^{13}C Nuclear Magnetic Resonance Spectra of Quinoxaline Derivatives

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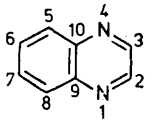
The ^{13}C n.m.r. spectra of a series of 5-, 6-, and 2-substituted quinoxalines have been analysed by consideration of their ^1H-coupled spectra. Typical values of the coupling constants are: C(2,3), $^1J_{CH}$ 181.9, $^2J_{CH}$ 11.4; C(5,8), $^1J_{CH}$ 162.6, $^3J_{CH}$ 6.5, C(6,7), $^1J_{CH}$ 159.4, $^3J_{CH}$ 9.1; C(9), $^3J_{CH(2)} = {}^3J_{CH(7)} = 10.0$, $^3J_{CH(5)}$ 5.4; C(10), $^3J_{CH(3)} = {}^3J_{CH(6)} = 10.0$, $^3J_{CH(8)}$ 5.4 Hz. The magnitudes of the coupling constants in the benzenoid ring [C(5)—C(10)] are similar to these for the corresponding positions in naphthalene, but application of naphthalene chemical shift substitutions effects leads in some cases to the wrong peak sequence in the related quinoxalines. Within the quinoxaline series itself, however, acceptable additivity of substituent effects is found (±0.8 p.p.m.), provided that the reference compounds are carefully chosen. Analysis of mixtures of quinoxalines from substituted *o*-phenylenediamines and α-oxo-aldehydes is possible by consideration of the multiplicity of the ring-junction quaternary carbon signals in the fully coupled spectra.

LITTLE work has been published so far on the ^{13}C n.m.r. spectra of the quinoxaline ring system (1). With the exception of an early study of the parent compound [1] and two specialised papers,[2,3] the only information in the literature concerns *N*-oxides [4] and 6-substituted derivatives.[5] The chemical shifts of the latter compounds



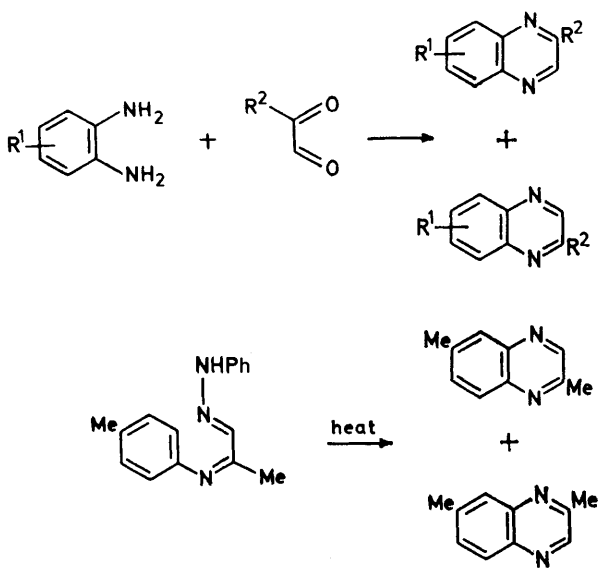
(1)

were correlated with substituent effects in naphthalenes and quinolines,[5] and the chemical shift assignments of quinoxaline itself were confirmed by specific deuterium labelling.[5]

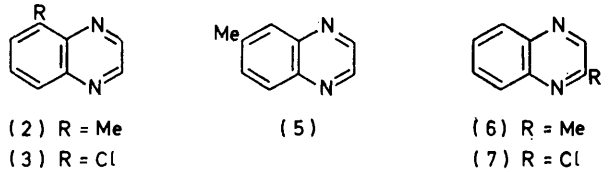
The present study has a number of objectives. First, to use fully coupled spectra to obtain chemical-shift and coupling-constant assignments for the monomethylquinoxalines. This proved possible by first-order analysis at 90 MHz and the data are given in Tables 1 and 2. The generality of the approach was tested by application to chloro- and methoxy-quinoxaline derivatives (Tables 1 and 3). The former substituent was chosen because it generally has only a small effect on chemical shift, while the latter was selected as an example of a polar substituent which might strongly influence that parameter. The results allow comparison with, and extension of, the earlier work on quinoxalines [5] and on naphthalenes.[6-8]

The second aim of this study was to investigate the effects (additive or otherwise) of multiple substitution in quinoxalines (Tables 1, 3, and 4). Alkylquinoxalines give a sensitive test of additivity effects since the methine signals of the benzenoid ring are generally separated by less than 5 p.p.m. Finally, it was hoped that these principles could be applied to the analysis of unsymmetrical quinoxaline mixtures, prepared either by condensation of a substituted *o*-phenylenediamine with an α-oxo-aldehyde, or by pyrolysis methods [9] (Scheme 1).

