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MULTINUCLEAR NMR AND *AB INITIO* MO STUDIES OF 7-METHYL-7*H*-PYRROLO[2,3-*b*]PYRIDINE AND RELATED COMPOUNDS

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The contribution of the polarized resonance structures to 7-methyl-7*H*-pyrrolo[2,3,-*b*]pyridine and 4-methyl-4*H*-pyrrolo[3,2-*b*]pyridine, which have recently attracted much attention in physico-chemical studies, was considered based on multinuclear (^{1}H, ^{13}C and ^{15}N) NMR spectroscopy and MO calculation. Comparison of the chemical shifts of the compounds with those of other relevant compounds and the effects of concentration and solvents observed by multinuclear NMR suggested that the contribution of the non-polarized structures to both compounds predominates over that of the polarized structures. This result was also supported by *ab initio* MO calculations using the 6–31G basis set.

INTRODUCTION

1*H*-Pyrrolo[2,3-*b*]pyridine (7-azaindole; **1**) and its derivatives are currently attracting much interest in biochemical and physico-chemical studies owing to their characteristic condensed ring system, consisting of pyridine and pyrrole rings which have opposite π-electron densities.[1] Thus studies on the biological activity of 7-azaindole derivatives have been expanded significantly in recent years,[2] since they are aza analogues of indoles whose skeleton is often found in natural alkaloids and in synthetic pharmaceuticals.[3] We have recently reported the facile direct introduction of a halogen atom on to the 6-position of 7-azaindole via its *N*-oxide[4] and the functionalization of 7-azaindole directed toward agrochemicals using haloazaindoles.[5] Further, the existence of a basic nitrogen atom on the pyridine ring and an acidic hydrogen atom on the pyrrole ring in 7-azaindole is of interest to physico-chemists. While 7-azaindole readily forms various binuclear complexes with metals,[6] its two nitrogen atoms are favourably located so that it interacts with an alcohol (1 : 1 adduct formation) or itself (dimerization) through hydrogen bonds.[7,8] It is known that these types of 7-azaindole complexes undergo a unique photoinducted double proton transfer reaction to form tautomers.[8] This behaviour was widely investigated by El-Bayoumi and co-workers,[8] who employed 7-methyl-7*H*-pyrrolo[2,3-*b*]pyridine (**3**) as the model compound of the tautomers. Since other physico-chemical properties of **3** are also of great interest, its structure, charge distribution, dipole moment and basicity were studied using molecular orbital (MO) calculations by comparison with those of its isomer, 1-methyl-7-azaindole (**13**).[9] Among them, the contribution of the polarized structure **3b** to **3** is one of the most important subjects, but the problem has only been discussed from the standpoints of absorption spectra[10] and ^{1}H and ^{13}C NMR spectra.[11] Further, detailed conclusions have not been established.

With this in mind, we report here studies of the contribution of the polarized structure to **3** and of the corresponding polar structure to 4-methyl-4*H*-pyrrolo[3,2-*b*]pyridine (**6**) on the basis of multinuclear magnetic resonance (^{1}H, ^{13}C and ^{15}N) and *ab initio* MO calculations using the 6–31G basis set.[12]

