Carbon-13 NMR Studies on some 5-Substituted Quinoxalines

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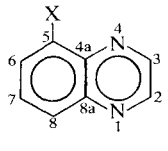
Eleven 5-substituted quinoxalines (NO_2, NH_2, COOH, OCH_3, CH_3, OH, F, Cl, Br, I, CN, the latter five not reported previously) have been synthesized by standard methods. Their ^{13}C NMR spectra have been measured in DMSO-d_6 and assigned on the basis of substituent parameters, by line widths and by intensities. The chemical shifts compare favorably with those calculated using benzene substituent parameters, and are very close to those of corresponding carbons in 1-substituted phenazines. The correlation with the chemical shifts of the corresponding positions in 1-substituted naphthalenes is also close except for those of carbons 4a and 8a in the quinoxalines which, due to their proximity to nitrogen, are downfield (in some cases 12 ppm) of the signals of the corresponding carbons in naphthalene. 5-Fluoroquinoxaline was also measured in $CDCl_3$, CD_3COCD_3, CD_3CN, CD_3OD, C_6D_6 and CD_3COOD. In all solvents an abnormally low $^2J(CF)$ (~12 Hz) was found for C-4a and no C—F spin–spin splitting could be detected for the three-bond coupling of C-8a. Similar abnormalities were found in 2-fluoroaniline and 2-fluoroacetanilide. There are linear relationships between the *Q* parameter of the substituent and the chemical shift of carbons 4a, 5 and 6. A linear relationship also exists between the chemical shift of C-8 ('*para*' position) and the Hammett σ_p parameter of the substituent.

The ^{13}C NMR spectra of quinoxalines are of theoretical interest because the electronic structure of quinoxalines, being diaza analogs of naphthalene, can be studied by ^{13}C NMR.[1] The chemical shifts of such aromatic compounds arise as a result of the characteristic polarization of the aromatic ring caused by the substituent, and are therefore related to chemical reactivity. Furthermore, a comparison with the recently studied phenazines[2] and naphthalenes[3] can be made.

We have synthesized 11 5-substituted quinoxalines, some of which had not been previously reported, and we have measured their ^{13}C NMR spectra in DMSO-d_6. Other solvents were also used for fluorine-substituted compounds, including 5-fluoroquinoxaline. Assignments were made by means of known benzene substituent effects applied to quinoxaline chemical shifts,[1] by the additivity rule for substituent effects, by line intensities and line widths, by nuclear Overhauser enhancement for protonated carbons, and by comparison with substituted phenazines[2] and naphthalenes.[3]

The following quinoxalines were measured:



1 X = –H	**7** X = –OH
2 X = $-NO_2$	**8** X = –F
3 X = $-NH_2$	**9** X = –Cl
4 X = –COOH	**10** X = –Br
5 X = $-OCH_3$	**11** X = –I
6 X = $-CH_3$	**12** X = –CN

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Quinoxaline (**1**) itself, measured in DMSO-d_6, showed slightly different chemical shifts from the literature values[1] reported for **1** in $CDCl_3$. The nitro substituent effects on benzene shifts[5] (1-, *ortho*, *meta*, *para*) were used in the assignment of 5-nitroquinoxaline. Similarly, the benzene–NH_2, –COOH, $-OCH_3$, $-CH_3$, –OH, –F, –Cl, –Br, –I and –CN substituent effects[5] served to assign the correspondingly substituted quinoxalines. Nuclear Overhauser enhancement and line widths aided in distinguishing the protonated from the nonprotonated carbons.

