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Ambident Heterocyclic Reactivity: The Alkylation of Pyrrolopyridines (Azaindoles, Diazaindenes)

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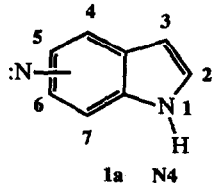
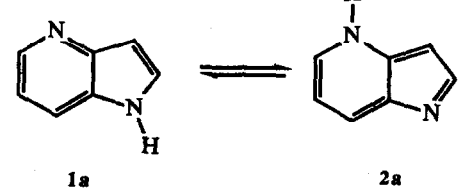
Abstract: 7-Methyl-6-azaindole, 7-acetamido-4-azaindole, the substituted 4-amino-, 2-methyl- and 6-methyl-7-azaindole, and the parent 4-, 5-, 6-, and 7-azaindole systems (as anions in dimethylformamide) were alkylated with a variety of primary alkylating agents. The relative importance of charge, product development, and steric approach control in determining the alkylation pattern (pyrrole *versus* pyridine ring alkylation) are discussed within a framework of variable S_N2 transition state structures. Frontier orbital factors appear to be relatively insignificant. The charge distribution, orbitals and energetics of these heterocyclic systems were modelled by *ab initio* molecular orbital calculations (STO-3G level). Specific association, involving hydrogen bonding between adjacent groups and the alkylating agent, is important in determining the alkylation pattern in some cases.

The alkylation of nitrogen heterocycles is of synthetic, commercial, and biological significance as well as being the subject of many mechanistic studies.[1,2] In unsymmetrical heterocyclic systems with more than one available alkylation site, the question of positional or site selectivity is of importance. Our earlier studies on the factors governing site selectivity of adenine alkylations revealed that alkylation at the four ring nitrogens is controlled by a complex interplay of structural features and experimental conditions.[3-6] Subsequent studies have been directed at simpler model systems, with only two competitive nitrogen sites, so as to distinguish the essential features and gauge their relative significance. Work on the alkylation of benzimidazoles has examined the electronic and steric effects of unsymmetrically disposed substituents, both distal and proximal, which cause differentiation between the two otherwise equivalent nitrogen sites.[7]



1a N4
b N5
c N6
d N7



1a **2a**

In the current pyrrolopyridine systems (**1a-d**), the two nitrogens are on different rings, pyrrole and pyridine, and thus have inherently dissimilar reactivities. There are six isomeric pyrrolopyridine systems, four of which, the azaindoles, are more stable than the other two, aza*iso*indole systems.[8] Despite their relatively simple structures, the synthesis of these bicyclic heterocycles still presents some challenges.[9,11] We have recently reported improved synthetic schemes to the parent 4-, 5-, 6-, and 7-azaindoles (**1a-d**) and some selected methyl and amino substituted derivatives.[13] Now we report a systematic study of their alkylation patterns, with discussion of the factors determining their site selectivity.

DISCUSSION AND RESULTS

Although the parent azaindoles (**1a-d**) are formally tautomeric systems, e.g. **1a** ⇌ **2a**, experimental evidence[14] is consistent with the presence in each system of only one tautomer, those with a pyrrole NH (**1a-d**). Theoretical calculations (see below) confirm very strong energetic preferences of around 100 kJ/mol for the pyrrolic ring tautomers.[15] Thus alkylation of the un-ionized azaindoles occurs essentially exclusively on the available σ lone pairs of the pyridine nitrogens. Such quaternizations typically require several hours at elevated temperatures to achieve moderate yields (see experimental section); under more vigorous conditions, proton exchange, dialkylation and subsequent dealkylations may lead to equilibration, with the consequent formation of the more stable pyrrole *N*-alkylated products.[16]

In contrast, alkylation of the corresponding anionic systems under mild alkaline conditions occurs smoothly at room temperature, especially in dipolar aprotic solvents, producing good yields of *N*-monoalkylated products. Such conditions have thus found wide use in synthesis.[2] With simple primary and many secondary alkyl halides, alkylation follows second order kinetics (see below) and is generally accepted as involving a S_N2 mechanism. Under these alkaline conditions, the alkylations are essentially irreversible and thus under *kinetic control*. Since single anionic ambident nucleophiles are involved, the alkylation pattern (site selectivity) is determined solely by the relative activation parameters ($\Delta\Delta G^{\ddagger}$) for attack at the alternate pyrrole and pyridine ring nitrogens.

Le Noble[17] has catalogued ten experimental variables that influence the site selectivity of such ambident nucleophiles, but conceptually there are only four or five major factors that are consistently invoked to explain and predict such reactivity patterns. These are:

- *charge control*[18-20],
- *frontier orbital control*[18,22],
- *product development control*[20,21],
- *steric approach control*[23], and in some cases,
- specific association of reactant species[7,24].

The interaction between these factors depends not only on the structural features of the nucleophilic substrate, but also on the detailed nature of the S_N2 transition states for the alkylations.

Changes in the alkylating agent can cause variations in the S_N2 transition state structures which are conveniently classified using More O'Ferrall / Jencks style diagrams[25]. These map the N....C bond making and the C....X bond breaking as independent variables along separate x,y axes; see Figure 1. Variations in the nucleophilicity of the base and the nucleofugacity of the leaving group affect the overall energetics of the alkylation and hence cause movement along the *early / late* diagonal axis. Such variations are well described by the classic Bell-Evans-Polanyi[26] (BEP) approach and also by the more popular Hammond's postulate[27]. Changes in the substituent on the primary alkyl group of the alkylating agent usually do not substantially

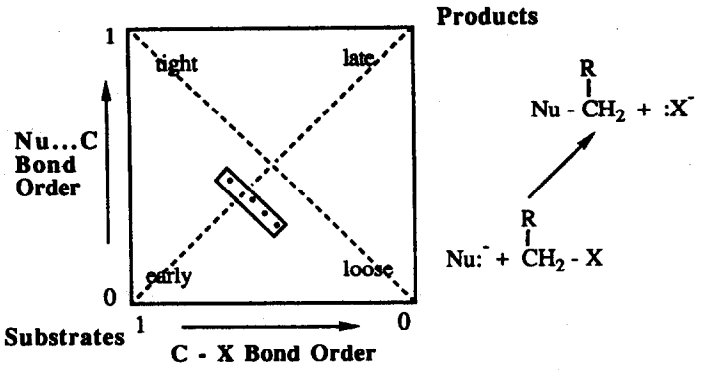


Figure 1. More O'Ferrall / Jencks Diagram of Variable S_N2 Transition States

affect the overall energetics of the alkylation but may induce so-called *perpendicular* effects, which significantly alter the rates. Such effects have been discussed by Thornton[28], Kurz[29], and others[30]. Electron donation or withdrawal at the alkylation centre induces movement along the *loose / tight* diagonal of the variable S_N2 transition state diagram, perpendicular to the early / late diagonal (see Figure 1). Such More O'Ferrall / Jencks diagrams have been used by Albery and Kreevoy[31] and by Lewis[32] to illustrate their extensions of Marcus theory[33] to methylations (methyl group transfers). In an alternate approach, Pross and Shaik have developed a Valence Bond configurational mixing model to describe general organic reactivity, including S_N2 reactions.[34] Thus well developed concepts and descriptions of variable S_N2 transition state structures are now available for interpreting site selectivity of ambident nucleophiles.

