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PROTON MAGNETIC RESONANCE SPECTRA OF CINNOLINES

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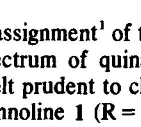
Abstract—The ^1H NMR spectra of cinnoline and some 8-substituted derivatives **1** in DMSO-d_6 are reported. A previous assignment of the chemical shifts of the heterocyclic ring protons H-3 and H-4 is confirmed by deuteration studies. The variations in the chemical shifts of H-3 to H-7 are discussed in terms of (a) solvent effects, (b) the perturbation effect of the heterocyclic ring, and (c) the electronic and proximity effects of the 8-substituents, using single-parameter (SCS_o, SCS_m, SCS_p, σ_o, σ_m, σ_p, σ_p^+, $\sigma_{4,1}$, $\sigma_{5,1}$, $\sigma_{6,1}$, Q) and dual-parameter (F, R; σ_I, σ_R) treatments to correlate the data. Marked proximity effects on H-7 are noted for the nitro and acetamido groups, and are correlated with conformational changes due to interaction of the groups with the N-1 lone pair. Variations in the coupling constants are attributed to partial double-bond fixation.

The ^1H chemical shifts and coupling constants of cinnoline, **1** (R = H), in $(CH_3)_2CO$[1] and $CDCl_3$[2] have been reported, but data for monosubstituted cinnolines, and hence substituent effects, are few and incomplete.[3] Here we report and analyse the ^1H NMR spectra of cinnoline and some 8-substituted derivatives **1** in DMSO-d_6, which has been used as the solvent in a number of related heteroaromatic ^1H NMR studies,[4-6] and is a suitable solvent for the study of substituent effects due to its ability to enhance these effects.[7]



1

RESULTS

The chemical shifts and coupling constant are presented in Table 1.

Since the original assignment[1] of the lowest-field signal in the ^1H NMR spectrum of quinazoline had required correction,[4] it was felt prudent to check the corresponding assignment in cinnoline **1** (R = H).[1] Confirmation of the assignment to H-3 was achieved by deuterium labelling at C-4 in **1** (R = H). This resulted in the collapse of the signal at τ 0.56 ppm from a doublet to a singlet, and in the disappearance of the signal at τ 1.75 ppm (Table 1; R = H).

The ABC system of **1** (R = Me) could not be analysed completely even at 220 MHz; only the chemical shift data could be obtained with precision. Similarly, the ABCX system of **1** (R = F) could not be analysed at 60, 100 or 300 MHz, nor at 100 MHz with heteronuclear spin decoupling of the ^{19}F resonance, possibly due to the near-coincidence of the chemical shifts of H-5, H-6 and H-7.

DISCUSSION

Solvent effects on chemical shifts. The ^1H NMR spectrum of cinnoline **1** (R = H) in DMSO-d_6 is similar to the corresponding spectra in Me_2CO[1] and $CDCl_3$,[2] showing the same order of chemical shifts (τ), i.e. H-3 < H-8 < H-4 < H-5 < H-7 < H-6 (Table 1). Comparison with the shifts in $CDCl_3$ shows that Me_2CO has an inconsistent effect whereas DMSO-d_6 has a consistent deshielding effect (Table 2). This is attributed to the more strongly solvating DMSO-d_6 producing interactions of the type $Ar\text{-}H^{\delta+}\text{-----}\overset{-}{O}\text{-}\overset{+}{S}(CD_3)_2$ at all the ring protons.[7] The effect is greatest at H-3, as predicted by VESCF calculations of ring-carbon π-electron densities (Table 2);[8] however, the lack of correlation between the chemical shift and π-electron density for each of the other positions indicates that this simple model is inadequate for solvents such as DMSO-d_6 due to additional factors, in particular the anisotropic effect of the $\overset{+}{S}\text{–}\overset{-}{O}$ bond, which varies with the distance from the site of interaction and may be predominant.