5-Substituted Quinoxalines.†—The fully-coupled ^{13}C n.m.r. spectrum of 5-methylquinoxaline (2) is completely resolved at 90 MHz and signals can be assigned on a first-order basis (Tables 1 and 2). In particular, the methine carbons of the benzenoid ring (δ 129.46, 129.26, and 126.94) give rise to a doublet of sextets, a doublet, and a



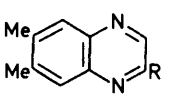
SCHEME 1



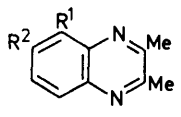
(2) R = Me
(3) R = Cl
(4) R = OMe

(5)

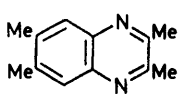
(6) R = Me
(7) R = Cl
(8) R = OMe



(9) R = H
(10) R = Me



(11) $R^1 = R^2 = H$
(12) R^1 = Me, R^2 = H
(13) R^1 = H, R^2 = Me



(14)

† A chemical shift study of a range of 5-substituted quinoxalines has been recently published (U. Hollstein and G. E. Krisov, *Org. Magn. Reson.*, **1980**, **14**, 300). Assignments are in broad agreement with the present work.

TABLE 1

^{13}C N.m.r. spectra (20 MHz) of quinoxalines (1)—(14) [a]

Compound	δ(2)	δ(3)	δ(5)	δ(6)	δ(7)	δ(8)	δ(9)	δ(10)	δ (other)
(1)	144.20	144.20	128.73	129.11	129.11	128.73	142.19	142.19	
(2)	144.10 [b]	143.18 [b]	137.22	128.46	129.26	126.94	142.73	141.72	Me, 16.80
(3)	145.43 [b]	145.03 [b]	133.14	129.93 [c]	129.62	128.58 [c]	143.91	139.72	
(4)	144.90 [b]	143.03 [b]	154.88	107.68	129.66	120.78	143.58	134.84	OMe, 55.89
(5)	143.61 [b]	144.39 [b]	127.79	140.02	131.79	128.50	141.04	142.61	Me, 21.29
(6)	152.71	145.00	128.25 [b]	127.80 [c,d]	128.86 [c]	127.80 [b,d]	141.09	140.01	Me, 21.59
(7)	147.08	144.66	130.93 [b]	128.26 [b]	129.86 [b]	129.04 [b]	141.69	140.71	
(8)	157.43	139.34	129.83 [b]	126.25 [b]	126.98 [b]	128.77 [b]	140.17	138.68	OMe, 53.40
(9)	143.77	143.77	128.16	140.23	140.23	128.16	141.74	141.74	Me, 19.98
(10)	152.37	144.72	127.95 [b]	138.84 [c]	140.04 [c]	127.52 [b]	140.75	139.67	6,7-Me, 19.88 20.04
									2-Me, 22.15
(11)	153.25	153.25	128.15	128.59	128.59	128.15	140.93	140.93	Me, 22.97
(12)	152.44 [b]	151.79 [b]	136.41	128.48	128.11	125.90	140.86	140.05	5-Me, 16.80 2,3-Me, 22.70 22.98
(13)	152.14 [b]	152.99 [b]	127.06	138.81	130.71	127.59	139.25	140.91	6-Me, 21.45 2,3-Me, 22.77 22.83
(14)	152.06	152.06	127.30	138.72	138.72	127.30	139.79	139.79	2,3-Me, 22.82 6,7-Me, 19.98

[a] Recorded for solutions in [^{2}H]chloroform. [b] Assignments may be interchanged. [c] Assignments may be interchanged. [d] Resolved at 90 MHz.

TABLE 2

Carbon–proton coupling constants (J_{CH}) for monomethylquinoxalines

Compd.	C(2)	C(3)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C (other)
(2)	$^1J_{CH}$181.73 $^2J_{CH}$11.49	$^1J_{CH}$182.00 $^2J_{CH}$11.40	$^2J_{CH(Me)}$6.53 $^3J_{CH(7)}$6.53	$^1J_{CH}$159.05 $^3J_{CH(Me)}$5.02 $^3J_{CH(8)}$10.04	$^1J_{CH}$160.49	$^1J_{CH}$163.67 $^3J_{CH(6)}$7.36	$^3J_{CH(3)}$9.84 $^3J_{CH(7)}$9.84	Not resolved	Me: $^1J_{CH}$127.8 [b] $^3J_{CH(6)}$4.3 [b]
(5)	$^1J_{CH}$182.01 $^2J_{CH}$11.35	$^1J_{CH}$181.64 $^2J_{CH}$11.47	$^1J_{CH}$161.08 $^3J_{CH(Me)}$5.56 $^3J_{CH(7)}$5.56	$^2J_{CH(Me)}$6.19 $^3J_{CH(8)}$8.85	$^1J_{CH}$158.69 $^3J_{CH(Me)}$4.49 $^3J_{CH(5)}$8.98	$^1J_{CH}$163.09	$^3J_{CH(3)}$10.13 $^3J_{CH(5)}$5.45 $^3J_{CH(7)}$10.13	$^3J_{CH(3)}$11.3 [b] $^3J_{CH(6)}$5.3 [b]	Me: $^1J_{CH}$127.0 [b] $^3J_{CH(5)}$4.4 [b] $^3J_{CH(7)}$4.4 [b]
(6)	$^2J_{CH(Me)}$6.59 $^2J_{CH(3)}$10.50	$^1J_{CH}$180.48 $^3J_{CH}$3.79	$^1J_{CH}$162.60 $^3J_{CH}$7.09	$^1J_{CH}$161.25 $^3J_{CH}$8.91	$^1J_{CH}$160.72 $^3J_{CH}$9.14	$^1J_{CH}$162.35 $^3J_{CH}$7.08	$^3J_{CH(5)}$5.13 $^3J_{CH(7)}$9.52	$^3J_{CH(3)}$9.64 $^3J_{CH(6)}$9.64 $^3J_{CH(8)}$5.37	$^1J_{CH}$127.7 [b]