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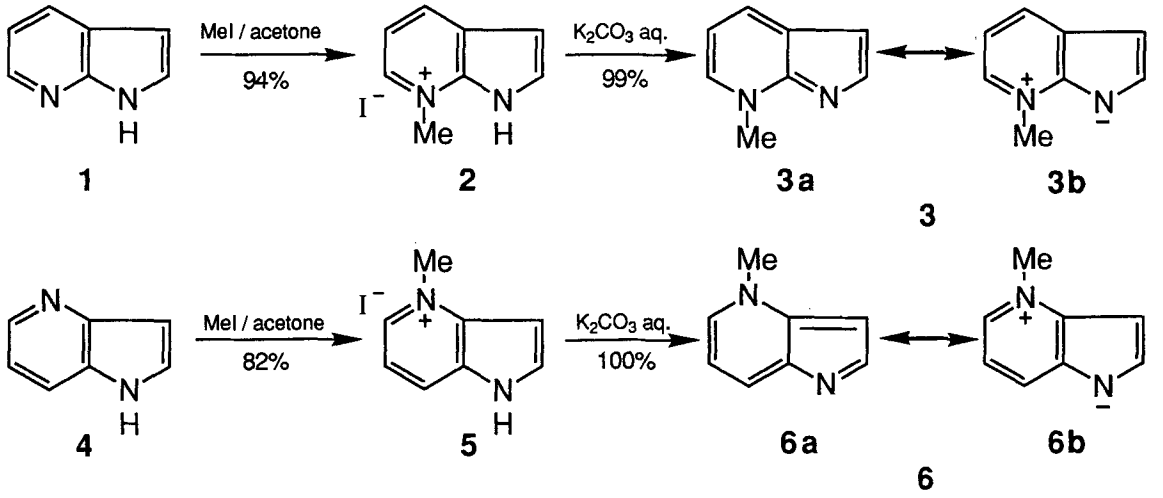
RESULTS AND DISCUSSION

7-Azaindole (**1**) or 4-azaindole (**4**) readily forms the quaternary derivative, 7-methyl-7-azaindolium iodide (**2**) or 4-methyl-4-azaindolium iodide (**5**), when stirred with excess of iodomethane. On treatment with alkali, these salts yield yellow basic substances (**3** and **6**), which can be readily extracted with diethyl ether or dichloromethane, respectively (see Scheme 1).[10]

To obtain a better insight into molecular structures, ^{15}N NMR spectra in DMSO-d_6 were measured on these six compounds[13] and their chemical shifts are shown in Figure 1 together with those of relevant heterocyclic compounds **7**–**12**. On quaternization of **1** to **2**, the



