen carbonate (15 g) in water (150 ml) was boiled for 30 min. From the resulting orange-colored solution a cream-white flocculent precipitate of **11d** settled out and after cooling was collected (8.03 g, 97%). Recrystallization from ethanol gave fine needles: mp 130–131°; λ_{max} 372 (br), 315 (br), 296 (infl), *255* nm (log ε 3.69, 3.65, 3.53, 4.58, respectively); ir (Nujol) 740, 820, 1180, 1300, 1310, 1560, 1650 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}N_2$: C, 81.1; H, 5.2; N, 13.5. Found: C, 81.1; H, 5.3; N, 13.5.

6-Methyl-2-phenyl-5-azaindolizinium Perchlorate (12b, X = ClO_4).—Perchloric acid (3.0 ml, 37% excess) was added to a solution of **11d** (0.414 g, 2 mmol) in ether–ethanol (10:1) (10 ml) and the mixture was gently warmed. On cooling white needles of **12b** (X = ClO_4) precipitated and were collected (0.52 g, 84%): mp 210–211° dec; ir (Nujol) 760, 1100 (ClO_4), 1595 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}ClN_2O_4$: C, 54.5; H, 4.2; N, 9.1; Cl, 11.5. Found: C, 54.5; H, 4.4; N, 9.1; Cl, 11.5.

3,6-Dimethyl-2-phenyl-5-azaindolizine (11e).—A solution of 3,6-dimethylpyridazine (10.8 g, 0.01 mol) and α-bromopropiophenone (13.6 ml, 0.01 mol) in ethanol (10 ml) was gently refluxed for 30 min and left to stand overnight. The resulting dark brown oil was taken up in water and the aqueous solution was extracted with ether. Sodium hydrogen carbonate (25 g) was added to the aqueous layer and the mixture refluxed for 30 min. The resulting orange-colored solution was extracted several times with ether, the combined ether extracts were washed with water and dried, and the ether was evaporated to leave a brown oil of crude **11e** (11.5 g, 52%). Chromatography on a short column of alumina, with benzene for absorption and elution, followed by vacuum distillation [185–195° (20 mm)] gave a golden yellow oil which solidified to yellow crystals: mp 47–49°; λ_{max} 253 (br), 250, 310 (br), 380 nm (br) (log ε 5.11, 5.53, 4.63, 4.58, respectively); ir (Nujol) 700, 780, 800, 1180, 1300, 1608 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.2; H, 6.3; N, 12.6. Found: C, 81.3; H, 6.1; N, 12.6.

3,6-Dimethyl-2-phenyl-5-azaindolizinium Perchlorate (12c/13b, X = ClO_4).—Perchloric acid (3.0 ml, 37% excess) was added to a solution of **11e** (0.45 g, 2 mmol) in ethyl acetate (2 ml). This solution on thorough cooling gave **12c**/**13b** (X = ClO_4)

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[17] C. Overberger, N. Byrd, and R. Mesrobian, *J. Amer. Chem. Soc.*, **78**, 1961 (1956).

as pale yellow needles (0.36 g, 56%): mp 120–122°; ir (Nujol) 695, 770, 895, 1090 (ClO_4), 1350, 1560, 1620 cm^{-1}.

Anal. Calcd for $C_{15}H_{15}ClN_2O_4$: N, 8.7; Cl, 11.0. Found: N, 8.7; Cl, 10.7.

Registry No.—**11a,** 274-55-5; **11b,** 31420-26-5; **11c,** 31420-27-6; **11d,** 31420-28-7; **11e,** 31420-29-8; **12a** (X = ClO_4), 31420-30-1; **12b** (X = ClO_4), 31420-31-2; **12c** (X = ClO_4), 31420-32-3; **13a** (X = ClO_4), 31489-80-2; **13b** (X = ClO_4), 31420-33-4; 1-acetonyl-3,6-dimethylpyridazinium bromide, 31420-34-5; 3,6-dimethyl-1-phenacylpyridazinium bromide, 31420-35-6.

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A Nuclear Magnetic Resonance Spectral Study of Some Organometallic Derivatives of Indoles[1]

Manfred G. Reinecke,*[2] John F. Sebastian, Harry W. Johnson, Jr., and Chongsuh Pyun

Department of Chemistry, Texas Christian University, Forth Worth, Texas 76129, and
Department of Chemistry, University of California, Riverside, California 92503

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The nmr spectra of several alkali metal and Grignard derivatives of indole in THF indicate these species to be essentially ionic but not necessarily dissociated *N*-metal derivatives. The proton chemical shifts for the alkali metal salts are in the order Li > K > Na suggesting that the first of these is a solvent-separated ion pair and the last two are contact ion pairs. Mixtures of indole and the alkali metal derivatives undergo rapid exchange on the nmr time scale in all solvents studied while the Grignard reagent does so only in HMPT. The unique reactivity of indolylmagnesium halides is accommodated with these results by assuming extensive association of the magnesium and nitrogen atoms of these reagents in all solvents studied except HMPT.

The constitution and chemistry of Grignard reagents which react at a position different from that where an atom was displaced in their preparation have intrigued chemists for many years.[3–7] Heterocyclic representatives of these reagents include the pyrrolyl- and indolylmagnesium halides.[8] Recent investigations[1,9–12] have substantiated the earlier generalization[8] that these Grignard reagents react with electrophiles predominantly at carbon and not at nitrogen in contrast to the corresponding alkali metal derivatives.[13–16] An explanation of these reactions reasonably requires a knowledge of the structure of the reactive, or at least the predominant species present in solution. Heeding the assertion that structural problems of this type are "incapable of purely chemical solution,"[17] an investigation of the organometallic derivatives of several indoles by the nmr method so successfully applied to allylic systems[6] was undertaken.

Preliminary examination established that the indole[18] as well as pyrrole[19] Grignard reagents consist primarily of N–MgX species. A more detailed study became possible[20] only after the solvent[21] and concentration[21,22] dependence of the nmr spectra of indole had been examined. This paper will report the results of that study.

Results and Discussion

The nmr spectrum of indolylmagnesium bromide in THF (Figure 1) consists of three complex multiplets, relative areas 3:2:1, centered at τ 2.65, 3.25, and 3.65, respectively. Indolyllithium, -sodium, and -potassium have similar nmr spectra (Table I) differing only in the detailed fine structure of the multiplets.

The high field quartet ($J_{3,7} = 0.9$, $J_{2,3} = 2.3$ Hz) was assigned to the 3 proton because it is absent in the nmr spectrum of 3-methylindolylmagnesium bromide.[18]

The 2-proton resonance occurs as a sharp doublet ($J_{2,3} = 2.3$ Hz) superimposed on the lowest field multiplet. This assignment is confirmed by the disappearance of the doublet and the decrease in the relative area of the multiplet from three to two in 2-methylindolylmagnesium bromide.[18]

The remaining two protons responsible for this low-field multiplet are those at the 4 and 7 positions while the broad peak centered at τ 3.25 arises from the 5 and 6 protons. These assignments were based on a comparison of chemical shifts with those of the same protons

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[1] Taken in part from the Ph.D. dissertation of J. F. Sebastian, University of California, 1965.

[2] To whom inquiries should be sent at Texas Christian University.

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