[a] Values are given in Hz for solutions in [^{2}H]chloroform; recorded at 90 MHz unless stated otherwise; peak assignments are as given in Table 1. [b] Recorded at 20 MHz.

doublet of doublets, respectively. The fine structure of the high-frequency signal is due to the expected three-bond coupling, both to a ring proton and to the 5-methyl group, and this signal is hence due to C(6). The central resonance shows no fine structure and is therefore due to C(7), since three-bond coupling from this position is blocked by the methyl substituent. The low-frequency multiplet shows the effect of three-bond coupling from C(8) to H(6). Two other features are apparent from these assignments. First, the magnitude of $^1J_{CH}$ for the 8-position is significantly larger (by 3—5 Hz) than for the 6(7)-position and, conversely, $^3J_{CH}$ is smaller for the 8-position (7 Hz) than for the 6-position (10 Hz). The latter effect has also been noted in the spectrum of naphthalene.[10] Secondly, the relative order of the signals is different from that of the corresponding 1-methylnaphthalene,[7] for which the peak at lowest frequency of those for the substituted ring is due to C(3).

As expected, the signals for C(2) and C(3) of structure (2) are at high frequency (δ 144.10 and 143.18) and show large values of $^1J_{CH}$ (*ca.* 182 Hz).[4,11] Large two-bond couplings of *ca.* 11 Hz are also a feature of these signals: however, differentiation between C(2) and C(3) is not possible with the present data, nor even by analogy with 1-methylnaphthalene.[7] Of the three quaternary carbon signals, that at δ 141.72 occurs as a broad singlet and is clearly due to C(10), which shows unresolved three-bond coupling to the 5-methyl group and to three ring protons. The quaternary C(9) can show only two three-bond couplings [to H(2) and H(7)] since the remaining position is blocked by the 5-methyl group. It appears as a clean triplet at δ 142.73 ($^3J_{CH(2)} = {}^3J_{CH(7)} = 9$ Hz) and so the presence of the nitrogen atoms in the ring can have little effect on this coupling mechanism (*cf.* naphthalene:[10] C(9), $^3J_{CH(2,7)}$ 8 Hz). The remaining quaternary carbon signal [δ 137.22, C(5)] occurs as an apparent quintet owing to approximately equal coupling from C(5) to H(7) and to the methyl group ($^2J_{CH(Me)} = {}^3J_{CH(7)} = 7$ Hz). This methyl signal itself (δ 16.80) shows a standard quartet structure ($^1J_{CH}$ 128 Hz) further split by three-bond coupling to H(6) ($^3J_{CH}$ 4 Hz).

The ^{13}C n.m.r. parameters of 5-chloroquinoxaline (3) and 5-methoxyquinoxaline (4) are shown in Tables 1 and 3; however these 20 MHz spectra could not be assigned completely on the basis of spin–spin coupling data alone. For example, the peak at δ 107.68 in the spectrum of the methoxy-derivative (4) shows a complex coupling

pattern, yet it is clearly due to C(6) because of its characteristically large shift to high frequency (*cf.* 1-methoxynaphthalene [7] [δ(2) 103.6]. Similarly, C(6) and C(7) of 1-methoxynaphthalene are, respectively, deshielded and shielded by *ca.* 1 p.p.m. relative to naphthalene itself: [7] an effect of comparable magnitude allows the probable assignment of the corresponding signals [C(2) and C(3)] of benzenoid ring occur as a doublet of sextets, a doublet, and a doublet of quintets at δ 130.09, 127.22, and 126.61, respectively. Only C(8) is incapable of three-bond coupling to a single proton, and therefore gives rise to the central peak ($^1J_{CH}$ 163 Hz). The C(5) and C(7) signals both show long-range coupling to a ring proton and to the methyl group, but they can be distinguished

TABLE 3

Available carbon–proton coupling-constants (J_{CH}) for substituted quinoxalines [a]