Table 1. Alkylation Patterns of Azaindole Anions (**1a-d**) in Dimethylformamide at 30°.

	4-Azaindole anion (**1a**)			5-Azaindole anion (**1b**)			6-Azaindole anion (**1c**)			7-Azaindole anion (**1d**)		
	*N*1	*N*4	ΔΔG‡	*N*1	*N*5	ΔΔG‡	*N*1	*N*6	ΔΔG‡	*N*1	*N*7	ΔΔG‡
tight												
t-BuOCOCH$_2$Cl	100.0	0.0	≥12.0	100.0	0.0	≥12.0	100.0	0.0	≥12.0	100.0	0.0	≥12.0
n-BuBr	92.9	7.1	6.4	94.2#	5.8#	6.9	92.6*	7.4*	6.3	98.0	2.0	9.7
$C_6H_5CH_2Cl$	92.2	7.8	6.1	87.0*	13.0*	4.7	78.5	21.5	3.2	90.7	9.3	5.7
$C_6H_5CH_2OCH_2Cl$	91.5	8.5	5.9	86.5§	13.5§	4.6	83.7	16.3	4.1	89.6§	10.4§	5.3
loose												

Results are % of alkylated material ±1% ; * ± 1.5%; # ± 2%; § ± 3%

$\Delta\Delta G^{\ddagger} = -RT \ln(\%N_X/\%N_1)$ kJ = $-RT \ln(k_{NX}/k_{N1})$ kJ, linearly related to the selectivity factor, S.

The alkylation patterns of the four parent azaindole anions using a standard set of primary alkylating agents, chosen to cover the range from very loose (chloromethyl ether)[35] to tight (chloromethyl ketone and ester)[36] S_N2 transition states, are shown in Table 1. Primary alkylating agents were used to minimize steric factors and favour the S_N2 mechanism. The azaindole anions were produced by reaction with sodium hydride in *N,N*-dimethylformamide or dimethylsulfoxide and reacted with the alkylating agents at 25-30°. These conditions, commonly used for synthesis, give fast clean reactions with smooth second order kinetics involving minimal solvation effects for the anionic heterocyclic systems of interest. In all cases, alkylation of the parent azaindole anions (Table 1) showed dominant reactivity at the pyrrole nitrogen, producing the

thermodynamically preferred *N*1-alkyl isomers in good yields. Increasing, but still minor amounts of alkylation on the pyridine nitrogens (*N*4, 5, 6, or 7) were observed as the transition states became looser.

Menshutkin reactions, involving the quaternization of neutral tertiary amines, have been established as involving relatively early transition states.[37] The reactions of related anionic nitrogen compounds are faster and more exothermic and can thus be expected to proceed via even earlier transition states (BEP analysis, Hammond's Postulate). Such reactions can be expected to show a high degree of charge control and diminished sensitivity to product development control.

Table 2. Energies (Hartrees) of Azaindole Tautomers (**1** ⇌ **2**) and their Anions GAUSSIAN 86 Program: STO-3G (fully optimised geometries)[38]

	4-Azaindole	5-Azaindole	6-Azaindole	7-Azaindole
Anion	-372.08659	-372.08938	-372.08906	-372.08650
n*H*-Azaindole (2)§	-372.74252	-372.74079	-372.74212	-372.74647
1*H*-Azaindole (1)	-372.78021	-372.78055	-372.77925	-372.78549
$\Delta E(nH - 1H)^*$	99.0	104.4	97.5	102.5
ΔE_{prot}#	-1821.1	-1814.7	-1812.1	-1835.2

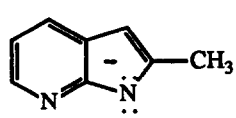
§ n = 4,5,6 or 7 depending on the azaindole system. * Tautomer energy differences, kJ/mol.
# Protonation energies, kJ/mol, for anion → *N*1-H tautomer (1a-d). Hartree = 2625.34 kJ/mol

Table 3. Atom Centre Charges, HOMO Coefficients and Energies of Azaindole Anions GAUSSIAN 86 Program: STO-3G (fully optimised structures)[38]

	4-Azaindole anion		5-Azaindole anion		6-Azaindole anion		7-Azaindole anion	
	*N*1	*N*4	*N*1	*N*5	*N*1	*N*6	*N*1	*N*7
Mulliken charge, q(M)	-0.376	-0.294	-0.376	-0.315	-0.370	-0.317	-0.369	-0.286
Lowdin charge, q(L)	-0.329	-0.212	-0.331	-0.244	-0.321	-0.246	-0.323	-0.205
$\Delta q(M) = (q_{N1}-q_{Nn})$	0.082		0.061		0.053		0.083	
$\Delta q(L) = (q_{N1}-q_{Nn})$	0.114		0.087		0.075		0.118	
σ-HOMO Coefficients	0.74	0.48	0.87	0.17	0.86	0.20	0.75	0.46
$\Delta c(\sigma) = (c_{N1} - c_{Nn})$	0.26		0.70		0.66		0.29	
σ-HOMO energy, kJ/mol	-233.3		-276.2		-280.6		-236.5	
π-HOMO Coefficients	0.54	0.28	0.53	0.20	0.53	0.26	0.54	0.25
$\Delta c(\pi) = (c_{N1} - c_{Nn})$	0.26		0.33		0.27		0.29	
π-HOMO energy, kJ/mol	+30.7		+22.1		+22.3		+28.4	

For quantitative data on the energetics and charge distribution in these heterocyclic systems, we used *ab initio* molecular orbital calculations. Owing to size constraints, calculations were performed at the relatively unsophisticated STO-3G level, albeit on fully optimised geometries.[38] These calculations (Tables 2 and 3) show that the pyrrole NH tautomers are consistently favoured by between 97 and 105 kJ/mol over the pyridine tautomers, e.g. **1a** ⇌ **2a**, and that in the anions the charge density on the nitrogens, along with the frontier (σ and π HOMO) orbital coefficients at these sites, also favour reaction at the pyrrole nitrogens.

Within this coherency there are, however, some discernible patterns. The large energetic preference for pyrrole *N*-substitution is most manifest in the tighter transition states (*t*-butyl chloroacetate), with their advanced N...C bond formation. As the transition states loosen, increasing charge control allows more pyridine *N*-alkylation to occur; charge control, whilst still favouring the pyrrole nitrogens, shows diminished selectivity. Given the coherence of these three factors - charge, product stability, and frontier orbitals - and in the absence of any significant steric differentiation between the two competing sites, it is perhaps surprising to see any significant reaction at the disfavoured pyridine nitrogens.