Perturbation and substituent effects on chemical shifts. The variations in the ^1H chemical shifts of 8-substituted cinnolines **1** are much more marked than the solvent effects described above, expecially at H-7 and H-5. Thus the chemical shift ranges ($\Delta\tau$) of H-7 and H-5 are 1.77 and 1.39 ppm respectively, while those of H-6, H-4 and H-3 are 0.56, 0.53, and 0.45 ppm respectively (Table 1). These variations are analysed below in terms of (a) the perturbation effect of the heterocyclic ring, and (b) the electronic and proximity effects of the 8-substituents, using single- and dual-parameter treatments to correlate the data.

H-7. The chemical shifts (τ) of H-7 were correlated with the corresponding *ortho* substituent chemical shifts (SCS_o) in monosubstituted benzenes,[9] according to eqn (1) ($P = SCS_o$).

$$\tau = aP + b. \qquad (1)$$

Table 1. Chemical Shifts (τ) and Coupling Constants (Hz) in 8-R-cinnolines 1[a]

R	H-3	H-4	H-5	H-6	H-7	J(3,4)	J(5,6)	J(6,7)	J(5,7)
H[b]	0.56	1.75	1.91	2.12	2.02	5.8	8.0	6.3	1.5
NH_2	0.77	2.03	2.95	2.47	2.99	6.0	8.2	7.8	1.2
OH	0.61	1.84	2.53	2.25	2.74	5.9	8.3	7.9	1.2
OMe	0.57	1.83	2.42	2.19	2.64	5.9	8.4	8.0	1.1
Me	0.57	1.82	2.25	2.12	2.25	5.8	-	-	-
NHAc	0.51	1.77	2.29	2.16	1.22	5.9	8.4	7.9	1.1
OAc	0.49	1.69	1.98	2.07	2.25	5.9	8.3	6.8	2.1
F	0.50	1.69	-	-	-	5.8	-	-	-
Cl	0.41	1.65	1.89	2.12	1.85	5.9	8.5	7.5	1.2
Br	0.46	1.70	1.86	2.20	1.66	5.8	8.4	7.4	1.2
I	0.50	1.82	1.89	2.37	1.41	5.9	8.3	7.3	1.2
NO_2	0.32	1.50	1.56	1.91	1.47	6.0	8.5	7.5	1.2

[a] Measured in DMSO-d_6 vs TMS.
[b] The chemical shift for H-8 is τ 1.52.

Table 2. Solvent effects on ^1H chemical shifts and VESCF charges for 1 (R = H)

Position	$\Delta\tau_1^a$	$\Delta\tau_2^a$	q^b
3	-0.03	-0.15	+0.032
4	+0.10	-0.07	+0.022
5	0.00	-0.08	+0.003
6	+0.02	-0.02	+0.006
7	+0.02	-0.03	+0.007
8	-0.05	-0.04	+0.008

[a] Using data in Refs. 1, 2.

$\Delta\tau_1 = \tau_{CDCl_3} - \tau_{(CH_3)_2CO}$; $\Delta\tau_2 = \tau_{CDCl_3} - \tau_{DMSO\text{-}d_6}$.

[b] Data from Ref. 8.

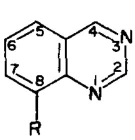
The correlation (entry 1; Table 3) is poor. Exclusion of either the NO_2 or the NHAc datum points improves the correlation (entries 2 and 3, respectively; Table 3), and exclusion of both datum points leads to an excellent correlation (entry 4; Table 3). The slope of the regression line shows that there is a 41% enhancement of the normal *ortho* substituent effect. Since all the substituents involved in this correlation are electron-donating, as the result of p–π interactions, or of σ–π interaction in the case of the Me group (Table 3), this pattern is attributed to the electron-deficient heterocyclic ring enhancing the normal electron-donating effect of the 8-R group with which it is conjugated. A figure of 22% has been reported for the corresponding enhancement in a series of α-substituted naphthalenes, quinolines, and quinoxalines.[10]

The interpolated shift for H-7 in 1 (R = NO_2) is τ 0.61 ppm. Thus, the NO_2 group deshields H-7 *less* than expected on SCS grounds by 0.86 ppm (Table 1). This can be attributed to the *peri*-effect of the N-1 lone pair in 1 (R = NO_2) forcing the NO_2 group out of coplanarity with the ring, and thus decreasing (a) its -M effect and (b) its anisotropic effect on H-7. A similar *peri*-effect occurs in the corresponding 8-nitroquinazoline 2 (R = NO_2) and 5-nitroquinoxaline 3 (R = NO_2);[4-6] the increased shieldings, calculated from the published data, are 0.84 and 0.62 ppm respectively.

