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Studies on Heterocycles Carbon-13 Magnetic Resonance Spectroscopy. XI.[1] Nitrogen Heterocycles. (1). 6-Substituted Quinoline and Quinoxaline Derivatives

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The assignment of ^{13}C nuclear magnetic resonance chemical shifts of 6-substituted quinoline and quinoxaline series were confirmed, and the additivity rules of ^{13}C chemical shifts of 2-substituted naphthalene derivatives were approved for both 6-substituted quinoline and quinoxaline derivatives. The correlation coefficient of *meta*-like position is promoted by the linear combination of chemical shifts at corresponding *meta* position of 2-substituted naphthalene derivatives and substituent constants σ_π.

Keywords——^{13}C magnetic resonance; chemical shift; assignment; 6-substituted quinoline; 6-substituted quinoxaline; additivity of s.c.s.; substituent constant; substituent effect

Introduction

In the previous report[1] of this series, the additivities of the shielding parameters of monosubstituted benzenes were confirmed in 2-substituted naphthalenes (1) and their 6-methoxy derivatives, where the observed chemical shifts were linear with some parameters such as the substituent constants σ_i and σ_π,[3] the substituent-induced chemical shifts (s.c.s.)[4] of monosubstituted benzenes, and/or their linear combinations. We extended here our discussions to 6-substituted quinoline (2) and quinoxaline (3) derivatives as the model of nitrogen heterocycles.

Experimental

Measurements of ^{13}C NMR Spectra——The details of measurements are all the same as described in the previous report.[1]

6-Substituted Quinolines——Materials were all prepared from *p*-substituted anilines by the Skraup reactions.[5]

6-Substituted Quinoxalines——Materials were all prepared from 4-substituted-*o*-phenylenediamine and glyoxal disodium bisulfite.[6]

6-Deuterioquinoxaline——To a D_2O (10 ml) solution of 4-chloro-*o*-phenylenediamine (1 g) and NaOH (2 g), added Raney-Ni (2 g) portionwise at 80°. The alkaline mixture was stirred for 1 hr at this temperature. The mixture was cooled and extracted by ether (10 ml × 3). After ether layer was dried over anhydrous $MgSO_4$, the solvent was removed. 4-Deuterio-*o*-phenylenediamine thus obtained was used without further purification for the condensation with glyoxal disodium bisulfite.[7] Bp 125—135°/15 mmHg, yield 330 mg (33%). Deuterium content determined by integral data of proton NMR was ~70%.

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1) Part X: H. Takai, A. Odani, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), 26, (8) (1978).
2) Location: *Yamadakami 133-1, Suita, Osaka 565, Japan.*
3) Y. Yukawa and Y. Tsuno, *Nippon Kagaku Zasshi*, **86**, 873 (1965).
4) Defined as the shifts of a carbon in the substituted system minus the shifts of the same carbon in the parent system.
5) R.H.F. Manske and M. Kulka, "Organic Reactions," Vol. VII, John Wiley & Sons, Inc., New York, 1953, p. 59.
6) G.R. Ramage and J.K. Landquist, "Chemistry of Carbon Compounds," Vol. VI-B, ed. by E.H. Rodd, Elservier Publishing Co., New York, 1959, p. 1345.
7) R.G. Jones and K.C. McLaughlin, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, 1963, p. 824.

Results and Discussion

The chemical shifts of ring carbons of **2** and **3** were estimated from the additivity of the substituent effect determined in the previous works.[1,8] For example, in the assignment of the ring carbons of **2**, s.c.s. of **1**[1] are added to chemical shifts of corresponding ring carbons of quinoline, and the values thus obtained are compared with observed shifts considering the peak height. The result summarized in Table I showed the same patterns with those of **1**. Namely, in the case of electron-donating substituent groups, contrary to the low field shifts of *ipso* carbons which spread over a wide range of about 50 ppm, the shifts of two *ortho* positions displace to the high field site. And, at *para* or quinonoid positions, the variations of shifts are in the range of 5 ppm, whereas those of the other positions equivalent to *meta* are in a few ppm. The changes of the ring carbons of benzene moiety (C-5~C-10) are larger than those of pyridine moiety (C-2, -3, and -4), and as a whole, wide spreads are observed in the neighbours of the substituent.