Scheme 1. Synthesis of compounds **2**, **3**, **4** and **6**

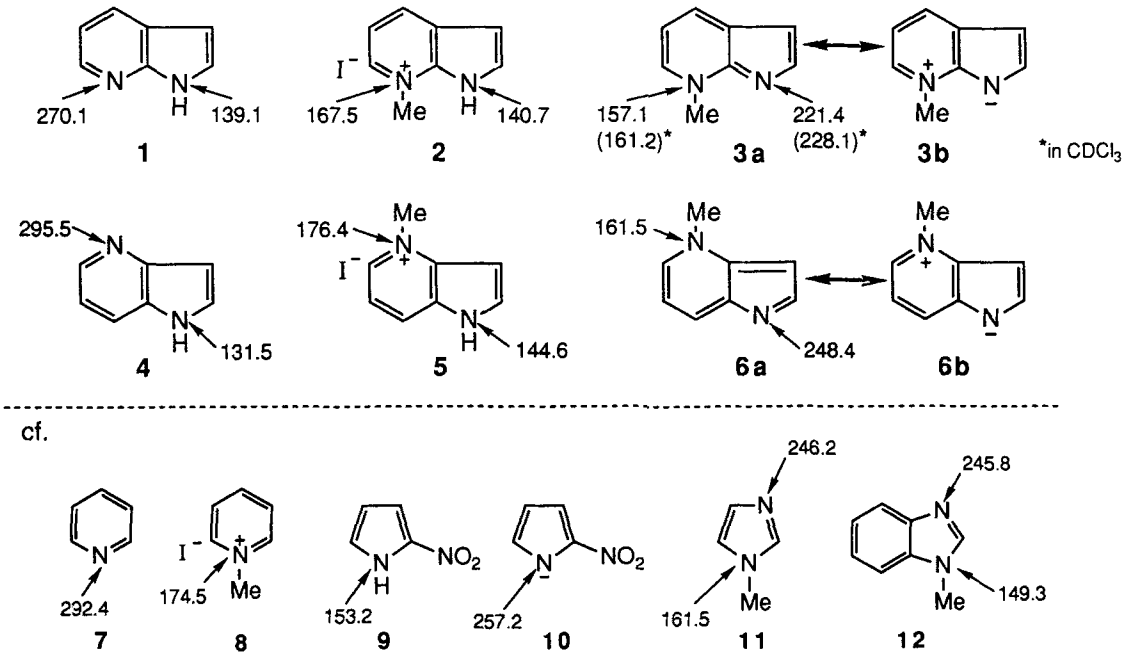


Figure 1. ^{15}N NMR chemical shifts (ppm from anhydrous liquid NH_3) of compounds **1**–**6** in DMSO-d_6

Table 1. ^{1}H and ^{13}C NMR chemical shifts of compounds **1–6**

Compound	^{1}H NMR chemical shift[a]						^{13}C NMR chemical shift[a]					
	H-2	H-3	H-4	H-5	H-6	H-7	C-2	C-3	C-4	C-5	C-6	C-7
1[b]	*7·37*[d]	6·50	7·95	*7·10*	*8·32*	–	*125·4*	100·4	129·0	115·6	*142·1*	–
2[c]	7·99	7·00	8·74	7·65	8·76	–	129·7	103·5	136·8	116·0	137·4	–
3[b]	*7·89*	6·66	8·08	*6·79*	*7·52*	–	*145·4*	101·4	130·5	108·8	*129·6*	–
4[b]	*7·50*	6·70	–	*8·49*	*7·12*	7·70	*128·7*	102·3	–	*142·6*	116·5	119·0
5[c]	8·33	7·06	–	8·76	7·68	8·58	123·9	92·8	–	134·9	113·4	132·2
6[b]	*8·27*	6·39	–	*7·50*	*6·87*	8·11	*152·6*	91·7	–	*130·0*	109·6	127·5

[a] In ppm from TMS.
[b] In $CDCl_3$.
[c] In DMSO-d_6.
[d] Values in italics showed remarkable shifts upon transformation from **1** to **3**, or **4** to **6**.