Table 1 shows the chemical shifts for the various quinoxalines. The chemical shifts of C-2 and C-3 are relatively little affected by the 5-substituent and their values remain relatively constant throughout the table. In some cases (Br, I, CN) they coincide. Arbitrarily, the upfield absorption has been assigned to C-3 and the two assignments may be interchanged. However, this choice is supported by an observed small C—F coupling to the carbon with the upfield signal in 5-fluoroquinoxaline in all solvents used (*vide infra*). Assignments for C-5, C-6/C-4a, C-7/C-8a and C-8 are secured by line width and intensity, benzene substituent parameters, and the additivity rule. In all spectra C-5, C-4a and C-8a showed narrow, relatively less intense lines. The 5-fluoroquinoxaline spectrum in DMSO-d_6 shows the typical $J(CF)$ spin–spin splitting with values close to the literature values for the corresponding positions in fluorobenzene[4] and 1-fluoronaphthalene[3] (Table 2) for C-5, C-6, C-7 and C-8, respectively. Splitting of C-4a, however, was only ~2/3 of the 'normal' $^2J(CF)$ value in these systems, and C—F coupling of C-8a in 5-fluoroquinoxaline was unobservable, although 1-fluoronaphthalene in $CDCl_3$ exhibits the expected splitting at the corresponding

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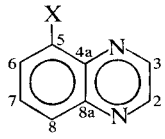
Table 1. Chemical shifts of 5-substituted quinoxalines and differences between chemical shift values calculated on the basis of benzene substituent parameters[a] and observed chemical shift values in 5-substituted quinoxalines (quinoxaline shift + benzene substituent parameter − observed shift)



	Solvent	C-2[b]	C-3[b]	C-4a	C-5	C-6	C-7	C-8	C-8a	X
H(Lit[1])	$CDCl_3$	145.5	145.5	143.2	129.8	129.9	129.9	129.8	143.2	
H	DMSO-d_6	145.6	145.6	142.1	129.0	130.1	130.1	129.0	142.1	
NH_2	DMSO-d_6	145.3	141.4	131.8	145.7	108.8	131.1	114.2	143.2	
				(−2.1)	(+2.5)	(+8.9)	(+0.3)	(+5.3)	(+0.2)	
OMe	DMSO-d_6	145.6	143.8	134.2	155.0	108.8	130.2	120.4	143.0	56.1
				(−7.6)	(+4.2)	(+5.8)	(−0.1)	(−0.3)	(−0.9)	
NO_2	DMSO-d_6	147.4	146.9	133.6	147.4	124.1	129.2	133.2	141.7	
				(+3.2)	(+1.2)	(+0.7)	(+1.7)	(+1.8)	(+1.2)	
OH	DMSO-d_6	145.6	143.1	133.4	153.6	112.2	130.7	118.8	143.1	
				(−3.9)	(+2.3)	(+5.3)	(+1.2)	(+2.3)	(+0.8)	
CH_3	DMSO-d_6	145.2	144.3	142.3	137.0	129.8	129.8	126.8	141.5	16.9
				(+0.4)	(+1.3)	(+0.9)	(+0.3)	(−0.9)	(+1.0)	
COOH	DMSO-d_6	146.5	144.9	141.9	129.2	131.8	130.0	132.8	139.0	166.4
				(+1.8)	(+2.2)	(−0.1)	(0.0)	(0.0)	(+3.0)	
F	DMSO-d_6	146.4	145.5	132.5	156.5	114.0	129.6	125.0	143.1	
				(−4.5)	(+7.6)	(+2.0)	(+1.1)	(−0.4)	(+0.6)	
Cl	DMSO-d_6	145.9	145.0	141.4	138.5	130.0	130.1	128.5	143.2	
				(+0.9)	(−3.1)	(+0.3)	(+1.0)	(−1.5)	(−0.1)	
Br	DMSO-d_6	146.3	146.3	143.1	123.3	133.5	130.7	129.2	139.5	
				(+2.3)	(+0.3)	(−0.1)	(+1.6)	(−1.2)	(+4.8)	
I	DMSO-d_6	146.5	146.5	150.4	102.9	140.1	131.4	129.9	141.5	
				(+1.9)	(−5.9)	(+0.2)	(+1.6)	(+0.1)	(+3.5)	
CN	DMSO-d_6	148.1	148.1	142.4	112.4	135.3	130.7	135.3	137.4	116.9
				(+1.1)	(−2.4)	(−3.8)	(−2.1)	(−4.9)	(+3.2)	

[a] Benzene shift parameters are taken from Ref. 5.
[b] Chemical shifts may be interchanged.

