SYNTHESIS AND PROTONATION OF DIPYRROLO[1,2-a:2',1'-c]PYRAZINES

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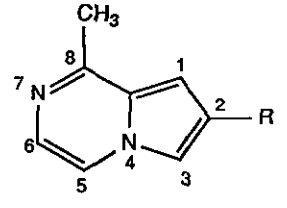
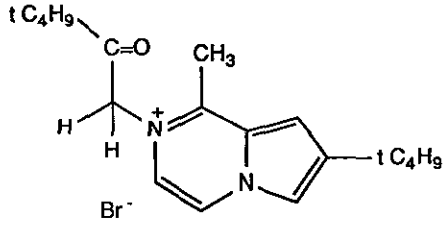
Abstract - The dipyrrolo[1,2-a:2',1'-c]pyrazines 3-9 were prepared by base catalysed cyclisation of the quaternary salt resulting from reaction of various 8-methyl-7-azaindolizines with an α-haloketone. Deuterium exchange and protonation were shown to occur preferentially at the 3(8)- and then 1(10)- positions.

In a recent note[1] we published the synthesis of a variety of 7-azaindolizines by Chichibabin quaternisation-cyclisation of methylpyrazines with an α-haloketone. Unlike 5-, 6- and 8-azaindolizines, 7-azaindolizines protonate solely at the N-7 non-bridgehead nitrogen and resist deuterium exchange[1-3]. In addition electron density calculations indicate the C-8 site of 7-azaindolizines to be markedly electron deficient[4]. These two factors suggest that 8-methyl-7-azaindolizine(s) 1 should themselves readily undergo Chichibabin quaternisation-cyclisation with an α-haloketone to give derivatives of the dipyrrolo[1,2-a:2',1'-c]pyrazine system 2. Indeed Boekelheide et al.[5] prepared one highly substituted derivative of 2 by reacting 1,2-dicarbomethoxy-5,8-dimethyl-7-azaindolizine with phenacyl bromide. The only other dipyrrolopyrazine reported is the parent 2 which was recently synthesised by dehydrogenative bridging of dipyrroloethane[6]. In this paper we report the Chichibabin synthesis of several simple alkyl and aryl derivatives of 2 together with deuterium exchange and protonation studies on these compounds.



1. R = H
11. R = tC_4H_9



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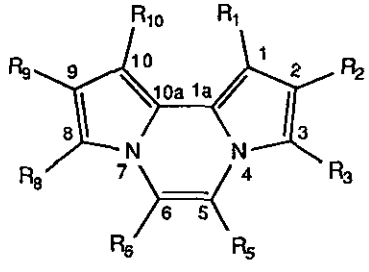


	R_1	R_2	R_3	R_5	R_6	R_8	R_9	R_{10}
2.	H	H	H	H	H	H	H	H
3.	H	CH_3	H	H	H	H	CH_3	H
4.	H	tC_4H_9	H	H	H	H	tC_4H_9	H
5.	H	CH_3	CH_3	H	H	CH_3	CH_3	H
6.	H	CH_3	H	CH_3	CH_3	H	CH_3	H
7.	H	CH_3	H	H	H	H	$COOC_2H_5$	H
8.	H	CH_3	H	H	H	H	C_6H_5	H
9.	H	CH_3	H	H	H	H	C_4H_9	H

The dipyrrolo[1,2-a:2',1'-c]pyrazines 3-9 were readily obtained by cyclisation of the quaternary salt resulting from reaction of the 8-methyl-7-azaindolizine with a variety of α-haloketones, the quaternisation was invariably exothermic. The salt 10 formed by reaction of 8-methyl-2-t-butyl-7-azaindolizine 11 and bromopinacolone was characterised, but generally the quaternary salt was not isolated prior to cyclisation. Dissolution of the salt and reflux of the bicarbonate basified solution gave the dipyrrolopyrazine in varying yields (13-60%). The ^{1}H nmr spectra deuteriochloroform of the dipyrrolopyrazines 3-6 consisted of four singlets, the simplicity of the spectra reflecting the symmetry of the compounds and of the dipyrrolo[1,2-a:2',1'-c]pyrazine ring system. The ring proton absorptions were found to occur at chemical shifts corresponding to that of the parent[6] 2 occurring at progressively lower field in the order $H_1(H_{10})$; $H_3(H_8)$; $H_5(H_6)$ (see Table I).