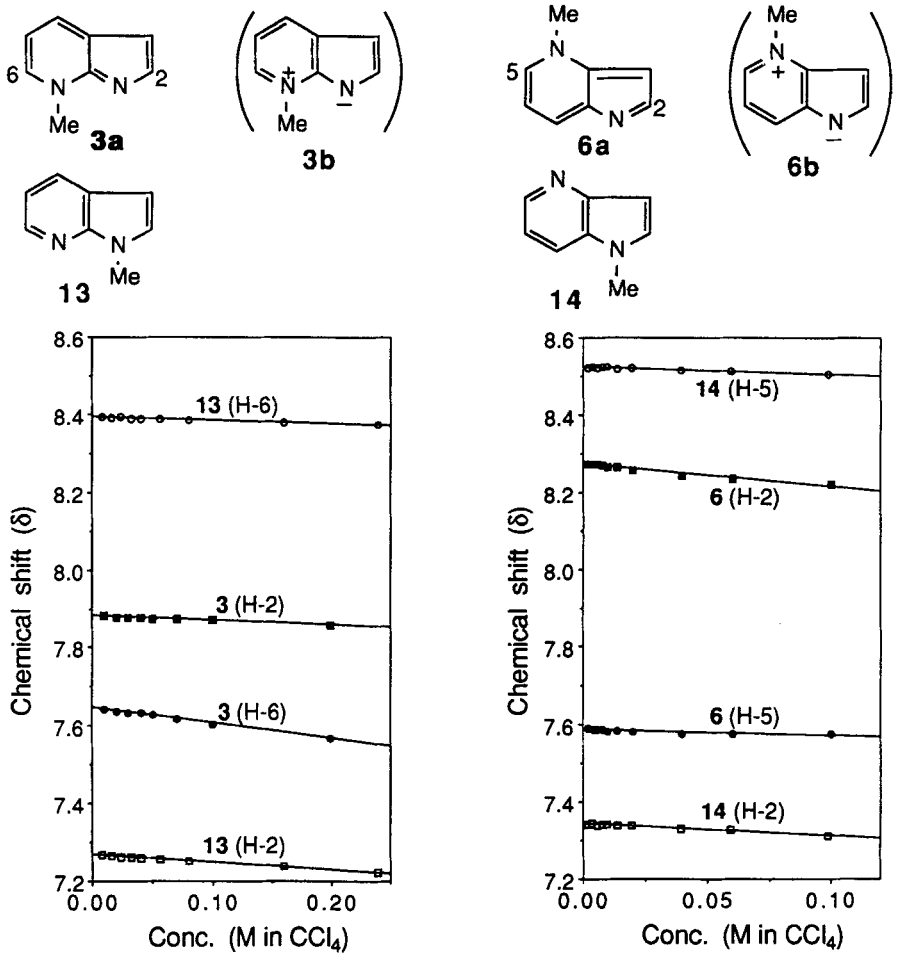


Figure 2. Effect of concentration on ^{1}H NMR chemical shifts

signal of the pyrrole nitrogen did not show any significant shift. The upfield shift of the pyridine nitrogen by about 100 ppm well agreed with the change of the ^{15}N chemical shift from pyridine (**7**) to the pyridinium salt (**8**).[14] In the deprotonation step of the pyrrole hydrogen from **2** to **3**, a considerable downfield shift of the pyrrole nitrogen was observed. This change was considered to correspond to anion formation of a pyrrole having an electron-withdrawing group, such as **10**.[15] This result appears to indicate that the contribution of the structure **3b** to **3** is larger than that of the structure **3a**. On the other hand, the chemical shifts of the two nitrogens of **3** were similar to those of *N*-methylimidazoles **11** and **12**,[14] and were not shifted in either a polar solvent (DMSO-d_6) or a non-polar solvent ($CDCl_3$). This result was not in accord with the above assumption that the contribution of the structure **3b** is predominant. A similar tendency of chemical shift changes was also observed for 4-azaindole derivatives. On the basis of these experimental results we could not confirm whether the major contributing structure is the non-polarized **3a** or the polarized **3b**.

In addition to the above ^{15}N NMR results, the contribution of the polarized structure to **3** was examined by means of ^1H and ^{13}C NMR spectra. The ^1H and ^{13}C chemical shifts of **1**–**6** are given in Table 1. For the ^1H NMR chemical shifts, marked changes were observed when the azaindole **1** was compared with the 7-methyl derivative **3**, with downfield shift of H-2 on the pyrrole ring and upfield shifts of H-5 and H-6 on the pyridine ring. If the contribution of the pyridinium salt **3b** is larger than that of **3a**, the α-hydrogen on the pyridine ring (H-6) would not show an upfield shift. In ^{13}C NMR measurements, the relationship between the chemical shifts of C-2 and C-6 was reversed when **1** was converted into **3**. This result suggested that the electronic natures of the pyrrole ring and the pyridine ring of the 7-azaindole skeleton were exchanged. Hence the contribution of **3a** becomes larger than that of **3b**. The 4-azaindole derivatives **4**–**6** also showed similar changes in chemical shifts, which seems to indicate a major contribution of the resonance structure **6a**.