Compd.	C(2)	C(3)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C (other)
(3)	$^1J_{CH}$183.5 $^2J_{CH}$11.4	$^1J_{CH}$184.9 $^2J_{CH}$11.3	*b*	$^1J_{CH}$166.9 $^3J_{CH}$ *ca.* 10	$^1J_{CH}$164.8	$^1J_{CH}$166.6 $^3J_{CH}$7.2	*b*	*b*	
(4)	$^1J_{CH}$182.4 $^2J_{CH}$11.6	$^1J_{CH}$184.0 $^2J_{CH}$11.5	*b*	*c*	$^1J_{CH}$162.5	$^1J_{CH}$166.3 $^3J_{CH}$7.5	*b*	*b*	OMe: $^1J_{CH}$144.8
(7) [d]	$^2J_{CH}$9.03	$^1J_{CH}$192.87	*c*	*c*	*c*	*c*	$^3J_{CH(5)}$5.62 $^3J_{CH(7)}$8.55	$^3J_{CH(3)}$8.12 [e] $^3J_{CH(6)}$ 10.56 [e] $^3J_{CH(8)}$4.58	
(8) [d]	$^2J_{CH}$7.32 $^3J_{CH}$3.66	$^1J_{CH}$187.01	*c*	*c*	*c*	*c*	$^3J_{CH(5)}$5.74 $^3J_{CH(7)}$9.40	$^3J_{CH(3)}$9.66 [e] $^3J_{CH(6)}$ 10.74 [e] $^3J_{CH(8)}$5.74	OMe: $^1J_{CH}$146.6
(9)	$^1J_{CH}$181.8 $^2J_{CH}$11.3	$^1J_{CH}$181.8 $^2J_{CH}$11.3	$^1J_{CH}$160.5 $^3J_{CH(Me)}$5.1	*b*	*b*	$^1J_{CH}$160.5 $^3J_{CH(Me)}$5.1	$^3J_{CH(2)}$11.0 $^3J_{CH(5)}$5.9	$^3J_{CH(3)}$11.0 $^3J_{CH(8)}$5.9	Me: $^1J_{CH}$127.0 $^3J_{CH}$5.5
(10)	*b*	$^1J_{CH}$180.3 $^3J_{CH}$3.8	$^1J_{CH}$160.1 $^3J_{CH(Me)}$ *ca.* 5	*b*	*b*	$^1J_{CH}$160.1 $^3J_{CH(Me)}$ *ca.* 5	*b*	*b*	2-Me: $^1J_{CH}$127.6 6,7-Me: $^1J_{CH}$126.8 $^3J_{CH}$ *ca.* 4.9
(11)	*b*	*b*	*c*	*c*	*c*	*c*	$^3J_{CH(5)}$5.9 $^3J_{CH(7)}$7.6	$^3J_{CH(8)}$5.9 $^3J_{CH(6)}$7.6	Me: $^1J_{CH}$127.6
(12)	*b*	*b*	*b*	$^1J_{CH}$158.3 $^3J_{CH(Me)}$5.2 $^3J_{CH(8)}$10.4	$^1J_{CH}$160.4	*c*	$^3J_{CH(7)}$7.5	*b*	2,3-Me: $^1J_{CH}$127.5 5-Me: *b*
(13)	*b*	*b*	$^1J_{CH}$160.1 $^3J_{CH(Me)}$5.4 $^3J_{CH(7)}$5.4	*b*	$^1J_{CH}$159.0 $^3J_{CH(Me)}$4.4 $^3J_{CH(5)}$8.5	$^1J_{CH}$162.6	*b*	$^3J_{CH(8)}$5.3	2,3-Me: $^1J_{CH}$127.6 6-Me: $^1J_{CH}$127.0 $^3J_{CH}$4.5
(14)	*b*	*b*	$^1J_{CH}$159.5 $^3J_{CH(Me)}$5.1	*b*	*b*	$^1J_{CH}$159.5 $^3J_{CH(Me)}$5.1	$^3J_{CH(5)}$5.8	$^3J_{CH(8)}$5.8	2,3-Me: $^1J_{CH}$127.4 6,7-Me: $^1J_{CH}$126.8 $^3J_{CH}$5.5

[a] Values are given in Hz for solutions in [^{2}H]chloroform; spectra recorded at 20 MHz unless otherwise stated; peak assignments are as given in Table 1. [b] Signals incompletely resolved at 20 MHz. [c] Non first-order at 20 MHz. [d] Recorded at 90 MHz. [e] Assignments may be reversed.

5-methoxyquinoxaline. Unfortunately, the situation is not so clear-cut for the 5-chloro-compound (3), since the assignments of the 1-chloronaphthalene resonances are themselves in some doubt.[8] The C(7) signal of compound (3) can be recognised readily as the central benzenoid methine peak from the fully coupled spectrum, but even the magnitudes of $^1J_{CH}$ and $^3J_{CH}$ cannot distinguish C(6) and C(8) in this case, probably because $^1J_{CH(6)}$ is increased by the electronegativity effect of the substituent. Even with these restricted assignments, the relative positions of the C(6)–C(8) signals clearly differ in the naphthalene [8] and quinoxaline series, and so direct comparisons must be made with caution.

The 6-Substituted Quinoxaline (5).—Since the spectra of a range of 6-substituted quinoxalines have been previously reported,[5] the present study is restricted to an analysis at 90 MHz of the coupling constants in a typical derivative, *viz.* 6-methylquinoxaline (5) (Tables 1 and 2). In this case the signals of the three methine carbon atoms in the by the relative magnitudes of their coupling constants (*cf.* above). Thus the high-frequency multiplet [C(7)] shows a small one-bond coupling ($^1J_{CH}$ 159 Hz) and a large three-bond coupling [$^3J_{CH(ring)}$ 9 Hz], while the opposite is true for the low frequency multiplet [C(5)] [$^1J_{CH}$ 161, $^3J_{CH(ring)}$ 6 Hz]. This analysis produces the same assignment as the earlier work,[5] which was based on substituent effects.