Table 3. Correlations of chemical shifts of **1** with single parameters[a]

Entry	H	P[a]	a[a]	b[a]	n[b]	r[c]	s[d]
1	7	SCS_o	1.08	1.99	11[e]	0.886	0.27
2	7	SCS_o	1.54	1.88	10[e,f]	0.966	0.15
3	7	SCS_o	1.02	2.06	10[e,g]	0.934	0.19
4	7	SCS_o	1.41	1.95	9[e,f,g]	0.997	0.04
5	7	$\underline{Q}$	-0.40	2.93	8[e,h]	-0.995	0.06
6	7	σ_o^-	-0.93	2.08	9[e,i]	-0.704	0.37
7	7	σ_o^-	-1.07	2.21	8[e,g,i]	-0.965	0.12
8	6	SCS_m	1.02	2.12	11[e]	0.927	0.06
9	6	SCS_m	1.31	2.09	9[e,f,g]	0.923	0.05
10	6	σ_m	-0.34	2.26	11[e]	-0.583	0.12
11	6	σ_m	-0.19	2.24	9[e,f,g,]	-0.316	0.13
12	5	SCS_p	1.36	1.90	11[e]	0.966	0.10
13	5	SCS_p	1.35	1.90	10[e,g]	0.965	0.11
14	5	SCS_p	1.59	1.83	10[e,f]	0.980	0.07
15	5	σ_p	-0.96	2.16	11[e]	-0.946	0.13
16	5	σ_p	-1.09	2.14	10[e,f]	-0.947	0.12
17	5	σ_p^+	-0.73	1.99	11[e]	-0.961	0.11
18	5	σ_p^+	-0.80	1.97	10[e,f]	-0.958	0.10
19	5	$\sigma_{4,1}$	-0.85	2.14	8[e,j]	-0.957	0.13
20	5	$\sigma_{4,1}$	-1.02	2.09	7[e,f,j]	-0.965	0.11
21	4	$\sigma_{5,1}$	-0.62	1.84	8[k]	-0.925	0.06
22	4	$\sigma_{5,1}$	-0.62	1.84	7[f,k]	-0.854	0.06
23	3	$\sigma_{6,1}$	-0.58	0.55	7[l]	-0.981	0.02
24	3	$\sigma_{6,1}$	-0.63	0.55	6[f,l]	-0.962	0.02

[a] See eqn (1). [b] Number of datum points. [c] Correlation coefficient. [d] Standard deviation (ppm). [e] τ value for F not available (see text). [f] Datum point for NO_2 omitted. [g] Datum point for NHAc omitted. [h] Q values for NO_2, NHAc and OAc not available.[15,17] [i] σ_o^- values for NO_2 and NH_2 not available.[18] [j] $\sigma_{4,1}$ values for OAc, NHAc and I not available.[24] [k] $\sigma_{5,1}$ values for OAc, NH_2, NHAc, F and I not available.[24] [l] $\sigma_{6,1}$ values for OAc, NH_2, NHAc, F and I not available.[24]



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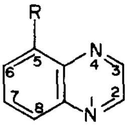

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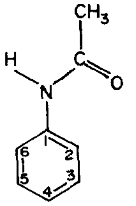
In contrast, the interpolated value (τ 1.71 ppm) for H-7 in **1** (R = NHAc) shows that the NHAc group deshields H-7 *more* than expected on SCS grounds by 0.49 ppm (Table 1). Deshielding of the *ortho* protons in anilides is well documented,[11] and has been attributed to the NHAc substituent adopting the *endo* conformation **4**, i.e. with the CO group pointing towards the ring and thus affecting H-2 by its anisotropy. In acetanilide, the dihedral angle between the plane of the ring and that of the NHAc group (with the N atom common to both planes) has been reported to be 17° 42′.[12] The additional deshielding of H-7 in **1** (R = NHAc) is ascribed therefore to N-1 being involved in H-bonding with the NHAc substituent as shown in **5**, with a subsequent decrease in the dihedral angle and closer approach of the anisotropic carbonyl group to H-7. This is substantiated by the N-H chemical shifts in **4** and **5** (τ 0.07 and −0.75 ppm respectively).