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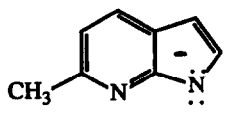

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Table 4. Alkylation Patterns of Methylazaindole Anions (3-5) in Dimethylsulfoxide at 30°

	2-Me-7-Azaindole anion (3)			6-Me-7-Azaindole anion (4)			7-Me-6-Azaindole anion* (5)		
	*N*1% :	*N*7%	ΔΔG‡	*N*1% :	*N*7%	ΔΔG‡	*N*1% :	*N*6%	ΔΔG‡
tight									
t-BuOCOCH$_2$Cl	95.8	4.2	7.75 (≥12.0)#	100.0	0.0	≥12.0 (≥12.0)	97.2	2.8	8.79 (≥12.0)
n-BuBr	87.6	12.4	4.85 (9.6)	100.0	0.0	≥12.0 (9.6)	92.7	7.3	6.30 (6.3)
C$_6$H$_5$CH$_2$Cl	81.0	19.0	3.60 (4.6)	100.0	0.0	≥12.0 (4.6)	87.4	12.6	4.80 (3.2)
C$_6$H$_5$CH$_2$OCH$_2$Cl	74.6	25.4	2.67 (3.5)	100.0	0.0	≥12.0 (3.5)	89.8	10.2	5.39 (4.1)
loose									

* In dimethylformamide at 30°. $\Delta\Delta G^{\ddagger} = -RT \ln(k_{Nx}/k_{N1})$ kJ, linearly related to the selectivity factor, S.

\# The values in parentheses are $\Delta\Delta G^{\ddagger}$ for the parent heterocyclic anions under equivalent solvent and temperature conditions (see Tables 1 and 7).

The alkylation patterns for three methylated pyrrolopyridine anions (3 - 5), under standard conditions, are given in Table 4. As well established in earlier studies[39,40], the introduction of a methyl substituent adjacent to the alkylation site causes significant steric retardation at that site. For 2-methyl-7-azaindole anions (3), the 2-methyl group retards attack at the pyrrolic *N*1 and thus causes a significant increase in reaction at the unaffected pyridine *N*7 site; this effect as measured by the change in selectivity $\delta\Delta\Delta G^{\ddagger} = (\Delta\Delta G^{\ddagger}_{1d} - \Delta\Delta G^{\ddagger}_{3})$ kJ/mol is, as expected, greater in the tighter transition states. A similar retardation of *N*7 attack on 6-methyl-7-azaindole anions (4) is more pronounced owing to the smaller external angle (about 120°) subtended by the *ortho*-methyl N-C-CH$_3$ bond in pyridine rings compared to in pyrrole rings (N-C-CH$_3$ angle about 126°). For the primary alkylating agents tested, 6-methyl-7-azaindole anions (4) reacted exclusively at the unhindered *N*1-site, although for methylation (methyl iodide) a small amount (5%) of attack at the hindered *N*7-site was found. In the 7-methyl-6-azaindole system (5), the 7-methyl group retards attack at both nitrogens, being *ortho* to the pyridine *N*6 and *peri* to the pyrrole *N*1. Interestingly these differing geometries cause a cross over effect; with tight transition states, the pyrrole ring is more affected (enhanced *N*6 attack compared to the parent) and in loose transition states the pyridine ring

is more affected. For the 'central' *n*-butylation, the 7-methylated system shows the same site selectivity as the parent 6-azaindole anion, indicating roughly equivalent steric effects on both nitrogen sites.

Table 5. Benzylation Rates, Selectivities and Basicities of Azaindole Anions.

	4-Azaindole Anion	5-Azaindole Anion	6-Azaindole Anion	7-Azaindole Anion
Rate constant, k_2 (L/mol.sec)*	0.26	0.18	0.13§	0.48
Site Selectivity, $\Delta\Delta G^{\ddagger}$ (kJ)*	6.12	4.71	3.21	5.65
pK_{a1} †	6.94	8.26	7.95	4.59
Protonation Energies# ΔE_{prot} (kJ/mol)	-1821.1	-1814.7	-1812.1	-1832.2

* Benzylation with benzyl chloride in *N,N*-dimethylformamide at 25°, see Table 1; estimated uncertainty ±5%.
§ In dimethylsulfoxide at 36°, the rate constant was 0.26 L/mol.sec
† Acidity of the *N4*, *N5*, *N6*, or *N7*-(pyridine)protonated conjugate acids of the azaindoles.
# *Ab initio* M.O. calculations, *N*1-protonation of the anion; see Table 2. $\Delta E \propto pK_{a2}$ (pyrrole N-H acidity).

The reactivity order for the 4-, 5-, 6-, and 7-azaindole anions was determined by measuring the second order rate constants for benzylation (Table 5) under our standard conditions. There is a reasonable Brønsted relationship (correlation coefficient, R^2 0.96) between the rate constants and the *ab initio* calculated protonation energies (ΔE_{prot}), used in place of the unknown pK_{a2} values (pyrrole ring N-H acidities; pK_{a1} data, involving pyridine ring N basicity, is given in Table 5).[41] The greater reactivity of the 7-azaindole system appears similar to the enhanced reactivity of 1,8-naphthyridine over its isomers[42] and to other heterocycles showing pseudo α-effects[43]. Whilst the origin of the α-effect in nucleophilic reactivity is still debated[44], the most commonly accepted explanation is based on frontier orbital concepts[22], involving lone pair / lone pair interactions raising the σ-HOMO energy. The greater reactivity of the 7-azaindole system is, however, simply in line with the Brønsted relationship with no special enhancement, and the σ-HOMO energies (Table 3), corresponding roughly to the nitrogen lone pair energies, are in the order $4 \geq 7 > 5 \geq 6$. This latter sequence, whilst not giving any support for an α-effect, does match the order, $4 \geq 7 > 5 > 6$, of site selectivities for benzylation of the anions (Tables 1, 5).

The reactivity index, as measured by *log* k_2, shows a good, positive correlation (R^2 0.993) with the site selectivity index [S = *log (k/k')*] for benzylation of the 4-, 5- and 6-azaindole anions, with increased reactivity matched by increased site selectivity. The benzylation of 7-azaindole, however, deviates substantially, being less selective than its reactivity would predict based on this correlation . These pyrrolopyridine anions thus represent yet another example of the failure of the controversial Reactivity Selectivity Principle[45].

The site selectivity of these heterocyclic anions is clearly not dominated by the protonation energies, but does show good correlation with the charge density differentials, $\Delta q = (q_{N1} - q_{Nn})$ both Mulliken and Lowdin, listed in Table 3. This is in keeping with Gompper's allopolarization concepts.[19] The calculated σ-HOMO coefficient differentials at the nitrogens (Table 3) show a negative correlation with site selectivity within each heterocycle and there is no correlation of the σ or π HOMO energies with the substrate reactivity pattern (*log* k_2). Thus frontier orbital control does not appear to be a significant factor in these systems.

Table 6. Leaving Group Effects: Benzylation of Azaindole Anions in Dimethylformamide at 30°.