Table I ^{1}H Nmr Spectra of Dipyrrolo[1,2-a:2',1'-c]pyrazines in $CDCl_3$ (δ values)

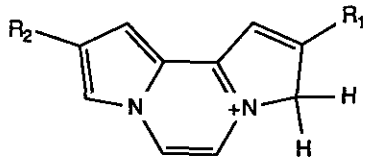
	R_1	R_2	R_3	R_5	R_6	R_8	R_9	R_{10}
2	6.50	6.55	6.98	7.05	7.05	6.98	6.55	6.50
3	6.40*	2.25(3H)	6.75*	6.88	6.88	6.75*	2.25(3H)	6.40*
4	6.40*	1.30(9H)	6.74*	6.92	6.92	6.74*	1.30(9H)	6.40*
5	6.22	2.16(3H)	2.28(3H)	6.87	6.87	2.28(3H)	2.16(3H)	6.22
6	6.30*	2.20(3H)	6.72*	2.28(3H)	2.28(3H)	6.72*	2.20(3H)	6.30*
7	6.38	2.21(3H)	6.81	6.94d J = 1.4Hz	7.49d J = 1.4Hz	6.93	1.36 t(3H,CH_3-2) J = 7.2Hz 4.21 q(2H,CH_2-2)	6.73 J=7.2Hz
8	6.37	2.25(3H)	6.73	6.94	6.94	7.11 to 7.63 6H complex H-8 and Ph-9		6.73
9	6.35*	2.21(3H)	6.72*	6.87	6.87	6.72*	1.30(9H)	6.27

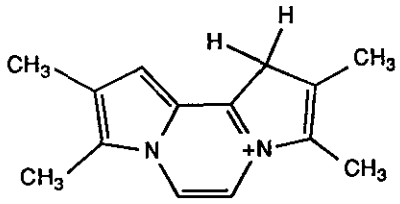
Signals marked by asterisk are broadened and/or weakly split.

For example 2,9-dimethyldipyrrolo[1,2-a:2,1'-c]pyrazine 3 showed in addition to its high field methyl signal at δ 2.25, three lower field singlets at δ 6.40, 6.75 and 6.88 assigned respectively to $H_1(H_{10})$,$H_3(H_8)$ and $H_5(H_6)$. The ^{13}C-nmr spectrum of 3 also reflected the symmetry of the system showing six signals, the non-quaternary ring carbons occurring at δ 100, 111 and 113. These ^{13}C shifts are comparable with ring carbon shifts of other electron rich heteroaromatic compounds[7] and suggest the dipyrrolo[1,2-a:2',1'-c]pyrazine system to be a π-excessive heteroaromatic involving 14π peripheral electrons. When the deuteriochloroform solutions of 3, 4 and 6 were mixed with a drop of deuteriotrifluoroacetic acid the resulting ^{1}H nmr spectra showed the disappearance of their H-3 and H-8 and a slight diminution of its H-1 and H-10 signal. The unsymmetrical

dipyrrolopyrazines 7, 8 and 9, gave more complex ^{1}H nmr spectra deuteriochloroform, signal assignments shown in Table I, are based on a comparative examination of related spectra, on the proximity of hydrogen to nitrogen, and with the assistance of deuterium exchange and double irradiation.

The trifluoroacetic acid spectra of 3, 4 and 6 showed these symmetrical dipyrrolopyrazines to protonate solely at the unsubstituted 3 (8) site to give the corresponding 3H monocations, for example 3 gave the 3H cation 12. 2,3,8,9-Tetramethyldipyrrolo[1,2-a:2',1'-c]pyrazine 5 gave a preponderance of the C-3 protonated cation (60%) together with an equilibrium concentration of the C-1 protonated cation 13 (40%).





12. $R_1 = R_2 = CH_3$
14. $R_1 = CH_3$, $R_2 = C_6H_5$
15. $R_1 = C_6H_5$, $R_2 = CH_3$

13.

However, the ^{1}H nmr spectrum of the trifluoroacetic acid solution of the perchlorate salt of 5 showed solely the presence of the 3H conjugate acid cation. On the other hand the ^{1}H nmr spectrum of the perchlorate of 5 in deuterated dimethyl sulphoxide showed a spectrum identical in pattern and with similar chemical shifts to that of the original base 5. This points to the weakly basic nature of the dipyrrolopyrazine system, and in particular it is distinctly less basic than its precursor 8-methyl-7-azaindolizine[8]. The unsymmetrical dipyrrolo[1,2-a:2,1-c]pyrazines 7, 8 and 9 in trifluoroacatic acid gave a mixture of the C-3 and C-8 conjugate acid cations for example 8 gave 14 (70%) and 15 (30%). The signal assignments of the ^{1}H nmr spectra trifluoroacetic acid of the dipyrrolopyrazines 3-9 are shown in Table II.

These protonation and deuterium exchange studies show the dipyrrolopyrazine system to be a π-excessive heteroaromatic with a propensity to preferentially protonate at carbons 3(8) and then 1(10). *Protonation at the bridgehead nitrogen* is not observed as this would lead to a non-aromatic conjugate acid whereas protonation at carbons 3(8) or 1(10) results in the formation of a 10π 7-azaindolizinium moiety in a manner similar to the establishing of a 6π pyridinium system as part of the conjugate acid cation formed on protonation of indolizine at C-3 or C-1.