Further, changes in chemical shifts depending on concentration were studied for azaindoles **3** and **6**, since it has been reported that the signals of H-2 and H-6 of **1** shift downfield with increasing concentration in CCl_4, which is due to formation of a dimer through hydrogen bonds.[7] As reference samples 1-methyl-7-azaindole (**13**) and 1-methyl-4-azaindole (**14**) were employed, to which a contribution of polarized resonance structures is unlikely. The effects of concentration on the chemical shifts of H-2, H-6 and H-5 of these four compounds (**3**, **13**, **6** and **14**) are shown in Figure 2. The signal for **3**, which was methylated at the 7-position, was shifted upfield to some extent with increasing concentration. If the slope of this variation due to intermolecular interaction is large, we may postulate that the betaine structure **3b** is the major contributing form. However, the slope of the variation for **3** was not very different from that for **13**, which does not dimerize. The 4-azaindole derivatives **6** and **14** also showed a similar tendency. Therefore, it is reasonable to conclude that the non-polarized resonance structure **3a** or **6a** contributes predominantly to **3** or **6**, respectively.

Catalan *et al.*[9e] studied the gas-phase basicity of heterobicyclic compounds including 7-azaindole derivatives using both experimental measurements and *ab initio* calculations at the STO-3G and 4–31G levels. In order to clarify the contribution of the polarized structure **3a** or **6a** to **3** or **6** respectively, more precisely, we carried out MO calculations for **1**, **3**, **4** and **6** using the *ab initio* 6–31G method. So far as we know, no report on MO calculations on 4-azaindole derivatives has appeared. The calculated bond lengths of these compounds are shown in Figure 3. It was found that the N1—C7a, C-3a—C-4 and C-5—C-6 bonds in **3** are shorter than the corresponding bonds in **1**. In the case of the 4-azaindole derivatives, the N-1—C-2, C-5—C-6 and C-7—C-7a bonds in **6** are shorter than those in **4**. As one of the characteristics of these azaindoles, the bridged bonds (C-3a—C-7a) in **3** and **6** were longer than those in **1** and **4**. These results imply that the structures **3** and **6** resemble **3a** and **6a**, respectively.

Figure 4 shows the total atomic charges and the dipole moments of **1**, **3**, **4** and **6**. Comparison of the calculated atomic charges of **3** and **6** with those of the azaindoles **1** and **4** indicated that some atomic charge migrates from the pyrrole ring to the pyridine ring. These atomic charges on carbons explain well the features of the aforementioned chemical shifts in ^{13}C NMR spectra of **3** and **6**. The remarkable changes in the

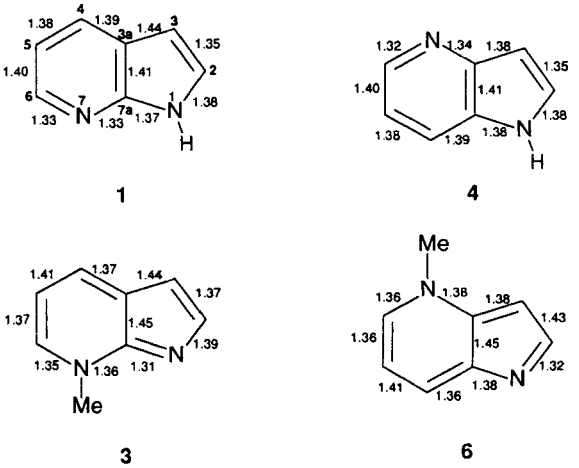


Figure 3. Bond lengths of compounds **1**, **3**, **4** and **6** calculated by the *ab initio* 6–31G method

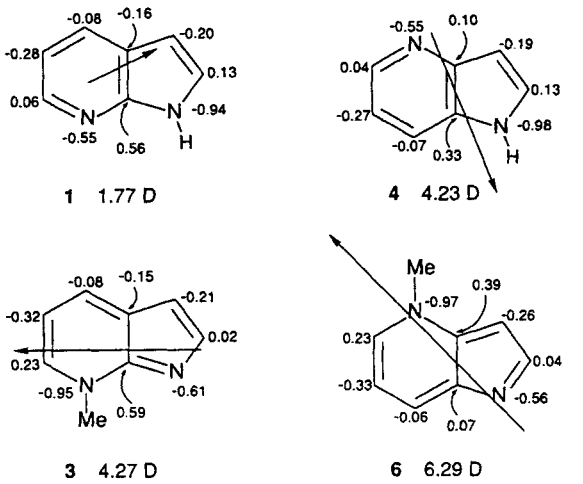


Figure 4. Dipole moments and total atomic charges of compounds **1**, **3**, **4** and **6** calculated by the *ab initio* 6–31G method

direction of the dipole moments also supported the charge migration. Thus, in **1** and **4** the dipole moments were directed toward the pyrrole ring from the pyridine ring, but the directions were reversed in **3** and **6**.