Table 2. Coupling constants (Hz) in some fluorine-substituted aromatic compounds

	Solvent	^1J(C-1, F)	^2J(C-2, F)	^3J(C-3, F)	^4J(C-4, F)	^3J(C-5, F)	^2J(C-6, F)
Fluorobenzene[4]	None	245.3	21.0	7.7	3.3	7.7	21.0
		^1J(C-2, F)	^2J(C-1, F)	^3J(C-6, F)	^4J(C-5, F)	^3J(C-4, F)	^2J(C-3, F)
2-Fluoro-aniline[a]	$CDCl_3$	237.8	12.7	3.5	3.4	6.8	18.5
	DMSO-d_6	241.6	12.6	4.3	3.0	6.5	18.3
2-Fluoro-acetanilide[a]	$CDCl_3$	245.3	11.1	0.0	3.7	7.5	19.6
	DMSO-d_6	244.4	11.7	0.0	3.6	7.4	19.3
	CD_3OD	245.9	9.1	0.0	3.6	7.5	20.0
		^1J(C-5, F)	^2J(C-4a, F)	^3J(C-8a, F)	^4J(C-8, F)	^3J(C-7, F)	^2J(C-6, F)
5-Fluoro-quinoxaline[a]	DMSO-d_6	258.9	12.3	0.0	4.4	8.7	18.4
		^1J(C-1, F)	^2J(C-9, F)	^3J(C-10, F)	^4J(C-4, F)	^3J(C-3, F)	^2J(C-2, F)
1-Fluoro-naphthalene[3]	$CDCl_3$	253.6	17.2	5.0	4.6	8.0	19.8
1-Fluoro-naphthalene[4]	None	251.1	16.4	4.8	4.0	8.2	19.9

[a] This study.

bridgehead carbons C-9 and C-10 (17.2 and 5.0 Hz, respectively) albeit with reduced magnitude[3,4] compared with the corresponding coupling constants in fluorobenzene.[5]

Thus, the bridgehead nature of C-4a and C-8a in 5-fluoroquinoxaline does not seem to be the only factor involved regarding their abnormally small coupling constants. The presence of nitrogens at these positions also appears to play a role. In 2-fluoroaniline, ^2J(C-1, F) and ^3J(C-6, F) are well below the corresponding values of fluorobenzene: 12.7 and 3.8 Hz (neat[4]), 12.7 and 3.5 Hz (in $CDCl_3$, this study), and 12.6 and 4.3 Hz (in DMSO-d_6, this study) (Table 2). We have also measured 2-fluoroacetanilide and

Table 3. Chemical shifts (ppm) and J(CF) values (Hz) of 5-fluoroquinoxaline in different solvents

Solvent	C-2	C-3	C-4a	C-5	C-6	C-7	C-8	C-8a
DMSO-d_6	146.4	145.5	132.5	156.5	114.0	129.6	125.0	143.1
	0.0	2.5	12.3	258.9	18.4	8.7	4.4	0.0
$CDCl_3$	145.1	144.2	132.9	156.6	113.3	128.7	124.6	143.2
	0.0	2.5	12.2	261.2	18.5	8.4	4.7	0.0
CD_3COCD_3	146.5	145.5	133.7	157.4	114.0	129.6	125.4	144.0
	0.0	2.5	11.3	259.9	18.4	8.6	4.7	0.0
CD_3CN	145.7	144.7	132.6	156.5	113.2	128.8	124.6	143.0
	0.0	2.7	12.3	258.6	18.6	8.8	4.4	0.0
CD_3OD	145.2	144.2	132.1	156.1	113.1	128.8	123.9	142.5
	0.0	2.5	13.6	260.1	18.5	8.7	4.5	0.0
C_6D_6	146.0	145.1	134.0	157.8	113.9	129.3	125.4	144.2
	0.0	2.7	12.3	261.3	18.4	8.2	4.7	0.0
CD_3COOD	144.9	144.3	131.8	155.9	113.5	129.2	123.4	141.8
	0.0	2.4	12.8	260.3	18.3	8.4	4.5	0.0