Table II ^{1}H Nmr Spectra of Dipyrrolo[1,2-a:2',1'-c]pyrazines in CF_3COOH (δ values)

Structure	Cation	%	R_1	R_2	R_3	R_5	R_6	R_8	R_9	R_{10}
3	C-3	100	7.5	2.48(3H)	5.26(2H)	8.00d J = 6.0Hz	7.50d J = 6.0Hz	7.85	2.40(3H)	7.00
4	C-3	100	7.55	1.48(9H)	5.35(2H)	8.00d J = 6.0Hz	7.48d J = 6.0Hz	7.95	1.48(9H)	7.05
5	C-3	60	6.93	2.40(3H)	1.78d (3H) J = 7.5Hz 5.10q (1H) J = 6.6HZ	7.45d J = 6.6Hz	7.80d J = 6.6Hz	2.60(3H)	2.47(3H)	7.40
	C-1	40	4.2(2H)	2.18(3H)	2.58(3H)	7.50d J = 6.6Hz	8.00d J = 6.6Hz	2.18(3H)	2.58(3H)	7.40
6	C-3	100	7.30	2.60(3H)	5.10(2H)	2.60(3H)	2.35(3H)	7.65	2.35(3H)	7.00
8	C-3	70		2.45(3H)	5.22(2H)	signals between 7.10-8.30(10H)				
	C-8	30		2.48(3H)	signals between 7.10-8.30(10H) 5.70(2H)					
9	C-3	42	7.40	2.49(3H)	5.34(2H)	8.00d J = 6.0Hz	7.50d J = 6.0Hz	7.40	1.48(9H)	7.00
	C-8	58	7.02	2.45(3H)	7.80	7.50d J = 6.0Hz	8.00d J = 6.0Hz	5.24(2H)	1.48(9H)	7.40

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared Spectra were recorded for Nujol mulls unless otherwise stated with a Perkin Elmer 781 Spectrophotometer. Ultraviolet Spectra were recorded on a Perkin Elmer 552 Spectrophotometer. Light absorption data refer to solutions in ethanol unless otherwise stated, inflections are given in parentheses. ^{1}H and ^{13}C nmr spectra refer to solutions in deuteriochloroform unless otherwise stated and were recorded with a Varian FT-80A or a Perkin Elmer R12B spectrometer using tetramethylsilane as an internal standard. Unless otherwise stated values given on a δ scale refer to singlet absorption, approximate coupling constants are in hertz and integration values and signal assignment are in parentheses. For multiplet d = doublet, t = triplet and q = quartet. Signals marked by asterisk are broadened and/or weakly split. Mass Spectroscopic and elemental analysis were performed by the analytical laboratories of ICI, Pharmaceutical Division.

The following general procedure was used in the Chichibabin synthesis of the dipyrrolo[1,2-a:2', 1'-c]pyrazines. The bromoketone was added to the 8-methyl-7-azaindolizine followed by a few drops of ethanol to moderate the exothermic reaction and the reaction mixture was maintained at 35-50°C for 1 to 7 days. Water was added and the aqueous solution was extracted with ether or chloroform,

warmed to remove dissolved solvent, before adding an excess of sodium hydrogen carbonate. The bicarbonate solution was refluxed for 30 min and the precipitated dipyrrolo[1,2-a:2',1'-c]pyrazine was collected and recystallised from ethanol.

2,8-Dimethyl-7-azaindolizine (2.0g, 0.0137 mol) and bromoacetone (1.8g, 0.0137 mol) gave 2,9-dimethyldipyrrolo[1,2-a:2',1'-c]pyrazine 3, 1.5g (60%) as colorless cystals: mp 172-174°C; λ max (246), 254, (270), 299, 311, log ε 4.65, 4.73, 4.07, 3.95, 3.93, ir 780, 1370, 1490, 3050 cm^{-1}; ^1H nmr (See Table I); ^{13}C-nmr: 12.12 (CH_3-2, CH_3-9); 100.49 (C-1, C-10, C-2 and C-9); 110.65 (C-3, C-8); 112.72 (C-5, C-6); 122.29 (C-1a, C-10a).

Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.22, H, 6.51; N, 15.21. Found: C, 78.26; H, 6.52; N, 15.22; ms: m/z 184 (M^+, 100).

2-t-Butyl-8-methyl-7-azaindolizine (7.9g, 0.042 mol) with bromopinacolone (7.7g, 0.042 mol) gave 2,9-di-t-butyldipyrrolo[1,2-a:2',1'-c]pyrazine 4 5.6g (48%) as colorless crystals: mp 155.7°C; λmax (247), 254, (269), (297), (309), log ε 4.71, 4.75, 4.03, 3.93, 3.92; ir 670, 785, 1550, 1670 cm^{-1}; ^1H nmr (See Table I).

Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.59; H, 8.96; N, 10.45. Found: C, 79.94; H, 8.96; N, 10.04.

2,3,8-Trimethyl-7-azaindolizine (3.5g, 0.022 mol) with bromobutan-2-one (3.3g, 0.022 mol) gave 2,3,8,9-tetramethyldipyrrolo[1,2-a:2',1-c]pyrazine 5 1.8g (39%) as pale yellow crystals: mp 199-200°C; λ max (249), 252, (264), (290), (303), (318), log ε 4.66, 4.76, 4.63, 3.93, 4.60, 4.05; ir 762, 1445, 1670, 1715, 3100 cm^{-1}; ^1H nmr (See Table I).

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.24; H, 7.55; N, 13.32. Found: C, 78.93; H, 7.51; N, 13.22.

2,5,6,8-Tetramethyl-7-azaindolizine (0.4g, 0.0023 mol) with bromoacetone (0.3g, 0.0023 mol) gave 2,5,6,9-tetramethyldipyrrolo[1,2-a:2',1'-c]pyrazine 6 0.2g (41%) as pale yellow crystals: mp 173-174°C; λ max (248), 256 (271), (296), (311), log ε 4.22, 4.28, 3.67, 3.50, 3.42; ir 750, 1460, 1540, 1560, 1600 cm^{-1}; ^1H nmr (See Table I).

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.24; H, 7.55; N, 13.32. Found: C, 78.92; H, 7.69; N, 12.94.

2-Carbethoxy-8-methyl-7-azaindolizine (0.4g, 0.002 mol) with bromoacetone (0.26g, 0.002 mol) gave a solid which was sublimated (70°C, 18mm) to give 9-carbethoxy-2-methyldipyrrolo[1,2-a:2',1'-c]pyrazine 7 0.20g (42%) mp 64°C, λ max (215), (238), 261.5, 269, 297, (307.5), log ε 4.57, 4.17, 4.65, 4.60, 3.90, 3.82; ir 745, 1220, 1680, 1710, 3140 cm^{-1}; ^1H nmr (See Table I).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.79; N, 11.57. Found: C, 69.64; H, 5.71; N, 11.42. ms: m/z 242 (M^+, 100).

2,8-Dimethyl-7-azaindolizine (3.2g, 0.022 mol) with phenacyl bromide (4.32g, 0.022 mol) gave 2-methyl-9-phenyldipyrrolo[1',2'-a:2',1'-c]pyrazine 8 0.6g (16%) as pale yellow crystals: mp 188-189°C; λ max (236), (244), 270, (303), log ε 4.32, 4.35, 4.72, 4.08: ir 740, 1220, 1540, 1740, 3110 cm^{-1}; ^1H nmr (See Table I).

Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.93; H, 5.69, N, 11.40. Found C, 83.14; H, 5.91; N, 11.24.

2,8-Dimethyl-7-azaindolizine (2.55g, 0.017 mol) with bromopinacolone (2.95g, 0.017 mol) gave 2-methyl-9-t-butyldipyrrolo[1',2'-a:2',1'-c]pyrazine 9 0.5g (13%) as colorless crystals: mp 132.6°C, λ max (246), 254, (270), (297), (310.5), log ε 4.67, 4.75, 4.12, 4.03, 4.01; ir 750, 1240, 1530, 1670, 3200 cm^{-1}; ^1H nmr (See Table I).

Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.65, H, 87.96; N, 12.39. Found C, 79.14; H, 8.03; N, 12.34.

8-Methyl-2-t-butyl-7-azaindolizine 11 (7.9g, 0.042 mol) and bromopinacolone (5.5g, 0.042 mol) gave salt 10, 10.2 g (66%) as colorless crystals: mp 285°C; ir 960, 1650, 1715, 3040 cm^{-1}; ^1H nmr $(CD_3)_2SO$ 1.12 (9H, t-butyl); 1.34 (9H, t-butyl); 2.74 (3H, CH_3-8); 5.80 (2H, CH_2); 7.55 (d, 1H,

H-5, J = 6.0 Hz); 7.90* (1H, H-1); 8.35* (1H, H-3); 8.56 (d, 1H, H-6, J = 6.0 Hz).

Anal. Calcd for $C_{18}H_{27}N_2OBr$: C, 58.88; H, 7.36; N, 7.63. Found: C, 58.54; H, 7.80; N, 7.54.

ACKNOWLEDGEMENT

The authors wish to thank Dr. N. Elmore for advice, ICI for analytical data and S.E.D. for a research studentship to P.K.T.L.

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Received, 30th August, 1988