The results of the calculation suggested that the anions on N-1 of the betaine structures **3b** and **6b** migrated to the pyridine ring to form the non-polarized structures **3a** and **6a**. As a consequence, the electronic natures of the pyrrole ring and the pyridine ring of the azaindole skeleton were exchanged. It is concluded from both the experimental and calculated results that the contribution of the non-polarized structure **3a** or **6a** to the azaindole **3** or **6** is greater than that of the polarized structure **3b** or **6b**.

EXPERIMENTAL AND CALCULATION

The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 spectrometer with tetramethylsilane as an internal standard. The ^{15}N NMR spectra in DMSO-d_6 or $CDCl_3$ solutions at a concentration of 1·0 M were recorded on a JEOL JNM-GSX400 spectrometer with formamide as an external standard and chemical shifts are given in ppm from anhydrous liquid ammonia. IR spectra were measured on a Hitachi 270-30 infrared spectrometer. Melting points were obtained with a Yanagimoto micro melting point apparatus or a Yamato melting point apparatus (Model MP-21) and are uncorrected. The molecular orbital calculations by the *ab initio* method at the 6–31G level were carried out using the GAUSSIAN 90 program system.

1*H*-Pyrrolo[2,3-*b*]pyridine (**1**), purchased from Aldrich Chemical, was used after recrystallization from hexane–benzene and 1*H*-pyrrolo[3,2-*b*]pyridine (**4**) was prepared as described previously.[16]

7-Methyl-7-azaindolium iodide (**2**). To a solution of 7-azaindole (**1**) (590 mg, 5 mmol) in anhydrous acetone (10 ml) was added iodomethane (7·1 g, 50 mmol) under a nitrogen atmosphere at room temperature. After stirring for 24 h at the same temperature, the precipitated solid was filtered and washed with diethyl ether. The crude product was subjected to recrystallization from methanol–diethyl ether to give **2** (1·28 g, 99%) as colourless plates; m.p. 153–154 °C (lit.[10] m.p., 154–155 °C). IR (KBr), 3392 cm^{-1} (NH). ^{1}H NMR (DMSO-d_6), δ (ppm) = 4·45 (3H, s, Me), 7·00 (1H, d, J = 3·4 Hz, H-3), 7·65 (1H, dd, J = 6·5, 7·7 Hz, H-5), 7·99 (1H, d, J = 3·4 Hz, H-2), 8·74 (1H, d, J = 7·7 Hz, H-4), 8·76 (1H, d, J = 6·5 Hz, H-6). ^{13}C NMR (DMSO-d_6), δ (ppm) = 42·5 (Me), 103·5 (C-3), 116·0 (C-5), 125·6 (C-3a), 129·7 (C-2), 136·8 (C-4), 137·4 (C-6), 139·5 (C-7a). MS (EI), m/z (relative intensity, %) = 133 (M^+, 12), 132 ($M^+ - H$, 100), 118 ($M^+ - Me$, 3).