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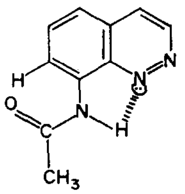

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A number of linear correlations have been reported between the parameter Q† and the chemical shifts of *ortho* protons.[13–17] Correlation of τ H-7 with available Q values according to eqn (1) (P = Q) is excellent (entry 5; Table 3). Interpolation gives the previously unrecorded Q-NHAc and Q-OAc values of 4.30 and 1.71 respectively. The Q-NO_2 value has been shown to depend critically on molecular geometry, varying from 6.33 when the NO_2 group is coplanar with the ring in nitrobenzene to 4.00 when it is forced out of the ring plane in *ortho*-disubstituted benzenes.[14] In this study, interpolation gives a Q-NO_2 value of 3.67, again indicating out-of-plane twisting, and suggesting that the *peri* interaction between a NO_2 group and a lone pair is larger than that between a NO_2 group and another group. The corresponding Q values for **2** and **3** (R = NO_2), cal-

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†The parameter $Q = P/Ir^3$, where P is the polarisability of the C–R bond for the substituent R, r is the C–R bond length, and I is the ionisation potential of R.[13]

culated from the available data,[4,5] are 3.62 and 3.75 respectively.

Linear correlations have also been established between σ_o^- and the chemical shifts of *ortho* protons of phenols in DMSO.[18] Correlation of τ H-7 with available σ_o^- values[18] according to eqn (1) ($P = \sigma_o^-$) is poor (entry 6; Table 3). Exclusion of the NHAc datum point again substantially improves the correlation (entry 7; Table 3). The interpolated σ_o^- values for the NH_2, the coplanar NHAc and the non-coplanar NO_2 groups are −0.73, 0.92 and 0.69 respectively. The corresponding σ_o^- value for **2** ($R = NO_2$) calculated from published data is 0.73,[4] while that for **3** ($R = NO_2$) is 0.61, based upon the published data[5] and the interpolated value for **1** ($R = NH_2$).

In an attempt to factorise the substituent effects, dual-parameter (*F*, *R*;[19] σ_I, σ_R[20]) treatments were used to correlate the data according to eqn (2) ($P_1 = F$, σ_I and $P_2 = R$, σ_R).

$$\tau = aP_1 + bP_2 + c \qquad (2)$$

The correlations are very poor (entries 1,3 respectively; Table 4). Exclusion of the NHAc and NO_2 datum points again improves the correlations (entries 2,4 respectively; Table 4), but not to the acceptable levels achieved in the specialised single-parameter treatments above, probably due to the exclusion of proximity and anisotropy factors in the dual-parameter treatments. Similar conclusions have been reached by Berger in a ^{13}C-study of substituted t-butylbenzenes.[21] However, the results suggest that there is a 60–65% resonance contribution to *ortho* substituent effects in **1** (entries 1–4, final column; Table 4).