	4-Azaindole anion			5-Azaindole anion			6-Azaindole anion			7-Azaindole anion		
	*N*1	*N*4	ΔΔG‡	*N*1	*N*5	ΔΔG‡	*N*1	*N*6	ΔΔG‡	*N*1	*N*7	ΔΔG‡
$C_6H_5CH_2Cl$	92.2	7.8	6.1	87.0*	13.0*	4.7	78.5	21.5	3.2	90.7	9.3	5.7
$C_6H_5CH_2Br$	91.9*	8.1*	6.0	86.2#	13.8#	4.5	79.7	20.3	3.4	90.0	10.0	5.5
$C_6H_5CH_2I$	91.0§	9.0§	5.7	87.5#	12.5#	4.8	77.2	22.8	3.0	87.7	12.3	4.9
$C_6H_5CH_2OTs$	88.5	11.5	5.1	86.0#	14.0#	4.5	77.2	22.8	3.0	86.3	13.7	4.6

Results are % of alkylated material ±1% ; * ± 1.5%; # ± 2%; § ± 3%. OTs = tosylate.
$\Delta\Delta G^{\ddagger} = -RT \ln(\%N_X/\%N_1)$ kJ $= -RT \ln(k_{NX}/k_{N1})$ kJ, linearly related to the selectivity factor, S.

Table 6 contains the results of benzylations of the four parent pyrrolopyridine anions with various benzyl leaving groups. The two, more reactive 7- and 4-azaindole anions, show a slight leaving group sensitivity, with increasing amounts of the less stable pyridine *N*-alkylated products formed with the more reactive benzylating agents. The effects are small, however, and benzylations of the less reactive 5- and 6-azaindole anions do not show any significant leaving group effect. This is surprising given the significant differences in reactivity between these benzylations with different leaving groups. Such reactivity changes should cause some shift along the early / late axis (Fig. 1) and thus changes in the charge / thermodynamic control balance. Berg *et al.* have, however, indicated that significant movements of the transition state structures in such series may occur only with very large rate changes.[46] Similar insensitivity to leaving group effects has been recorded in other heterocyclic ambident nucleophiles.[5,47] In these azaindoles, the 4- and 7-isomers and the 5- and 6-isomers are bundled together in keeping with the leaving group effects, but based on differences in both σ-HOMO coefficients and energies (Table 3), one would expect the 5,6 pair to be more sensitive than the 4,7 pair to leaving group effects. Again the frontier orbital approach seems to be inadequate to explain the reactivity differences here.

Table 7. Alkylation Patterns of Azaindole Anions (**1a-d**) in Dimethylsulfoxide at 30°.

	4-Azaindole anion			5-Azaindole anion			6-Azaindole anion			7-Azaindole anion		
	*N*1	*N*4	ΔΔG‡	*N*1	*N*5	ΔΔG‡	*N*1	*N*6	ΔΔG‡	*N*1	*N*7	ΔΔG‡
tight												
t-$BuOCOCH_2Cl$	100.0	0.0	≥12.0	75.0§	0.0[a]	≥12.0	79.0	0.0[b]	≥12.0	100.0	0.0	≥12.0
n-BuBr	89.5	10.5	5.3	92.0#	8.0#	6.1	89.9*	10.1*	5.4	98.0	2.0	6.1
$C_6H_5CH_2Cl$	89.8	10.2	5.4	84.4*	15.6*	4.2	68.0§	11.0§[c]	5.2	86.6	13.4	4.6
$C_6H_5CH_2OCH_2Cl$ loose	48.5	51.5	-0.1	22.5§	77.5§	-3.1	8.0	92.0	-6.1	80.1§	19.9§	3.5

Results are % of alkylated material ±1% ; * ± 1.5%; # ± 2%; § ± 3%.
[a] 25.0±5% *N*1,*N*5-dialkylated product detected. [b] 21.0±1% *N*1,*N*6-dialkylated product detected.
[c] 22.0±5% *N*1,*N*6-dialkylated product detected.

The results of an alkylation study on the parent pyrrolopyridine anions in the other commonly used dipolar aprotic solvent, dimethylsulfoxide, are shown in Table 7. Whilst the trends are similar to those found in dimethylformamide, see Table 1, the reactions are about twice as fast (Table 5 footnote) and there is a general increase in pyridine *N*-alkylation which is most dramatic in reactions with benzyl chloromethyl

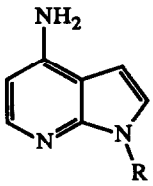
ether. In benzyloxymethylations, three of the four systems now show dominant pyridine *N*-alkylation giving the less stable isomers as the major products! Also in several cases, involving benzylation and reaction with *t*-butyl chloroacetate, substantial amounts of dialkylated products were observed. The latter products were easily identified by their characteristic ultraviolet, infrared and ^{1}H n.m.r. spectra. These dialkylated materials are most probably derived from the corresponding pyridine *N*-mono-alkylated precursors. Evidence for this comes both from theoretical and experimental considerations. Alkylation of the neutral, un-ionized heterocycles (exclusive pyrrole NH tautomers) in dimethylformamide and dimethylsulfoxide requires 4 - 5 hours at 140 - 160° to achieve moderate yields of the quaternary salts; reaction rates at room temperature are negligible.[16] The corresponding pyrrole *N*-alkylated isomers should show similar low reactivities. Also the pyridine NH tautomers (hence the corresponding *N*-R isomers as well) are calculated to be less stable (Table 2) and to have a higher basicity (see ΔE_{prot}, Table 2) which should mean a greater nucleophilic reactivity (Brønsted relationship).[41] Thus the di-alkylated fraction in dimethylsulfoxide should be included with the pyridine *N*-alkyl percentage, further enhancing the fraction of initial mono-alkylation at these thermodynamically disfavoured sites in this solvent.

The absence of dialkylation with 4- and 7-azaindole anions and with *n*-butyl bromide and benzyl chloromethyl ether was puzzling. The 5- and 6-azaindole anions are less reactive towards initial mono-alkylation (Table 5), but once formed these mono-alkylated products are then expected to be more reactive towards further alkylation than those derived from the 4- and 7-azaindole isomers which would be sterically retarded. Thus the pK_{a1} values (Table 5), 5-AI (8.26) > 6-AI (7.95) > 4-AI (6.94) >> 7-AI (4.59), indicate a greater reactivity of the 5- and 6-azaindole systems towards quaternization and the pyridine *N*-substituted systems are expected to have higher pK_as than their corresponding pyrrole *N*1-substituted isomers (the pK_{a1} values in Table 5 correspond to the *N*1-H tautomers).[41] Whilst the lower reactivity of *n*-butyl bromide may explain the absence of dialkylation with this reagent, a similar absence with the most reactive chloromethyl ether and the abnormally high percentage of pyridine *N*-alkylation with this reactive reagent require further consideration. Paradoxically the very high reactivity of the chloromethyl ether appears to provide the answer. Benzyl chloromethyl ether reacts readily with the dimethylsulfoxide solvent (but not so readily with dimethylformamide), giving $PhCH_2OCH_2OS(CH_3)_2^+$; this reaction can be conveniently followed by ^{1}H n.m.r. which shows extensive reaction within 15-20 min at room temperature. The sulfoxonium cationic species is also an alkylating agent, and with such a large change in leaving group and charge character of the transition state for alkylation, a significant change in site selectivity may be expected.[48] The amount of pyridine *N*-alkylation (Table 7) now matches the charge density order at the pyridine nitrogens, i.e. N6- ≥ N5- > N4- > N7- (see Table 3) and is in keeping with a substantive increase in charge control for a very early transition state with a highly polar leaving group, although the extent of enhancement of charge control was unexpected.