7-Methyl-7H-pyrrolo[2,3-b]pyridine (**3**). To a solution of 7-methyl-7-azaindolium iodide (**2**) (780 mg, 3·0 mmol) in water (15 ml) was added gradually solid K_2CO_3 (15 g) at room temperature. After stirring for 24 h at the same temperature, the solution was extracted with diethyl ether (5 × 30 ml), dried (K_2CO_3) and concentrated *in vacuo*. The residue was stored in a refrigerator to afford a yellow solid, which was recrystallized from hexane to give **3** (425 mg, 100%) as yellow plates; m.p. 42 °C (lit.[10] m.p., 44 °C). IR (NaCl), 1622, 1564 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ (ppm) = 4·26 (3H, s, Me), 6·66 (1H, d, J = 2·5 Hz, H-3), 6·79 (1H, dd, J = 6·1, 7·6 Hz, H-5), 7·52 (1H, d, J = 6·1 Hz, H-6), 7·89 (1H, d, J = 2·5 Hz, H-2), 8·08 (1H, d, J = 7·6 Hz, H-4). ^{13}C NMR ($CDCl_3$), δ (ppm) = 40·1 (Me), 101·4 (C-3), 108·8 (C-5), 129·6 (C-6), 130·3 (C-7a), 130·5 (C-4), 145·4 (C-2), 149·1 (C-3a). MS (EI), m/z (relative intensity, %) = 132 (M^+, 100), 131 ($M^+ - H$, 80), 104 ($M^+ - H - HCN$, 21).

4-Methyl-4-azaindolium iodide (**5**). Following the procedure for the preparation of **2**, **4** (118 mg, 1 mmol) was treated with iodomethane (1·42 g, 10 mmol) in acetone (2 ml) to afford **5** (213 mg, 82%) as colourless plates; m.p. 180–181 °C (deccomp.). IR (KBr), 3116 (NH), 1596 cm^{-1}. ^{1}H NMR (DMSO-d_6), δ (ppm) = 4·42 (3H, s, Me), 7·06 (1H, d, J = 2·6 Hz, H-3), 7·68 (1H, dd, J = 6·0, 8·6 Hz, H-6), 8·33 (1H, d, J = 2·6 Hz, H-2), 8·58 (1H, d, J = 8·6 Hz, H-7), 8·76 (1H, d, J = 6·0 Hz, H-5). ^{13}C NMR (DMSO-d_6), δ (ppm) = 40·3 (Me), 92·8 (C-3), 113·4 (C-6), 123·7 (C-2), 128·6 (C-7a), 133·2 (C-7), 134·9 (C-5), 134·3 (C-3a). MS (EI), m/z (relative intensity, %) = 133 (M^+,

10), 132 ($M^+ - H$, 100), 118 ($M^+ - Me$, 41). Found, *m/z* 132·0678; calculated for $C_8H_8N_2$, 132·0687 ($M^+ - H$).

4-Methyl-4H-pyrrolo[3,2-b]pyridine (**6**). Following the procedure for the preparation of **3**, **5** (260 mg, 1 mmol) was treated with K_2CO_3 (5 g) in water (5 ml) to afford **6** (131 mg, 100%) as yellow plates from the ethereal extract on storage in a refrigerator; m.p. 40 °C. IR (NaCl), 1620, 1574 cm^{-1}. ^1H NMR ($CDCl_3$), δ (ppm) = 4·06 (3H, s, Me), 6·39 (1H, d, J = 1·7 Hz, H-3), 6·87 (1H, dd, J = 6·1, 7·6 Hz, H-6), 7·50 (1H, d, J = 6·1 Hz, H-5), 8·11 (1H, d, J = 7·6 Hz, H-7), 8·27 (1H, d, J = 1·7 Hz, H-2). ^{13}C NMR ($CDCl_3$), δ (ppm) = 42·8 (Me), 91·7 (C-3), 109·6 (C-6), 127·5 (C-7), 130·0 (C-5), 141·2 (C-7a), 144·8 (C-3a), 152·6 (C-2). MS (EI), *m/z* (relative intensity, %) = 132 (M^+, 100), 105 (M^+ – HCN, 11). Found, *m/z* 132·0677; calculated for $C_8H_8N_2$, 132·0687.

Supplementary material is available on request from the authors [calculated bond lengths and angles for **1**, **3**, **4** and **6** (6–31G)].

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