As found with 5-methylquinoxaline, the signals due to C(2) and C(3) of the 6-methyl derivative (5) appear as double doublets ($^1J_{CH}$ 181, $^2J_{CH}$ 11 Hz); these can only be further assigned by tentative analogy with naphthalene [5] (Table 1). However, the three quaternary carbon signals can be uniquely assigned, though the resonance to highest frequency is confused by overlap with a limb of the C(2,3) multiplets. Nevertheless, it is resolved at 20 MHz as a double doublet ($^3J_{CH}$ 11 and 5 Hz) as might be expected for C(10). By analogy with the results for compound (2), the larger coupling is

clearly due to interaction with H(3) and the smaller to interaction with H(8). Coupling constants of similar magnitude ($^3J_{CH}$ 10, 10, and 5 Hz) are observed for the C(9) signal, which occurs as a triplet of doublets. All eight lines expected for the quaternary C(6) are resolved: the two-bond coupling to the methyl group is similar ($^2J_{CH}$ 6 Hz) to that of the 5-methyl derivative (2), but, as anticipated, the three-bond coupling from C(6) to H(8) is rather larger (9 Hz) than from C(5) to H(7) in (2). The methyl group itself (δ 19.75) shows equal long-range coupling to H(5) and to H(7) ($^3J_{CH}$ 4 Hz).

Taken together, compounds (2) and (5) allow the assignment of average coupling constants for the quinoxaline ring system as follows: C(2,3), $^1J_{CH}$ 181.9, $^2J_{CH}$ 11.4; C(5,8), $^1J_{CH}$ 162.6, $^3J_{CH}$ 6.5; C(6,7), $^1J_{CH}$ 159.4, $^3J_{CH}$ 9.1; C(9), $^3J_{CH(2)} = {}^3J_{CH(7)} = 10.0$, $^3J_{CH(5)}$ 5.4; C(10), $^3J_{CH(3)} = {}^3J_{CH(6)} = 10.0$; $^3J_{CH(8)} = 5.4$ Hz. These may be compared with the corresponding values for naphthalene[10] (using the same notation): C(2) [= C(3)], $^1J_{CH}$ 159.5, $^2J_{CH(3)}$ 1.6; C(5) [= C(8)] $^1J_{CH}$ 158.8, $^3J_{CH}$ 6.7; C(6) [= C(7)] $^1J_{CH}$ 159.5, $^3J_{CH}$ 8.5; C(9) [= C(10)], $^3J_{CH(2,7)}$ 8.0, $^3J_{CH(4,5)}$ 5.9 Hz. The influence of the heteroatoms is clearly responsible for the increase in the sizes of the couplings from C(2,3) in quinoxalines, and probably influences the size of the one-bond coupling constant from C(5,8). Otherwise the two sets of data are remarkably similar: the close correspondence of the values for the quaternary carbons C(9,10) is particularly noteworthy.

2-*Substituted Quinoxalines.*—The above analysis for 5- and 6-substituted quinoxalines has depended on the presence of the substituent in the benzenoid ring to disrupt the coupling pattern. This clearly does not obtain for the 2-substituted compounds [*e.g.* (6)—(8)], and the treatment is correspondingly less successful.

Since the substituent is remote from the benzenoid ring, it exerts only a small influence on the chemical shifts of positions 5—8, and has little effect on the coupling pattern. Thus these four carbon atoms of 2-methylquinoxaline (6) resonate within a range of only 1 p.p.m., and each signal occurs as a doublet of doublets in the ^{1}H-coupled spectrum (90 MHz). Distinction between C(6,7) and C(5,8) can be made on the basis of the magnitudes of $^1J_{CH}$ and $^3J_{CH}$ (Tables 1 and 2) but the peak sequence is again different from that of the corresponding naphthalene.[7] Otherwise, the spectrum of (6) shows few features which would not be predicted by analogy with the spectrum of (5). Thus the quaternary C(2) shows standard two-bond couplings to H(3) and to the methyl group (11 and 7 Hz, respectively), while C(3) shows one- and three-bond couplings of expected magnitude (180 and 4 Hz, respectively). The ring-junction quaternary carbon atoms show a pattern similar to that of the 6-methyl compound (5). Only the signal due to the methyl group itself is exceptional, since no long-range coupling is apparent: this may be used as a diagnostic feature of 2(3)-methyl substituents.