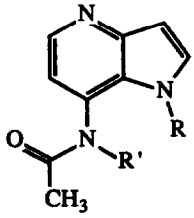
Finally as a model for alkylation of adenine and 6-acyladenine systems, which we had earlier found to exhibit unusual alkylation reactivity[3-6], we examined the alkylation of 4-amino-7-azaindole (**6b**) and 7-acetamido-4-azaindole anions, (**7b/c**).

Alkylation of 4-amino-7-azaindole anions (**6b**) with the standard set of alkylating agents showed an enhanced amount of attack at the pyridine *N*7-site when compared to the parent 7-azaindole system (**1d**): *N*1/*N*n ratios: *t*-BuOCOCH$_2$Cl 95.9:4.1 (100:0), *n*-BuBr 93.0:7.0 (98:2), $C_6H_5CH_2Cl$ 82.9:17.1 (94.5:5.5), $C_6H_5CH_2OCH_2Cl$ 85.5:14.5 (89.6:10.4), the ratios in parenthesis are for the parent system **1d**.

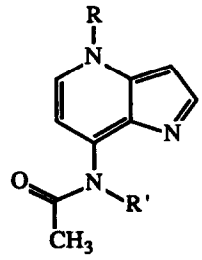
This is consistent with activation of the *N*7-site by the electron donating *para*-amino group. The effect is, however, not very large especially when compared to the significant increase in basicity of pyridine (pK_a 5.2) caused by introducing a 4-amino group (4-aminopyridine: pK_a 9.1).



6a R=H
b R=:
c R=$CH_2C_6H_5$



7a R=R'=H
b R=: R'=H
c R=H R'=:
d R=^{t}BuOCOCH$_2$ R'=H



8a R=$C_6H_5CH_2$ R'=H
b R=R'=$C_6H_5CH_2$
c R=^{t}BuOCOCH$_2$ R'=H
d R=R'=^{t}BuOCOCH$_2$

With only small amounts of 7-acetamido-4-azaindole (**7a**) available[13], its alkylation reactions were restricted to benzylation and reaction with *t*-butyl chloroacetate under standard conditions in dimethylformamide. Benzylation unexpectedly gave no pyrrole *N*1-alkylation, giving instead a mixture of 88.6% *N*4-mono- and 11.4% *N*4,*N*7'-dibenzylated products (**8a, 8b** respectively). Reaction with -butyl chloroacetate showed a more 'normal' pattern, 68.6% *N*1-mono-, 13.6% *N*4-mono-, and 17.8% *N*4,*N*7'-dialkylation (**7d, 8c,** and **8d** respectively), although dialkylation had not been observed in the earlier reactions in dimethylformamide (Tables 1, 6, and 8), only in the more polar dimethylsulfoxide (Table 7).

7-Acetamido-4-azaindole, **7a**, has two acidic protons and can thus form a dianion. It is unlikely, however, that dianions are involved as the alkylation pattern was unchanged in alkylations with sodium hydride / heterocycle ratios of from 1:1 to 20:1. Estimates of the relative pK_as of the pyrrole NH and the amide NH of **7a** (based on literature values for related systems) indicate they should be close. Thus either, or more likely both mono-anions, **7b** and **7c**, may be formed under the basic conditions, with the tautomeric proton shift between the two nitrogen sites expected to be very facile given the small nuclear motion required.

Benzylation of **7b** at the pyrrole *N*1-site should be retarded by the bulky peri 7-acetamido group (hydrogen bonded to a solvent molecule) thus leaving the pyridine *N*4 site to react preferentially. Alternately, and more likely, benzylation at **7b** should preferentially occur at *N*4 for inherent reactivity reasons as well as a steric retardation of reaction at the amide nitrogen. The 4,7'-dibenzylation requires a proton exchange reaction to generate the mono-anion of the 4- (or less likely the 7'-) mono-alkylated system, which then reacts further.

The corresponding reactions with *t*-butyl chloroacetate are modified by hydrogen bonding association with the amide NH on **7b**. This specifically enhances attack at the adjacent pyrrole *N*1 site, with a slight rotation of the 7-amido group out of the aromatic ring plane allowing the hydrogen bond to be maintained during the alkylation transition state. Similar enhanced reactivity adjacent to hydrogen bonding groups have been previously reported in reactions of phenacyl halides.[49] Alkylation of the alternate anion, **7c**, should however favour the pyridine *N*4 site, as now a similar rotation is not possible and a *N*1-H hydrogen

bond cannot be maintained to the reagent whilst achieving proper geometry for alkylation at the adjacent 7-amido nitrogen. Thus a mixture of *N*4- and *N*1-mono-alkylation occurs. Again some of the *N*4-mono-alkylated product must undergo proton exchange and further alkylation to the 4,7'-dialkylated product. The *N*1-mono-alkylated product would be less prone to proton exchange as the steric congestion at the *N*1 / 7-region would force the 7-amido group out of conjugation with the pyridine ring, substantially diminishing the amido acidity.

CONCLUSIONS

Significant charge control in relatively early transition states permits substantial amounts of pyridine *N*-alkylation to occur in the pyrrolopyridine systems investigated, despite large thermodynamic energy disadvantages compared to pyrrolic *N*-alkylation. Changing the alkylating agent causes small variations on this basic pattern consistent with the changing loose/tight nature of the S_N2 transition states involved; increasing tightness causes more product development control and hence more pyrrolic alkylation. As found in related heterocycles[39], these systems show significant sensitivity to steric effects from adjacent methyl substituents. Leaving group modifications, whilst causing substantial rate changes, are ineffective in altering the alkylation pattern. Frontier orbital factors appear to have little influence in these reactivity patterns. Alkylation of the pyrrolopyridine systems showed some solvent differences between dimethylformamide and dimethylsulfoxide, particularly with benzyl chloromethyl ether; the more polar dimethylsulfoxide supports enhanced reaction at the pyridine nitrogens. As found in previous studies[3,5], significant variations in alkylation patterns may be induced by specific associative effects between the two reactants when they have hydrogen bonding donor and acceptor groups in an appropriate geometrical relationship.