assigned the peaks on the basis of substituent parameters for F[5] and NHAc[6] and find ^3J(C-6, F) = 0.0 Hz in $CDCl_3$, DMSO-d_6, or CD_3OD. The theory of coupling constants does not provide an obvious explanation for this behavior, although there is evidence that the magnitude of the coupling constant can be affected by the presence of proximate lone pairs of electrons.[7]

To investigate the role of the solvent as acceptor for the nitrogen lone pair and, thus, possibly its influence on the C—F coupling constants of C-4a and 8a we have measured the ^{13}C NMR spectrum of 5-fluoroquinoxaline in a variety of other solvents (Table 3). However, no such effects were found. Chemical shifts and C—F coupling constants were found to vary little with solvent while ^3J(C-8a, F) remained unobservable. Table 3 also shows a small coupling constant (2–3 Hz) for the upfield doublet of the two intense absorptions in the 144–146 ppm region. This supports the tentative assignment of these absorptions to C-2 and C-3 because of their expected nuclear Overhauser enhancements. It also supports the tentative assignment of the upfield doublet to C-3 because its four-bond coupling to F would be expected to be larger than the five-bond coupling between C-2 and F.

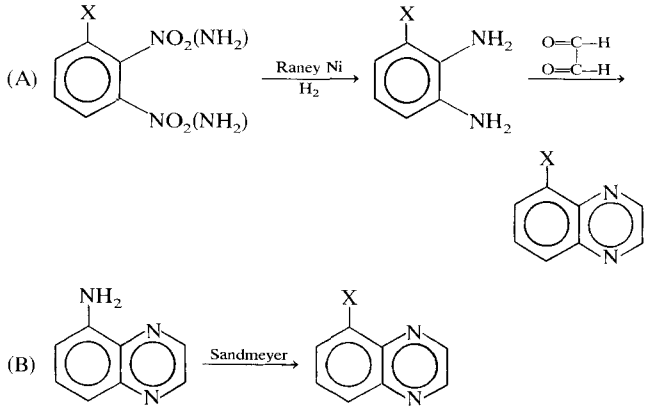
Table 1 also shows the difference in ppm between the chemical shift values calculated on the basis of benzene substituent parameters[5] and the observed chemical shift values in the 5-substituted quinoxalines. With a few exceptions (e.g. C-6 in 5-aminoquinoxaline the values agree within a few ppm.

Table 4 presents a comparison of the chemical shifts of 5-substituted quinoxalines with those of 1-substituted phenazines[2] and 1-substituted naphthalenes.[3] While there is good agreement between the quinoxaline and phenazine values, naphthalene values are only (and to a lesser degree) close to the quinoxaline chemical shifts at quinoxaline C-5 through C-8. The quinoxaline C-8a and C-4a shifts are invariably 5–12 ppm downfield of the corresponding naphthalene shifts for C-10 and C-9, respectively, because of the deshielding effect of the hetero ring.

It is of interest to detect correlations of the quinoxaline ^{13}C NMR chemical shifts with systematic variations in molecular structure. It has been proposed that the parameter Q[7,8] might be an empirical measure of the paramagnetic portion of the fundamental shielding equation, derived by Ramsey.[9] Q values have been found to correlate ^{13}C chemical shifts at the position of attachment and at the *ortho* carbons in substituted benzenes.[8] That such a correlation also exists for the 5-substituted quinoxalines at C-4a, C-5 and C-6 is shown in Fig. 1 for which correlation coefficients r have been calculated by regression analysis. The C-7 and C-8a (*meta* carbons) showed little variation with the substituent at C-5. At these carbons only weak inductive effects should be felt; magnetic anisotropy effects are too weak and the *meta* carbons are isolated from resonance interactions. The *para* carbon (C-8) showed a reasonably linear relationship with the Hammett σ_p parameter of the substituent at C-5 (Fig. 2) for which the correlation coefficient has been calculated by regression analysis. At the *para* carbon the resonance effect of the substituent is largely operative, inductive and magnetic anisotropy effects from the substituent being negligible.