Table I. ^{13}C Chemical Shifts[a] of 6-Substituted Quinolines[b]

Substituent	Carbon No.								
	2	3	4	5	6	7	8	9	10
$N(CH_3)_2$	146.18	121.13	133.83	105.00	148.46	119.27	129.88	142.40	129.88
NH_2	146.60	121.25	133.59	107.22	144.68	121.49	130.42	143.36	129.76
OCH_3	147.86	121.25	134.61	105.13	157.69	122.15	130.84	144.44	129.28
CH_3	149.36	120.89	135.15	126.46	136.17	131.56	129.10	146.90	128.20
H	150.32	121.01	135.93	127.72	126.46	129.40	129.40	148.34	128.32
Cl	150.44	121.73	134.85	126.28	132.16	130.74	131.08	146.60	128.68
Br	150.62	121.79	134.85	129.70	120.41	132.82	131.20	146.84	129.28
$COOCH_3$	152.36	121.76	137.25	130.93	128.16	128.93	129.70	149.97	127.39
CN	153.13	122.62	136.23	134.01	110.40	130.00	131.01	149.06	127.57
NO_2	153.67	122.80	137.73	124.48	145.52	122.80	131.31	150.13	127.02

a) In ppm downfield from internal TMS.
b) The numbering is as follows:

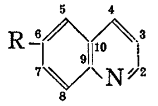
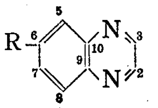


Table II. ^{13}C Chemical Shifts[a] of 6-Substituted Quinoxalines[b]

Substituent	Carbon No.							
	2	3	5	6	7	8	9	10
$N(CH_3)_2$	140.24	144.02	105.54	150.97	119.39	129.70	137.01	144.92
OCH_3	142.35	144.80	106.68	160.68	123.35	130.42	139.23	144.68
CH_3	144.02	144.80	128.26	140.55	132.28	128.98	141.57	143.12
H	144.86	144.86	129.46	129.88	129.88	129.46	143.00	143.00
Cl	144.92	145.64	128.38	135.87	130.72	131.02	141.51	143.24
$COOCH_3$	146.48	145.82	132.16	131.44	129.46	129.76	144.92	142.29
CN	147.26	146.66	135.57	113.76	131.20	130.72	144.38	142.11
NO_2	147.56	146.96	125.92	147.98	123.41	131.32	145.34	141.93

a) In ppm downfield from internal TMS.
b) The numbering is as follows:



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[8] G. Miyajima, Y. Sasaki, and M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **19**, 2301 (1971); G.B. Savitsky, *J. Phys. Chem.*, **67**, 2723 (1963), and references cited therein.

For **3** at first, the ring carbon shifts of quinoxaline must be determined. Among the four peaks (144.86, 143.00, 129.88, and 129.46 ppm), the peak at the lowest field is assigned to C-2 and C-3 of α-positions of nitrogen, and the weakest peak at 143.00 ppm to quarternary C-9 and C-10. To distinguish the remaining two peaks, 6-deuterioquinoxaline was prepared. In the case of 6-deuterio-quinoxaline, the signal intensity at 129.88 ppm (C-6 and C-7) showed a decrease of about 30%, but not at 129.46 ppm (C-5 and C-8). The assignments of the ring carbon chemical shifts of **3** are summarized in Table II, where the same conclusions proposed for **2** are also accepted.

Chemical shifts of the corresponding positions of **2** and **3** afford the same patterns with those of **1**. For example, as illustrated in Fig. 1, the correlations between C-6 of **2** and C-2 of **1** are linear (slope=1.0; intercept=0.0; r^2=0.999). So we are able to estimate the C-6 chemical shifts of **2** from those of **1**. The correlation coefficients of the chemical shifts between **2** or **3** *vs.* **1** are summarized in Table III.