H-6. The chemical shifts of H-6 were correlated with the corresponding *meta* substituent chemical shifts (SCS_m) in monosubstituted benzenes[9] according to eqn (1) ($P = SCS_m$). The correlation (entry 8; Table 3) is better than that obtained for H-7 (entry 1; Table 3), but, unlike the latter, is not improved by exclusion of the NO_2 and NHAc groups (entry 9; Table 3). This is attributed to the absence of direct conjugation and proximity effects of the R group in **1** at the 6-position, a situation

Table 4. Correlations of chemical shifts of **1** with dual parameters

Entry	H	P_1[a]	P_2[a]	a[a]	b[a]	c[a]	n[b]	r[c]	s[d]	%P_2[a]
1	7	*F*	*R*	-0.51	-1.28	1.97	11[e]	0.677	0.43	65.3
2	7	*F*	*R*	-0.64	-1.46	2.04	9[e,f]	0.801	0.31	65.4
3	7	σ_I	σ_R	-0.90	-1.28	1.97	11[e]	0.679	0.43	63.6
4	7	σ_I	σ_R	-1.14	-1.46	2.03	9[e,f]	0.803	0.31	64.5
5	6	*F*	*R*	-0.07	-0.40	2.11	11[e]	0.712	0.10	81.8
6	6	*F*	*R*	-0.01	-0.35	2.11	10[e,g]	0.538	0.11	95.2
7	6	*F*	*R*	-0.07	-0.40	2.12	10[e,h]	0.706	0.11	82.5
8	6	*F*	*R*	-0.01	-0.35	2.12	9[e,f]	0.519	0.11	96.2
9	6	σ_I	σ_R	-0.10	-0.41	2.10	11[e]	0.733	0.10	82.9
10	6	σ_I	σ_R	-0.03	-0.35	2.11	10[e,g]	0.573	0.10	94.7
11	6	σ_I	σ_R	-0.10	-0.41	2.10	10[e,h]	0.727	0.11	83.6
12	6	σ_I	σ_R	-0.02	-0.35	2.11	9[e,f]	0.554	0.11	95.3
13	5	*F*	*R*	-0.36	-1.18	2.02	11[e],	0.952	0.12	70.9
14	5	*F*	*R*	-0.44	-1.26	2.02	10[e,g]	0.950	0.11	70.3
15	5	*F*	*R*	-0.36	-1.17	2.01	10[e,h]	0.957	0.12	71.6
16	5	*F*	*R*	-0.45	-1.26	2.01	9[e,f]	0.960	0.11	69.6
17	5	σ_I	σ_R	-0.65	-1.16	2.02	11[e]	0.953	0.12	68.6
18	5	σ_I	σ_R	-0.80	-1.26	2.01	10[e,g]	0.954	0.11	69.3
19	5	σ_I	σ_R	-0.65	-1.16	2.01	10[e,h]	0.958	0.12	69.7
20	5	σ_I	σ_R	-0.81	-1.27	2.00	9[e,f]	0.965	0.10	66.7
21	4	*F*	*R*	-0.20	-0,31	1.78	12	0.919	0.05	53.5
22	4	*F*	*R*	-0.19	-0.30	1.78	11[g]	0.860	0.05	54.2
23	4	*F*	*R*	-0.20	-0.31	1.78	11[h]	0.916	0.05	53.4
24	4	σ_I	σ_R	-0.35	-0.31	1.78	12	0.919	0.05	51.5
25	4	σ_I	σ_R	-0.34	-0.30	1.78	11[g]	0.861	0.05	54.3
26	4	σ_I	σ_R	-0.35	-0.31	1.78	11[h]	0.917	0.05	53.4
27	3	*F*	*R*	-0.19	-0.25	0.55	12	0.948	0.04	49.4
28	3	*F*	*R*	-0.20	-0.26	0.55	11[g]	0.922	0.04	49.6
29	3	*F*	*R*	-0.19	-0.25	0.55	11[h]	0.949	0.04	49.3
30	3	σ_I	σ_R	-0.31	-0.25	0.55	12	0.944	0.04	49.4
31	3	σ_I	σ_R	-0.33	-0.27	0.55	11[g]	0.919	0.04	52.3
32	3	σ_I	σ_R	-0.32	-0.25	0.55	11[h]	0.945	0.04	51.1

[a] See eqn (2). [b] Number of datum points. [c] Correlation coefficient. [d] Standard deviation (ppm). [e] τ value for F not available (see text). [f] Datum points for NO_2 and NHAc omitted. [g] Datum point for NO_2 omitted. [h] Datum point for NHAc omitted.