The four benzenoid carbon resonances of the 2-chloro- and 2-methoxy-quinoxalines (7) and (8) are spread over 3 and 4 p.p.m. respectively but, in contrast to the earlier examples, first-order coupling patterns are not shown even at 90 MHz (Tables 1 and 3): the fully-coupled spectra are further confused by overlapping peaks. The application of specific decoupling techniques is also inappropriate since the ^{1}H n.m.r. spectra of the benzenoid protons cannot be readily assigned (see Experimental section), while deuterium labelling would serve only to distinguish C(5,8) from C(6,7), if the standard synthesis

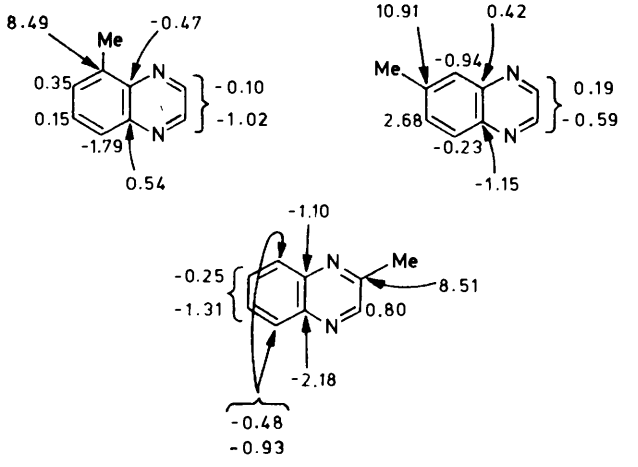


FIGURE 1 Substituent effects for compounds (2), (5), and (6) [positive values indicate δ(derivative) > δ(parent)]

of these compounds is used.[12] The assignments of these carbon resonances of compounds (7) and (8) given in Table 1 are therefore based reluctantly on naphthalene effects, since no better model is available. Nevertheless, the other peaks in the spectra can be assigned unambiguously, and these follow the same sequence as in the corresponding naphthalene derivative. The only other feature of interest in these spectra is the large size of the one-bond coupling from C(3) (Table 3), due to the influence of the electronegativity of the substituent.

Effect of Multiple Substituents.—It is clear from the above discussion that attempts to apply naphthalene substituent effects to the quinoxaline system have met with only limited success. In this section the ability to predict the spectra of polyalkylquinoxalines on the basis of the spectra of compounds (2), (5), and (6) is examined critically. Figure 1 displays the substituent effect of a methyl group at positions 5, 6, and 2 calculated from these spectra only, and it is apparent that the change in chemical shift due to substitution at one site (*e.g.* the 6-position[5]) cannot be applied directly to the same substituent at another position. The substituent effects of the dimethyl compounds (9) and (11) are shown in Figure 2. Assignment of the peaks of 6,7-dimethylquinoxaline (9) is possible by inspection; the 2,3-dimethyl derivative (11) gave a complex spectrum, even at 90 MHz, but the benzenoid resonances could be assigned by using 'fingerprint' rules for symmetrical *o*-disubstituted benzenes[13] (Table 1). The peak sequence so obtained is the same as for quinoxaline itself.[5]

The experimental shifts for the dimethyl derivatives (9) and (11) are generally much less than would be predicted from adding the effects of two methyl groups. For example, the ring junction quaternary carbon atoms of the 6,7-derivative (9) experience the combined effect

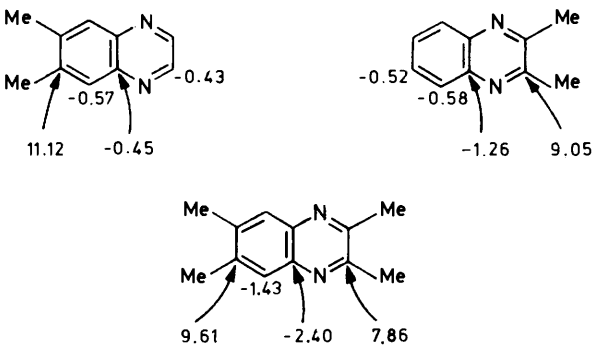
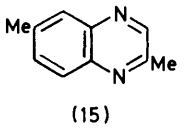


FIGURE 2 Substituent effects for symmetrical polymethyl quinoxalines (9), (11), and (14)

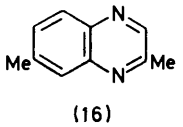
of a *para*-[6(7)-] methyl group (−1.15 p.p.m.) and a *meta*-[7(6)-] methyl group (−0.92 p.p.m.) and so a total shielding of 2.07 p.p.m. relative to the parent (1) is predicted. In fact, a shift of only 0.45 p.p.m. is observed. The failure of additivity effects is often associated with steric interaction between the substituents [8] and such is probably the case in the present examples. In agreement with this, the chemical shifts of the two dimethyl compounds (9) and (11), taken together, predict each carbon signal of the tetramethyl derivative (14) to within 1 p.p.m. (Figure 2). Thus the ring junction quaternary carbon atoms in this case experience the effects of 2,3-dimethyl substitution (−1.26 p.p.m.) and of 6,7-dimethyl substitution (−0.45 p.p.m.). The expected shielding of 1.71 p.p.m. is now markedly closer to the experimental result of 2.40 p.p.m. Table 4 demonstrates the utility of this approach by comparing experimental and calculated chemical shifts for the trimethylquinoxalines (10), (12), and (13). For all the carbon atoms, the deviation in chemical shift is again less than 1 p.p.m., and the correct peak sequence is predicted.

Another problem in quinoxaline analysis concerns disubstituted derivatives, in which there is one substituent in each ring. Standard methods of quinoxaline synthesis (*e.g.* by condensation of an *o*-phenylenediamine with an α-oxo-aldehyde) will in general give mixtures of two isomers (Scheme 1), and it is clearly important to be able to assign to individual compounds specific peaks in the spectra of the mixtures.