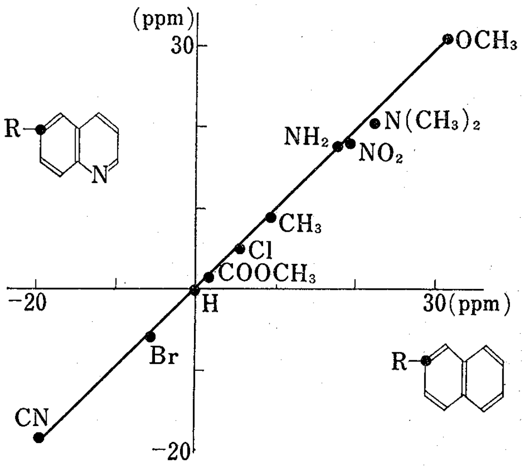

Fig. 1. Correlation between Chemical Shifts of Quinoline (C-6) and Naphthalene (C-2) Derivatives

Table III. Correlation Coefficients of Chemical Shifts of 6-Substituted Quinolines and Quinoxalines *vs.* 2-Substituted Naphthalenes

Carbon No.[a]	Correlation for[b]	Correlation coefficient (r^2) Quinolines	Correlation coefficient (r^2) Quinoxalines
2	δ_{C-6}	0.990	0.984
3	δ_{C-7}	0.920	0.889
4	δ_{C-8}	0.973	—
5	δ_{C-1}	0.999	0.997
6	δ_{C-2}	1.000	0.997
7	δ_{C-3}	0.998	0.985
8	δ_{C-4}	0.920	0.865
9	δ_{C-10}	0.998	0.997
10	δ_{C-9}	0.971	0.916

a) For the numbering, *cf.* Table I and II.
b) δ's are chemical shifts of 2-substituted naphthalenes.[1]

Ipso (C-6) and *ortho* (C-5 and C-7) positions, with a wide spread of the chemical shifts, afford the correlation coefficients near 1, whereas for the positions equivalent to *meta* the coefficient decreases (minimum: 0.865 at C-8 of **3**). This is ascribed to the fact that the shifts of these carbons distribute in a range of a few ppm, which is comparable with the theoretical resolution of 0.06 ppm.

In the previous study of 1-substituted-3,4-dimethoxybenzene series,[9] we already concluded that chemical shifts of C-3 and C-5 correlate linearly with $a\sigma_\pi + b\delta_{meta}$ (a,b=empirical factors; δ_{meta}=s.c.s. of monosubstituted benzenes at *meta* position) by the contribution of the resonance interaction between OCH_3 at C-4 and substituent at C-1. In the 6-substituted quinoxaline series, owing to the resonance interaction between N-4 and substituent at C-6, the correlation coefficients between the s.c.s. of **3** and **1** at the position equivalent to *meta* are markedly diminished than those between **2** and **1**. However, these coefficients of **3** are increased by the linear combination of the s.c.s. of **1** at corresponding position and substituent constants σ_π (*cf.* Table IV), where both coefficients (**2** *vs.* **1** and **3** *vs.* **1**) become nearly the same magnitude.

Fig. 2 shows a correlation pattern between C-8 of **3** and C-4 of **1** (r^2=0.865), where the plot of $N(CH_3)_2$ deviates 0.7 ppm from the linear line. With a few exceptions, the s.c.s. of **2** and

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[9] H. Takai, K. So, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 1303 (1978).

3 deviate from those of **1** within a range of 1 ppm as shown in Table V and VI, so we are able to assign the chemical shifts of **2** and **3** by the additive character of the substituent effect referring the s.c.s. of **1**.

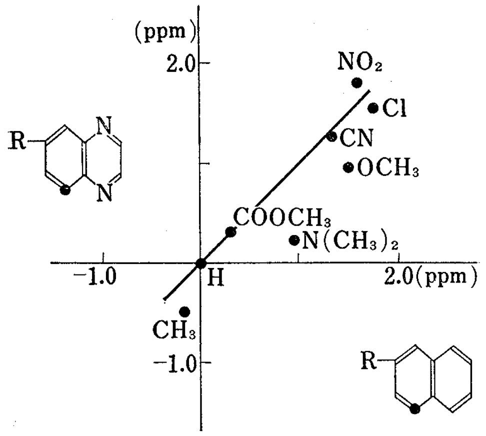

Fig. 2. Correlation between Chemical Shifts of Quinoxaline (C-8) and Naphthalene (C-4) Derivatives