EXPERIMENTAL

Materials:

The azaindoles were synthesized by previously reported routes.[13] Commercial samples of benzyl chloride, benzyl bromide, and *n*-butyl bromide were distilled before use and phenacyl chloride was recrystallized from petroleum. Benzyl tosylate[50], benzyl iodide[51], benzyl chloromethyl ether[52], and *t*-butyl chloroacetate[53] prepared according to literature procedures were used directly, after establishing their purity by ^{1}H n.m.r. spectroscopy. The solvents, *N,N*-dimethylformamide and dimethylsulfoxide, were dried and purified using the procedures of Perrin *et al.* [54] and stored under dry nitrogen, over 4Å molecular sieves.

General Alkylation Procedure

All alkylation reactions were performed at 25-28°, under dry nitrogen. The appropriate azaindole (about 80 mg for c.w. and 40 mg for p.f.t. n.m.r. analysis) was dissolved in dimethylformamide (30 - 50 mL). A 10 - 15% molar excess of sodium hydride was added, and the contents stirred for about 45 min to obtain a homogeneous solution. The alkylating agent (RCH_2X; 95% mole equivalent by weight) in dimethylformamide (5 mL) was then added and the resulting solution left for 3 hr. Dimethylformamide was removed by co-distillation with toluene (3 × 30 mL) (rotary evaporator, about 50°), the residue thus

obtained was dissolved in chloroform or dichloromethane (about 30 mL), and extracted with saturated sodium carbonate solution (2 × 15 mL). The oil obtained after evaporation of the dried organic layer was analysed by thin layer chromatography (silica gel, 20% ethanol / chloroform) and ^{1}H n.m.r. spectroscopy. The toluene distillates containing dimethylformamide, and the aqueous sodium carbonate extracts were checked by uv. spectroscopy to confirm the absence of the alkylated materials.

Alkylation reactions in dimethylsulfoxide were similar to those described above, except for a different work-up procedure. Typically, after 3 hr, 30 mL of chloroform was added to the reaction mixture and the resulting solution was repeatedly extracted with saturated sodium carbonate solution (6 × 30 mL) until there was no change in the volume of the chloroform layer. ^{1}H n.m.r. and t.l.c. analyses were carried out on the oil / solid that was obtained on evaporation of the dried organic layer. The sodium carbonate extracts were combined, and checked by uv. spectroscopy for the absence of the alkylated materials.

All alkylation reactions were performed in duplicate and the results averaged. Reproducibility of alkylation product ratios was generally ±0.5%.

Quantitative Analyses

The relative proportions of the two isomers in the crude product mixture were estimated by quantitative ^{1}H n.m.r. spectroscopy, either by the cut and weigh technique (c.w. ^{1}H n.m.r. spectroscopy, 100 MHz Minimar Jeol) or by a computer generated listing of the integral intensities (p.f.t.^{1}H n.m.r. spectroscopy, Varian XL-200E) of the *N*-methylene signals. Careful precautions were taken to avoid saturation and other problems affecting quantitative n.m.r. measurements.

Most alkylation mixtures were also subjected to preparative t.l.c. or radial chromatography separation (silica gel, 10-20% ethanol / chloroform) and the individual isomers characterised by mass spectrometry, uv. and ^{1}H n.m.r. spectroscopy. The spectral details of the benzylated azaindole isomers are reported below. The minor pyridine ring *N*-benzylated isomers were independently synthesized by alkylation under neutral conditions (see below) to give reference samples for t.l.c. and spectral comparison.

N*1-Benzyl-4-azaindole*

Isolated by column chromatography (alumina, chloroform) eluted first; recrystallized from petroleum /benzene as pale yellow prisms, m.p. 81-83°. (Found: mol wt 208.1001. $C_{14}H_{12}N_2$ requires mol wt 208.1000). Mass spectrum: m/z 209 (5%), 208 (M^+, 34), 207 (4), 131 (2), 92 (8), 91 ($C_6H_5CH_2^+$, 100), 77 (2), 65 (15), 51 (3). Uv., λ_{max} (H_2O) nm: 291; (pH 2) 288, 333; (pH 12) 293. ^{1}H n.m.r. ($CDCl_3$) δ 8.47 (d, 1H, $J_{5,6}$ = 4.8 Hz, H-5), 7.55 (d, 1H, $J_{7,6}$ = 8.2 Hz, H-7), 7.37 (d, 1H, $J_{2,3}$ = 3.2 Hz, H-2), 7.32 - 7.00 (m, 6H, C_6H_5, H-6), 6.76 (d, 1H, $J_{3,2}$ = 3.2 Hz, H-3), 5.32 (s, 2H, N-CH_2).

N*4-Benzyl-4-azaindole*

4-Azaindole (0.1 g, 0.85 mmol) was dissolved in dry dimethylformamide (2 mL), benzyl chloride (0.11 g, 0.85 mmol) in dimethylformamide (1 mL) was added and the mixture heated at 140° (bath temperature) for 6 hr. The dimethylformamide was removed by codistillation with toluene, the residue dissolved in dichloromethane (30 mL), and extracted with saturated sodium carbonate solution (2 × 15 mL). Evaporation of the dried organic layer gave a yellow residue (0.24 g) which was purified by

chromatography on alumina (16 g). Initial elution with chloroform removed unreacted starting material; the slowest moving yellow band was then eluted with 10% ethanol / chloroform to afford 0.18 g (100%) of a yellow-brown oil which could not be crystallized but was distilled onto a cold-finger (bath temperature 160 °C, 0.1 mm) to give a heavy yellow oil. (Found: mol wt 208.1001. $C_{14}H_{12}N_2$ requires mol. wt. 208.1000). Mass spectrum: m/z 209 (13%), 208 (M^+, 63), 207 (16), 180 (2), 104 (4), 92 (21), 91 ($C_6H_5CH_2^+$, 100), 89 (9), 78 (2). Uv., λ_{max} (H_2O) nm: 288, 332; (pH 2) 286, 333.(pH 12) 298, 370. ^1H n.m.r. ($CDCl_3$) δ 8.29 (d, 1H, $J_{2,3}$ = 1.8 Hz, H-2), 8.24 (d, 1H, $J_{7,6}$ = 7.8 Hz, H-7), 7.63 (d, 1H, $J_{5,6}$ = 6.2 Hz, H-5), 7.40 - 7.20 (m, 5H, C_6H_5), 6.98 (dd, 1H, $J_{6,7}$ = 7.8 Hz, $J_{6,5}$ = 6.2 Hz, H-6), 6.48 (d, 1H, $J_{3,2}$ = 1.8 Hz, H-3), 5.57(s, 2H, N-CH_2).

N*1-Benzyl-5-azaindole*

Isolated by column chromatography (alumina, chloroform), eluted first. Recrystallization from cyclohexane produced pale yellow prisms, m.p. 61-62°. (Found: C, 80.9; H, 5.9; N, 13.3. $C_{14}H_{12}N_2$ requires C, 80.7; H, 5.8; N, 13.5%). Mass spectrum: m/z 209 (4%), 208 (M^+, 24), 104 (1), 92 (8), 91 ($C_6H_5CH_2^+$, 100), 77 (2), 65 (16), 63 (4), 57 (2), 51 (3). Uv., λ_{max} (H_2O) nm: 270; (pH 2) 275, 295 (sh); (pH 12) 270. ^1H n.m.r. ($CDCl_3$) δ 8.82 (s, 1H, H-4), 8.15 (d, 1H, $J_{6,7}$ = 5.8 Hz, H-6), 7.20 - 6.80 (m, 7H, C_6H_5, H-7, H-2), 6.50 (d, 1H, $J_{3,2}$ = 3 Hz, H-3), 5.12 (s, 2H, N-CH_2).