also reflected by the low (2%) figure for the enhancement of the substituent effect by the heterocyclic ring (cf. the reduction of 10% in the substituent effect in related systems).[10]

Correlation of τ H-6 with σ_m[19] according to eqn (1) ($P = \sigma_m$) is very poor (entry 10; Table 3), and again is not improved by exclusion of the NO_2 and NHAc datum points (entry 11; Table 3). Similar poor correlations have been reported in other systems,[22] and attributed to inductive polarisation of the π-electron density at the *meta* position.[23]

Dual-parameter (*F*, *R*; σ_I, σ_R) correlations of the H-6 data according to eqn (2) are equally unsuccessful (entries 5, 9 respectively; Table 4). The omission of the NO_2 and NHAc datum points, either individually (entries 6, 7; 10, 11 respectively; Table 4), or collectively (entries 8, 12 respectively; Table 4), result in no improvement in the correlations. It is particularly noticeable that the removal of the NHAc datum point has virtually no effect. In view of the very poor correlation coefficients, the surprisingly high resonance contributions to the *meta* substituent effects in **1** (entries 5–12, final column; Table 4) may be unreliable.

H-5. The correlation of τ H-5 with the corresponding *para* substituent chemical shifts (SCS_p) in monosubstituted benzenes[9] according to eqn (1) ($P = SCS_p$) (entry 12; Table 3) is considerably better than those obtained for H-6 and H-7 (entries 8 and 1; Table 3). In this case, there is no improvement on exclusion of the NHAc datum point (entry 13; Table 3), thus confirming the attribution of the deshielding effect of the NHAc group on H-7 to the proximity effect (see above), but omission of the NO_2 datum point leads to a significant improvement (entry 14; Table 3). Interpolation shows that the NO_2 group deshields H-5 *less* than expected on SCS grounds by 0.34 ppm; this is attributed solely to the decreased -M effect of the group since proximity effects of R in **1** are negligible at H-5. As expected, the enhancement (59%) by the heterocyclic ring of the substituent effect at the conjugated 5-position is larger than that (41%) at the 7-position due to differences in the inductive effect of R in **1** at these positions. The corresponding *para*-enhancement figure in related systems is 52%.[10]

Correlations of τ H-5 with appropriate Hammett parameters (eqn (1), $P = \sigma_p$,[19] σ_p^+,[19] $\sigma_{4,I}$[24]) are consistently good (entries 15, 17, 19 respectively; Table 3), but, since the correlations are not significantly improved by exclusion of the NO_2 datum points (entries 16, 18, 20 respectively; Table 3), these parameters appear to be less sensitive than SCS parameters to changes in the coplanarity of the ring and the NO_2 group. Interpolation gives the following previously unrecorded $\sigma_{4,I}$ values:

$$0.11\ (\mathrm{OAc}), -0.20\ (\mathrm{NHAc}), \text{and } 0.19\ (\mathrm{I}).$$

Dual-parameter (*F*, *R*; σ_I, σ_R) correlations of the H-5 data according to eqn (2) are much more successful (entries 13, 17; Table 4) than for H-6 and H-7 (see above), and are virtually insensitive to the omission of the NO_2 and NHAc datum points (entries 14–16; 18–20 respectively; Table 4). These dual-parameter treatments indicate an approximately 70% resonance contribution to *para*-substituent effects in **1** (entries 13–20, final column; Table 4).

H-4 *and H*-3. Correlations of τ H-4 and τ H-3 with appropriate Hammett parameters[24] (eqn (1), $P = \sigma_{5,I}, \sigma_{6,I}$) are good (entries 21 and 23 respectively; Table 3), although it should be noted that the number of datum points for H-4 and H-3 is small in each case, and the datum point for the NHAc group is not available. The correlations are not improved by the exclusion of the respective NO_2 datum points (entries 22 and 24; Table 3), indicating that the anomalous behaviour of the NO_2 group does not affect the heterocyclic ring protons significantly. Interpolation gives the following previously unrecorded σ values: $\sigma_{6,I}$ 0.10 (OAc), −0.39 (NH_2), 0.06 (NHAc), 0.08 (F) and 0.08 (I); $\sigma_{5,I}$ 0.24 (OAc), 0.11 (NHAc), 0.24 (F) and 0.03 (I).