Table IV. Dual Parameter Analysis of 6-Substituted Quinolines and Quinoxalines

Carbon No.[a]	Correlation coefficient (r^2)	Equation[b]
Quinoline		
3	0.956	$0.73\delta_{C-7}+0.54\sigma_\pi$
8	0.991	$1.07\delta_{C-4}+0.75\sigma_\pi$
10	0.977	$0.67\delta_{C-9}-0.82\sigma_\pi$
Quinoxaline		
3	0.961	$0.77\delta_{C-7}+1.01\sigma_\pi$
8	0.985	$0.98\delta_{C-4}+0.97\sigma_\pi$
10	0.952	$0.14\delta_{C-9}-3.18\sigma_\pi$

a) For the numbering, *cf.* Table I and II.
b) Factors are estimated by least square method.
δ's are chemical shifts of 2-substituted naphthalenes.[1]

Table V. ^{13}C Chemical Shift Differences of 6-Substituted Quinolines from 2-Substituted Naphthalenes at Corresponding Positions[a]

Substituent	Carbon No.[b] 2	3	4	5	6	7	8	9	10
$N(CH_3)_2$	−0.43	−0.30	−0.42	−1.50	−0.84	−0.84	−0.42	0.66	0.01
NH_2	−0.49	−0.36	−0.36	−1.32	−0.18	−0.48	−0.36	0.48	−0.05
OCH_3	−0.25	−0.30	−0.18	−0.59	−0.66	−0.04	−0.06	0.60	−0.11
CH_3	−0.07	−0.12	−0.12	−0.24	0.24	−0.12	−0.12	0.36	−0.24
Cl	−0.36	−0.71	−0.24	−0.31	−0.18	−0.30	−0.08	0.12	−0.26
Br	−0.24	0	−0.18	−0.18	−0.18	−0.12	0.06	0.12	−0.26
$COOCH_3$	−0.36	−0.09	−0.18	0.03	0.14	0.01	0	−0.40	0.04
CN	0.17	−0.25	−0.34	0.06	0.18	0.06	0.29	−0.41	0.51
NO_2	−0.54	−0.37	−0.29	0.12	−0.48	−0.13	0.30	−0.48	0.27

a) (S.c.s. of **2**)—(s.c.s. of **1**), in ppm.
b) For the numbering, *cf.* Table I.

Table VI. ^{13}C Chemical Shift Differences of 6-Substituted Quinoxalines from 2-Substituted Naphthalenes at Corresponding Positions[a]

Substituent	Carbon No.[b] 2	3	5	6	7	8	9	10
$N(CH_3)_2$	−0.91	−0.36	−2.70	−0.75	−1.20	−0.66	0.61	0.37
OCH_3	−0.30	−0.60	−0.78	−1.09	0.68	−0.54	0.73	0.61
CH_3	0.05	−0.06	−0.18	1.20	0.12	−0.30	0.37	−0.06
Cl	−0.42	−0.65	0.05	0.11	−0.30	−0.20	0.37	−0.38
$COOCH_3$	−0.78	0.12	−0.48	0	0.06	0	−0.11	0.26
CN	−0.24	−0.06	−0.12	0.12	0.78	−0.06	0.25	0.37
NO_2	−1.19	−0.06	−0.18	−1.44	0	0.25	0.07	0.50

a) (S.c.s. of **3**)—(s.c.s. of **1**), in ppm.
b) For the numbering, *cf.* Table II.

By introducing nitrogen atom(s) in naphthalene nucleus (C-1 of **2** or C-1 and C-4 of **3**), the chemical shifts are affected by nitrogen, but the relative values to quinoline and quilnoxaline are not. From above results, the additivity of the ring carbon chemical shifts already approved for substituted benzene[8) and naphthalene[9) series, are also confirmed for **2** and **3**.

As the relationships of the chemical shifts between monosubstituted benzenes and **1** are already confirmed, we are able to conclude that the interrelationships between monosubstituted benzenes and **2** or **3** *via* **1** are also established.