N*5-Benzyl-5-azaindole*

A mixture of benzyl chloride (0.11 g, 0.85 mmol), dimethylformamide (~3 ml) and 5-azaindole (0.1 g, 0.85 mmol) was heated at 140° (bath temperature) for 6 hr. Dimethylformamide was removed by codistillation with toluene, the resulting residue dissolved in dichloromethane (25 mL), (pale yellow solution), and extracted with saturated sodium carbonate solution (2x15 mL). Evaporation of the dried organic layer afforded a pale yellow oil (0.2 g) which solidified on standing. It was purified by chromatography on alumina (25 g). Initial elution with chloroform removed parent heterocycle. The pale yellow band was then eluted with 20% ethanol / chloroform to give a pale yellow solid (0.17 g, 96%). Recrystallization from benzene/cyclohexane furnished *5-benzyl-5-azaindole*, as small yellow needles, m.p. 136-137°. (Found: C, 81.0; H, 5.8; N, 13.4. $C_{14}H_{12}N_2$ requires C, 80.7; H, 5.8; N, 13.5%). Mass spectrum: m/z 209 (4%), 208 (M^+, 26), 118 (2), 104 (1), 92 (8), 91 ($C_6H_5CH_2^+$, 100), 89 (2), 65 (14), 51 (3). Uv., λ_{max} (H_2O) nm: 268, 295 (sh); (pH 2) 268, 295 (sh); (pH 12) 278, 310 (sh). ^1H n.m.r. ($CDCl_3$) δ 8.36 (d, 1H, $J_{4,7}$ =1.8 Hz, H-4), 8.05 (d, 1H, $J_{2,3}$ = 2.4 Hz, H-2), 7.69 (d, 1H, $J_{6,7}$ = 7 Hz, H-6), 7.50 (dd, 1H, $J_{7,4}$ = 1.8 Hz, $J_{7,6}$ = 7 Hz, H-7), 7.45 - 7.10 (m, 5H, C_6H_5), 6.80 (d, 1H, $J_{3,2}$ = 2.4 Hz, H-3), 5.42 (s, 2H, N-CH_2).

N*1-Benzyl-6-azaindole*

Isolated by column chromatography (alumina, chloroform). Crystallization from cyclohexane furnished colourless crystals, m.p. 79-81°. (Found: C, 80.4; H, 6.1; N, 13.0. $C_{14}H_{12}N_2$ requires C, 80.7; H, 5.8; N, 13.5%). Mass spectrum: m/z 209 (3%), 208 (M^+, 21), 104 (1), 92 (6), 91 ($C_6H_5CH_2^+$, 100), 89 (1), 65 (13), 57 (1). Uv., λ_{max} (95% EtOH) nm: 261, 267 (sh), 300; (pH 2) 265, 270 (sh), 331; (pH 12) 261, 268 (sh), 300. ^1H n.m.r. ($CDCl_3$) δ 8.75 (s, 1H, H-7), 8.27 (d, 1H, $J_{5,4}$ = 5.5 Hz, H-5), 7.56 (d, 1H, $J_{4,5}$ = 5.5 Hz, H-4), 7.40 - 7.10 (m, 6H, C_6H_5, H-2), 6.56 (d, 1H, $J_{3,2}$ = 3.0 Hz, H-3),

5.41 (s, 2H, N-CH_2). ^{1}H n.m.r. (C_6D_6) δ 8.80, 8.60 (2bs, 2H, 2 ring protons), 7.40 - 6.20 (m, 8H, C_6H_5 and three ring protons), 4.48 (s, 2H, N-CH_2).

N*6-Benzyl-6-azaindole*

A mixture of 6-azaindole (0.0925 g, 0.78 mmol), dimethylformamide (~3 ml) and benzyl chloride (0.0993 g, 0.78 mmol) was heated at 140 °C (bath temperature) for 4 hr. The resulting brown liquid was evaporated to dryness with toluene, the residue taken up in dichloromethane (25 ml), extracted with saturated sodium carbonate solution (2x15 ml) and the yellow-brown organic layer dried. The pale brown solid (0.19 g) obtained on removal of the solvent, was purified on alumina (25 g). After removing parent heterocycle with chloroform, *6-benzyl-6-azaindole* was eluted with 20% ethanol / chloroform to furnish a pale brown solid (0.13 g, 82%). Crystallization from benzene-cyclohexane gave pale yellow needles, m.p. 125-127°. (Found: C, 80.9; H, 5.9; N, 13.4. $C_{14}H_{12}N_2$ requires C, 80.7; H, 5.8; N, 13.5%). Mass spectrum: m/z 209 (3%), 208 (M^+, 17), 118 (3), 104 (1), 92 (8), 91 ($C_6H_5CH_2^+$, 100), 89 (2), 78 (1), 65 (15), 63 (5), 51 (3). Uv., λ_{max} (95% EtOH) nm: 270, 275, 340; (pH 2) 270, 275, 327; (pH 12) 280, 355. ^{1}H n.m.r. ($CDCl_3$) δ 8.49 (s, 1H, H-7), 8.37 (d, 1H, $J_{2,3}$ = 1.4 Hz, H-2), 7.62 (d, 1H, $J_{5,4}$ = 6.8 Hz, H-5), 7.50 - 7.15 (m, 6H, C_6H_5, H-4), 6.74 (d, 1H, $J_{3,2}$ = 1.4 Hz, H-3), 5.41 (s, 2H, N-CH_2). ^{1}H n.m.r. (C_6D_6) δ 8.70 (bs, 1H, ring proton), 8.22 (bs, 1H, ring proton), 7.20 - 6.20 (m, 8H, C_6H_5 and three ring protons), 4.18 (s, 2H, N-CH_2).