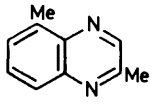
For example, condensation of 3,4-diaminotoluene with pyruvaldehyde gives the quinoxalines (15) and (16) in approximately equal amounts. All the resonances are resolved in the ^{13}C n.m.r. spectrum of the mixture, but assignment of the peaks by the application of substituent effects is complicated by two factors. First, the ring carbon signals cannot be assigned completely,



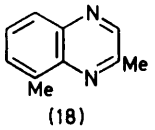
(15)



(16)



(17)



(18)

because of the remaining ambiguities in the spectra of the model compounds (5) and (6). Secondly, although the shifts of the quaternary carbons can be calculated, six of these atoms resonate in the range 138.5—141.5 p.p.m. and so use of substituent effects with an estimated accuracy of ±0.8 p.p.m. is clearly inappropriate. However, these difficulties can be overcome by again using fully coupled spectra at high field-strength. In the spectrum of the mixture, the quaternary peak to highest frequency (δ 141.51) is a doublet ($^3J_{CH}$ 5.9 Hz) as expected of C(9) in the 2,7-dimethyl compound (16), while the sextet predicted for C(10) in this compound is found at δ 138.83 ($^3J_{CH}$ 10.3, 10.3, and 5.5 Hz). Similarly, the ring-junction quaternary carbon atoms of 2,6-dimethylquinoxaline (15) give rise to quartets at δ 140.41 and 139.88 ($^3J_{CH}$ 10.0 and 5.9; $^3J_{CH}$ 9.3 and 5.4 Hz, respectively).

Similarly, the mixture formed from pyruvaldehyde and 2,3-diaminotoluene contains 2,5- and 2,8-dimethylquinoxalines (17) and (18), though in this case one isomer is predominant (2 : 1 ratio). As found for a methyl substituent at C(5), the adjacent ring-junction quaternary peaks are broad and poorly resolved, but the mixture

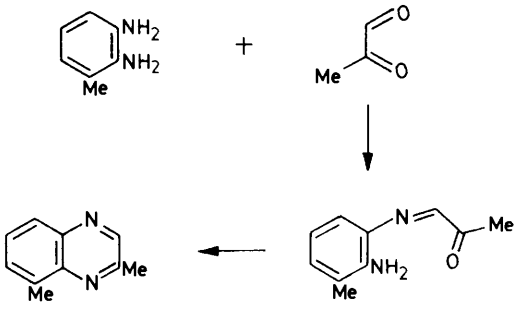
TABLE 4

Comparison of observed and calculated ^{13}C n.m.r. chemical shifts for compounds (10), (12), and (13) [a]

Compd.	Frequency (MHz)		δ(2)	δ(3)	δ(5)	δ(6)	δ(7)	δ(8)	δ(9)	δ(10)
(10)	20	Obs.	152.37	144.72	127.95 [b]	138.84 [c]	140.04 [c]	127.52 [b]	140.75	139.67
		Calc.	152.77	144.57	127.68	138.92	139.98	127.23	140.64	139.56
(12)	20	Obs.	152.44 [b]	151.79 [b]	136.41	128.48	128.11	125.90	140.86	140.05
		Calc.	153.15	152.23	136.64	128.94	128.74	126.36	141.47	140.46
(13)	20	Obs.	152.14 [b]	152.99 [b]	127.06	138.81	130.71	127.59	139.25	140.91
		Calc.	152.66	153.44	127.21	139.50	131.27	127.92	139.78	141.35

[a] Recorded for solutions in [^2H]chloroform. [b] Assignments may be interchanged. [c] Assignments may be interchanged.

can be analysed completely on the basis of the other ring-junction quaternary signals which are sharp in both cases. The minor isomer shows a doublet at δ 141.73 ($^3J_{CH}$ 9.8 Hz), as expected for C(9) of compound (17), while the major isomer shows a triplet at δ 140.52 ($^3J_{CH}$ 10.1 Hz) which is consistent with C(10) of compound (18).



SCHEME 2

This result suggests that quinoxaline formation is a kinetically controlled reaction under the conditions employed (see Experimental section), since the first step of the reaction apparently involves condensation of the less hindered amino-group with the more reactive carbonyl function (Scheme 2).

EXPERIMENTAL

N.m.r. spectra (^1H and ^{13}C) were recorded for solutions in [^2H]chloroform.

Preparation of o-Phenylenediamines.—These compounds were generally commercial samples, used without purification. 2,3-Diaminochlorobenzene [14] and 2,3-diaminoanisole [15] were made by reduction (sodium borohydride–palladium–charcoal) [16] of 2-nitro-6-chloroaniline [14] and 2,3-dinitroanisole,[15,17] respectively.