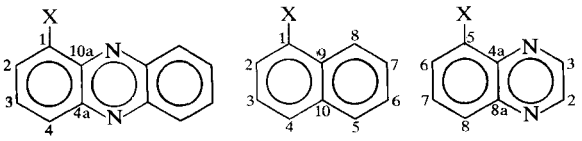
EXPERIMENTAL

The quinoxalines were synthesized by established procedures. Two general methods for synthesis were employed:



Either the 2,3-dinitro- or 2,3-nitroamino-1-X-benzene was reduced over Raney nickel to the 2,3-diamino-1-X-benzene followed by coupling with

Table 4. Comparison of 5-substituted quinoxaline chemical shifts with those of 1-substituted phenazines and 1-substituted naphthalenes



		Phenazine C-1 Naphthalene C-1 Quinoxaline C-5	C-2 C-2 C-6	C-3 C-3 C-7	C-4 C-4 C-8	C-4a C-10 C-8a	C-10a C-9 C-4a
NO_2	P	147.95	126.65	130.6	133.75	146.6	142.25
	N	146.54	123.93	123.93	134.48	134.29	125.07
	Q	147.4	124.1	129.2	133.2	141.7	133.6
NH_2	P	145.35	106.4	130.85	114.6	141.4	134.7
	N	142.2	109.5	126.3	118.6	134.3	123.6
	Q	145.7	108.8	131.1	114.2	143.2	131.8
OMe	P	155.4	107.1	130.1	121.85	143.4	130.75
	N	155.50	103.81	125.92	120.26	134.57	126.69
	Q	155.0	108.8	130.2	120.4	143.0	134.2
OH	P	153.4	110.6	131.3	119.3	142.2	135.85
	Q	153.6	112.2	130.7	118.8	143.1	133.4
CH_3	P	138.0	130.15	129.45	127.6	143.15	143.7
	N	134.30	126.43	125.58	126.59	133.61	132.67
	Q	137.0	129.8	129.8	126.8	141.1	142.3
F	N	159.5	109.8	126.0	124.2	135.7	124.3
	Q	156.5	114.0	129.6	125.0	143.1	132.5
Br	N	122.73	129.7	125.75	127.7	134.6	132.0
	Q	123.3	133.5	130.7	129.2	139.5	143.1
CN	N	108.83	131.05	123.53	131.78	131.38	130.75
	Q	112.4	135.3	130.7	135.3	137.4	142.4
COOH	N	126.5	129.49	123.45	132.29	132.78	130.35
	Q	129.2	131.8	130.0	132.8	139.0	141.9

glyoxal to the 5-X-quinoxaline, or 5-aminoquinoxaline was converted via a Sandmeyer reaction to the 5-X-quinoxaline. Melting points were taken on a Kofler hot stage apparatus and are uncorrected. Mass spectra were taken on a Dupont 21-491 mass spectrometer. All elemental analyses and mass spectra were satisfactory. 5-Fluoro, 5-chloro, 5-bromo, 5-iodo and 5-cyanoquinoxaline had not been previously reported. Table 5 shows the synthetic methods and results.