Dual-parameter (*F*, *R*; σ_I, σ_R) correlations of the H-4 and H-3 data according to eqn (2) are also satisfactory (entries 21, 24; 27, 30 respectively; Table 4) and are not improved by exclusion of either the NO_2 or the NHAc datum points (entries 22, 23, 25, 26; 28, 29, 31, 32 respectively; Table 4). Both dual-parameter treatments indicate a resonance contribution of about 50% to substituent effects on both τ H-4 and τ H-3 (entries 21, 24, 27, 30, final column; Table 4); this may be due to transmission of resonance effects of R in **1** to the formally conjugated C-4 position being attentuated by partial fixation of the N=N bond in **1**.

Coupling constants. The *ortho* coupling constants lie in the following ranges: $J_{3,4} = 5.8$ to 6.0 Hz; $J_{5,6} = 8.0$ to 8.5 Hz; $J_{6,7} = 6.3$ to 8.0 Hz, (Table 1). The electron withdrawal by the diazo group is reflected in the lower values of $J_{3,4}$. A similar situation occurs with iso-quinoline.[25] The difference in the values of $J_{5,6}$ and $J_{6,7}$ can be explained in terms of partial double-bond fixation. This was reported previously for quinazolines[4] and quinoxalines.[5] The ratio of $J_{6,7}:J_{5,6}$ in the diazanaphthalenes is 0.79 for **1** and 0.82 for **2** and **3**. These values can be compared with 0.82 for naphthalene.[26]

Most of the *meta* coupling constants, $J_{5,7}$, lie in the range 1.1 to 1.5 Hz, (Table 1). However, the value for **1** (R=OAc) (2.1 Hz) is anomalously large. The reason for this is not obvious.

It is possible that cross-ring coupling, $J_{3,6}$, is present, as in the derivatives the line-widths of the H-3 resonance are generally broader than those of the H-4 resonance. Alternatively, since there is an adjacent nitrogen atom, quadrupolar relaxation effects could account for the broadening. Attempts to determine the cause of the broadening were inconclusive.

EXPERIMENTAL

Cinnoline syntheses. Compounds **1** (R = H), (R = Me, OH, F, Cl), (R = NH_2, NHAc) and (R = NO_2) were prepared by the methods of Jacobs,[27] Barber,[28] Alford,[29] and Morley[30] respectively. Compounds **1** (R = Br, I) were prepared by diazotisation of **1** (R = NH_2), and subsequent treatment with CuBr/Cu powder and NaI respectively. Acetylation of **1** (R = OH) gave **1** (R = OAc). 4-^{2}H-Cinnoline was prepared in 80% isotopic purity from the K- salt of cinnoline-4-carboxylic acid, by treatment with deuterium chloride followed by decarboxylation of the product in benzophenone at 160°.[27] All compounds were tested for purity by tlc and mass spectrometry before use.

PMR measurements. Spectra were obtained routinely at 60 MHz for 0.5 M solutions in dry DMSO-d_6 with TMS as internal reference, using Varian A60A and T60 spectrometers. Additionally, some spectra were obtained at 100, 220 and/or 300 MHz to aid the analysis.

Spectral analysis. The PMR spectrum of **1** (R = H) was considered as independent ABCD and AB systems. The spectra of the derivatives **1** were considered as independent ABC and AB systems with the exception of **1** (R = F) which was treated as separate ABCX and AB systems. Analyses were carried out by iterative procedures using the LAOCOON II (Fortran) program[31] on an I.C.T. Atlas computer (National Institute of Research in Nuclear Science, Didcot). The RMS errors obtained were better than 0.07 Hz, except **1** (R = H, 0.22 Hz; R = OAc, 0.15 Hz), in fitting observed and calculated spectra.

Statistical analyses. Data were correlated by the least-squares method using a BASIC program and the multiple least squares method using the LMCL2 program of Swain and Unger.[32]

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