N*1-Benzyl-7-azaindole*

Isolated by column chromatography (alumina, chloroform), eluted first as a pale yellow oil (42 mg). (Found: mol wt 222.1158. $C_{15}H_{14}N_2$ requires mol wt 222.1157). Mass spectrum: m/z 223 (4%), 222 (M^+, 24), 145 (1), 131 (1), 111 (2), 104 (2), 92 (7), 91 ($C_6H_5CH_2^+$, 100), 85 (2), 77 ($C_6H_5^+$, 2), 65 (10). Uv., λ_{max} (95% EtOH) nm: 260, 269 (sh), 295, 304 (sh); (pH 12) 260, 269 (sh), 296, 304 (sh); (pH 2) 260, 324. ^{1}H n.m.r. ($CDCl_3$) δ 8.13 (d, 1H, $J_{5,4}$ = 5.5 Hz, H-5), 7.43 (d, 1H, $J_{4,5}$ = 5.5 Hz, H-4), 7.40 - 6.80 (m, 5H, C_6H_5), 7.21 (d, 1H, $J_{2,3}$ = 3.1 Hz, H-2), 6.57 (d, 1H, $J_{3,2}$ = 3.1 Hz, H-3), 5.61 (s, 2H, N-CH_2), 2.75 (s, 3H, 7-CH_3). ^{1}H n.m.r. (C_6D_6) δ 8.42 (d, 1H, $J_{5,4}$ = 5.5 Hz, H-5), 7.32 (d, 1H, $J_{4,5}$ = 5.5 Hz, H-4), 7.00 - 6.50 (m, 6H, C_6H_5, H-2), 6.37 (d, 1H, $J_{3,2}$ = 3.0 Hz, H-3), 4.82 (s, 2H, N-CH_2), 2.64 (s, 3H, 7-CH_3).

N*7-Benzyl-7-azaindole*

Isolated by column chromatography (alumina, chloroform) as a deep-brown solid (5 mg). (Found: mol wt 222.1158. $C_{15}H_{14}N_2$ requires mol wt 222.1157). Mass spectrum: m/z 223 (4%), 222 (M^+, 20), 149 (10), 145 (1), 132 (3), 131 (2), 125 (2), 111 (4), 104 (3), 97 (5), 92 (9), 91 ($C_6H_5CH_2^+$, 100), 85 (5), 83 (5), 77 ($C_6H_5^+$, 3), 71 (9), 65 (13), 63 (5), 57 (15). Uv., λ_{max} (95% EtOH) nm: 275, 283 (sh), 326; (pH 2) 270, 320 ; (pH 12) 284, 350. ^{1}H n.m.r. ($CDCl_3$) δ 8.20 (d, 1H, $J_{2,3}$ = 2.2 Hz, H-2), 7.63 (2d, J = 6.7 Hz, H-4, H-5), 7.50 - 7.00 (m, 5H, C_6H_5), 6.75 (d, 1H, $J_{3,2}$ = 2.2 Hz, H-3), 5.50 (s, 2H, N-CH_2), 3.10 (s, 3H, 7-CH_3). ^{1}H n.m.r. (C_6D_6) δ 8.66 (d, 1H, $J_{2,3}$ = 1.3 Hz, H-2), 8.45 (d, 1H, $J_{5,4}$ = 5.6 Hz, H-5), 7.35 (d, 1H, $J_{4,5}$ = 5.6 Hz, H-4), 7.00 - 6.20 (m, 6H, C_6H_5, H-3), 4.23 (s, 2H, N-CH_2), 2.55 (s, 3H, 7-CH_3).

N4-Benzyl-7-(N-benzylacetamido)-4-azaindole

Isolated by radial chromatography (alumina, chloroform); eluted first as a yellow gum (~2 mg). (Found: mol wt 355.1685. $C_{23}H_{21}N_3O$ requires mol wt 355.1685). Mass spectrum: m/z 356 (3%), 355 (M^+, 10), 278 (4), 222 (10), 149 (41), 133 (3), 111 (11), 105 (3), 97 (19), 95 (11), 92 (9), 91 ($C_6H_5CH_2^+$, 100), 85 (23), 71 ($C_6H_5^+$, 39), 69 (24), 65 (13), 57 (57), 43 (CH_3CO^+, 53). Uv., λ_{max} (H_2O) nm: 258, 295, 338; (pH 2) 258, 295, 337; (pH 12) 304, 338. ^{1}H n.m.r. ($CDCl_3$) δ 7.84 (d, 1H, $J_{5,6}$ = 7.3 Hz, H-5); 7.60 - 7.00 (m, 12H, 2xC_6H_5, H-6, H-2), 6.20 (d, 1H, $J_{3,2}$ = 3.2 Hz, H-3), 6.16 (s, 2H, N-CH_2), 5.30 (s, 2H, N-CH_2), 2.26 (s, 3H, $COCH_3$). Ir. ($CHCl_3$) ν_{max} 1650 cm^{-1} (tertiary amide).

7-Acetamido-N4-benzyl-4-azaindole

Isolated by radial chromatography (alumina, chloroform); the second band gave a yellow oil (14 mg). (Found: mol wt 265.1215. $C_{16}H_{15}N_3O$ requires mol wt 265.1215). Mass spectrum: m/z 266 (2%), 265 (M^+, 10), 250 (8), 223 (12), 222 (8), 148 (10), 133 (2), 105 (3), 97 (3), 91 ($C_6H_5CH_2^+$, 100), 85 (3), 69 (4), 65 (13), 57 (9), 55 (5), 43 (CH_3CO^+, 15). Uv., λ_{max} (H_2O) nm: 255, 292, 320 (b); (pH 2) 255, 293, 325; (pH 12) 307, 333. ^{1}H n.m.r. ($CDCl_3$) δ 8.17 (d, 1H, $J_{5,6}$ = 7.0 Hz, H-5), 7.92 (d, 1H $J_{2,3}$ = 2.0 Hz, H-2), 7.60 (d, 1H, $J_{6,5}$ = 7.0 Hz, H-6), 7.45 - 7.10 (m, 5H, C_6H_5), 6.42 (d, 1H, $J_{3,2}$ = 2.0 Hz, H-3), 5.49 (s, 2H, N-CH_2), 2.34 (s, 3H, $COCH_3$). Ir. ($CHCl_3$) ν_{max} 3300 (b, NH), 1670, 1580, and 1300 cm^{-1} (secondary amide).

Kinetic Measurements

The azaindoles (50 - 60 mg) were reacted with freshly prepared, equimolar amounts of sodium ethoxide (sodium in dry ethanol, 5 mL) under nitrogen. Ethanol was removed by codistillation with toluene and the white solid dried (0.05 mm, 0.5 hr, room temp.). The sodium salts were then dissolved in dry *N,N*-dimethylformamide or dimethylsulfoxide (40 mL) and thermally equilibrated in a constant temperature water-bath (25.0°). Benzyl chloride (1 equivalent in 5 mL dry *N,N*-dimethylformamide or dimethylsulfoxide) was also equilibrated in the water-bath for 0.5 hr. The two reactant solutions were rapidly mixed and homogenized. At known intervals over a one hour period, 1.6 mL aliquots of the reaction mixture were withdrawn and quenched with glacial acetic acid (1 mL). These aliquots were then analysed by h.p.l.c. using a 12.5 × 0.45 cm spherisorb S5 ODS2 column using gradient elution with mixtures of 80:20 water/acetonitrile and 70:30 water/acetonitrile containing 0.5% triethylamine and pH adjusted to 2.8 with phosphoric acid. Standard solutions were injected for calibration purposes at the beginning, in the middle, and at the end of each series of h.p.l.c. measurements. The rate constants, k_2, were calculated from a least squares regression analysis using the second order rate law equation.

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