C-13 spectra of the nonfluorine-containing compounds were taken at 35 °C on a Varian XL-100 instrument with a Nicolet TT-100 computer. The frequency was 25.5 MHz for ^{13}C and 100.1 MHz for ^{1}H decoupling with a 2000 Hz band width for noise decoupling. The solvent, DMSO-d_6, was used as internal solvent reference. Concentrations in the order of 1 mole % were measured and no concentration shifts within a factor 2 of the concentration could be detected. The pulse repetition time was 0.8 s for 9000 free induction decays and the spectral width was

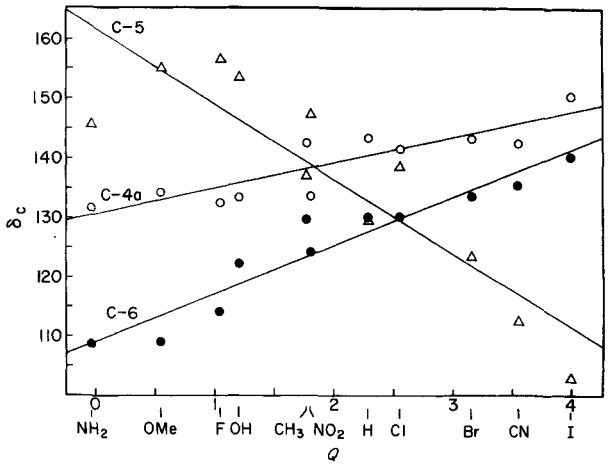


Figure 1. Correlation between the parameter Q and ^{13}C chemical shifts of C-4a (○, $r = 0.882$), C-5 (△, $r = 0.893$), and C-6 (●, $r = 0.954$) of 5-X-substituted quinoxalines.

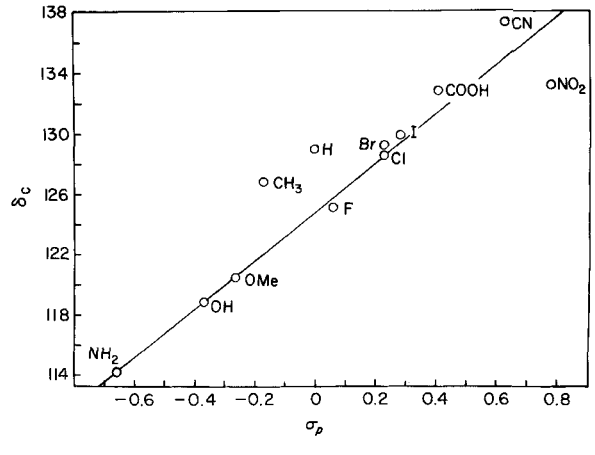


Figure 2. Correlation between C-8 ^{13}C chemical shifts of 5-X-substituted quinoxalines with Hammett σ_p parameters of X ($r = 0.942$).

Table 5. Methods and results of synthesized 5-substituted quinoxaline

Substituent	Method	Reference	m.p. (°C)	m/z (M^+)
H	Purchased from Aldrich		30	
NO_2	Diamine+glyoxal	10	97	175
NH_2	Diamine+glyoxal	11–14	90	145
COOH	Diamine+glyoxal	15–18	178	174
OCH_3	Diamine+glyoxal	19, 20	72	160
CH_3	Diamine+glyoxal	21, 22	18–20	144
OH	From 5-methoxyquinoxaline	23	103–104	146
F	Diamine+glyoxal	24, 25	77–79	148
Cl	Diamine+glyoxal and diazotation of 5-aminoquinoxaline	26, 27	Oil	
Br	Diamine+glyoxal	28	66–67	208/210
I	Diamine+glyoxal and diazotation of 5-aminoquinoxaline	28	139–141	256
CN	Diazotation of 5-aminoquinoxaline		118–118.5	155

5000 Hz. The transform size was 8 K. All absorptions are reported relative to TMS, downfield positive, by adding 39.60 ppm to the chemical shifts with respect to DMSO-d_6.

The fluorine-substituted compounds were measured at 35 °C on a Varian FT-80A instrument. The frequency was 20.0 MHz for ^{13}C and 79.542 MHz for ^1H decoupling with a 2000 Hz band width for noise decoupling. The deuterated solvents were used as internal solvent reference. The pulse repetition time was 2 s for 3000–6000 free induction decays and the spectral width was 4000 Hz (5000 Hz for the acetone-d_6 solvent). The transform size was 16 K.

Acknowledgements

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