Preparation of Quinoxalines.—Quinoxaline (1) was a commercial sample. 2-Chloroquinoxaline [12] (7), m.p. 46—48 °C (lit.,[12] 49 °C), δ_H 8.69 (1 H, s), 7.85—8.1 (2 H, complex), 7.6—7.8 (2 H, complex), and 2-methoxyquinoxaline [12] (8), b.p. 145—150 °C at 16 mmHg (lit.,[12] 101—102 °C at 1.5 mmHg), δ_H 8.39 (1 H, s), 7.4—8.0 (4 H, complex), 4.05 (3 H, s) were prepared from quinoxalin-2(1*H*)-one by standard methods.[12] All the other quinoxalines were made by condensation of the *o*-phenylenediamine with the α-dicarbonyl compound in the presence of sodium hydrogen sulphite.[18] The following procedure is typical: pyruvaldehyde (40%, 0.68 ml) was added to a solution of sodium disulphite (1.04 g) in water (5 ml). The mixture was heated to 70 °C and was then added to a solution of 2,3-diaminotoluene (0.61 g, 5 mmol) in hot water (8 ml). After 15 min, during which time the solution had cooled to room temperature, the solution was basified with a solution of sodium carbonate (2.2 g) in water (5 ml), and extracted with ether (3 × 20 ml), and the organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was distilled (Kugelrohr) to give a mixture of 2,5- and 2,8-dimethylquinoxaline, (17) and (18), (0.55 g, 70%), b.p. 150—155 °C at 16 mmHg, δ_H 8.64 and 8.63 (1 H, 2s), 7.4—7.9 (3 H, complex), and 2.74 and 2.71 (6 H, 2s). (The substance reported [19] as 2,5-dimethylquinoxaline is in fact 5,8-dimethylquinoxaline.)

The following quinoxalines were made by this method: 5-methylquinoxaline (2), b.p. 125—127 °C at 16 mmHg (lit.,[20] 120 °C at 15 mmHg), δ_H 8.79 (2 H, s), 7.9—8.0 (1 H, m), 7.6—7.7 (2 H, m), and 2.79 (3 H, s); 5-chloroquinoxaline (3), m.p. 58—59 °C (lit.,[20] 60—62 °C), δ_H 8.94 (1 H, d, $^3J_{HH}$ 1.7 Hz), 8.87 (1 H, d, $^3J_{HH}$ 1.7 Hz), 8.04 (1 H, dd), 7.88 (1 H dd), and 7.64 (1 H, t); 5-methoxyquinoxaline (4), m.p. 73—75 °C (lit.,[21] 72—73 °C), δ_H 8.82 (2 H, br, s), 7.68 (2 H, d), 7.09 (1 H, t), and 4.09 (3 H, s); 6-methylquinoxaline (5), b.p. 118—120 °C at 16 mmHg (lit.,[22] 245 °C), δ_H 8.71 and 8.69 (2 H, 2d), 7.90 (1 H, d), 7.76 (1 H, br s), 7.42 (1 H, dd), and 2.46 (3 H, s); 2-methylquinoxaline (6), b.p. 127—129 °C at 16 mmHg (lit.,[23] 125—127 °C at 11 mmHg), δ_H 8.66 (1 H, s), 7.9—8.1 (2 H, complex), 7.6—7.8 (2 H, complex), and 2.71 (3 H, s); 6,7-dimethylquinoxaline (9), m.p. 99—100 °C (lit.,[20] 100—101 °C), δ_H 8.68 (2 H, s), 7.90 (2 H, s), and 2.46 (6 H, s); 2,6,7-trimethylquinoxaline (10), m.p. 114—116 °C (lit.,[24] 116 °C). δ_H 8.58 (1 H, s), 7.75 (1 H, s), 7.70 (1 H, s), 2.69 (3 H, s), and 2.43 (6 H, s); 2,3-dimethylquinoxaline (11), m.p. 102—104 °C (lit.,[25] 104—106 °C), δ_H 7.9—8.0 (2 H, complex), 7.6—7.7 (2 H, complex), and 2.69 (6 H, s); 2,3,5-trimethylquinoxaline (12), m.p. 70—71 °C (lit.,[24] 72—73 °C), δ_H 7.7—7.8 (1 H, complex), 7.4—7.6 (2 H, complex), 2.73 (3 H, s), and 2.67 and 2.66 (6 H, 2s); 2,3,6-trimethylquinoxaline (13), m.p. 88—90 °C (lit.,[26] 91 °C), δ_H 7.81 (1 H, d), 7.70 (1 H, br, s), 7.41 (1 H, dd), 2.64 (6 H, s), and 2.51 (3 H, s); 2,3,6,7-tetramethylquinoxaline (14), m.p. 189—190 °C (lit.,[24] 189—190 °C), δ_H 7.70 (2 H, s), 2.66 (6 H, s), and 2.43 (6 H, s); 2,6- and 2,7-dimethylquinoxaline (15) and (16), b.p. 140—145 °C at 16 mmHg (lit.,[22] 267—268 °C), δ_H 8.55 and 8.53 (1 H, 2s), 7.83 and 7.80 (1 H, 2d), 7.72 and 7.65 (1 H, 2 br, s), 2.62 (3 H, s), and 2.45 (3 H, s).

I am grateful to Dr. I. H. Sadler for the 90 MHz ^{13}C n.m.r. spectra, and to Mr. J. R. A. Millar and Dr. D. M. Smith for discussions.

[1/923 *Received*, 9th *June*, 1981]

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