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Studies on ^{13}C Magnetic Resonance Spectroscopy. XIII.[1) ^{13}C and ^{1}H NMR of 4-Substituted Pyridazine and 2-Substituted Pyrazine Derivatives

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^{13}C chemical shifts of 4-substituted pyridazines and 2-substituted pyrazines, together with ^{1}H chemical shifts of the former compounds were measured. Linear correlations of the ^{13}C and ^{1}H chemical shifts of 4-substituted pyridazines with those of monosubstituted benzenes and monosubstituted pyridines and with substituent constants σ_π were found. In addition, similar trends were noted for 2-substituted pyrazines. Chemical shifts of pyridazines and pyrazines can be predicted on the basis of these relationships.

Keywords——^{13}C NMR chemical shift; ^{1}H NMR chemical shift; 4-substituted pyridazines; 3,6-dichloro-4-substituted pyridazines; 2-substituted pyrazines; substituent cosntants; additivity rule

Introduction

In the previous paper of this series,[1) the additivity of the substituent chemical shifts (SCS) of monosubstituted benzenes[3) was confirmed in 5-substituted pyrimidine— a diazabenzene with an additional nitrogen atom at the β-position of pyridine— derivatives, where the observed shifts were linear with respect to some empirical parameters such as substituent constants σ_R,[4) and SCS of monosubstituted benzenes or 3-substituted pyridines.[5)

In this work, we have measured the ^{13}C and ^{1}H chemical shifts of 4-substituted- (I) and 3,6-dichloro-4-substituted pyridazines (II) as well as the ^{13}C spectra of 2-substituted pyrazines (III). These two kinds of shifts were correlated with the SCS of monosubstituted benzenes or substituent constants σ_π,[6) and the empirical correlations were examined.

Experimental

Measurement of Nuclear Magnetic Resonance (NMR) Spectra

The details of the CMR and PMR measurements of 4-substituted pyridazines (I and II) were as described in the previous report,[1) and the CMR spectra of 2-substituted pyrazines (III) were measured at 22.6 MHz using a Nichiden-Varian NV-21 spectrometer in the pulse Fourier transform mode. Spectra were taken in dil. $CDCl_3$ solution (~1.0 mol) with TMS as an internal reference.

Materials

4-Substituted-3,6-pyridazinediols——3,6-Pyridazinediol (IVa),[7) and its 4-methyl (IVb)[8) or 4-chloro (IVc)[8) derivatives were obtained by the condensation reaction between NH_2–$NH_2 \cdot 2HCl$ and maleic, citraconic or chloromaleic anhydride.

[1) Part XII: T. Tsujimoto, C. Kobayashi, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **27**, 691 (1979).

[2) Location: *Yamadakami 133-1, Suita, Osaka 565, Japan.*

[3) *a*) K. Hayamizu and O. Yamamoto, *J. Mol. Spectrosc.*, **28**, 89 (1968); *b*) H. Takai, K. So, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 1301 (1978); *c*) H. Takai and Y. Sasaki, unpublished data.

[4) Y. Tsuno, "Riron Yuki Kagaku," ed. by Y. Yukawa, Kagaku-Dojin, Kyoto, 1974, p. 89.

[5) *a*) G. Miyajima, Y. Sasaki, and M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **20**, 429 (1972); *b*) Y. Sasaki, M. Hatanaka, I. Shiraishi, M. Suzuki, and K. Nishimoto, *Yakugaku Zasshi*, **89**, 21 (1969); *c*) H. Takai and Y. Sasaki, unpublished data.

[6) Y. Yukawa and Y. Tsuno, *Nippon Kagaku Zasshi*, **86**, 875 (1965).

[7) R.H. Mizzoni and P.E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1873 (1951).

[8) R.H. Mizzoni and P.E. Spoerri, *J. Am. Chem. Soc.*, **76**, 2201 (1954).

3,6-Dichloro-4-substituted Pyridazines——All of the 3,6-dichloro-4-substituted pyridazines were prepared by the chlorination of 4-substituted-3,6-pyridazinediols as follows.

R_4=N,N-Me_2:[9] Methylamination of 3,4,6-trichloro pyridazine (IIc).
R_4=NH_2:[10] Amination of IIc.
R_4=OMe:[11,12] Methoxylation of IIc with NaOMe.
R_4=Me(IIb):[8] Chlorination of IVb by $POCl_3$.
R_4=H(IIa):[7] Chlorination of IVa by $POCl_3$.
R_4=Cl(IVc):[8] Chlorination of IVc by $POCl_3$.
R_4=COOH:[13] Oxidation of IIb by $K_2Cr_2O_7$.

4-Substituted Pyridazines——Almost all of the 4-substituted pyridazines were prepared by the dechlorination of 3,6-dichloro-4-substituted pyridazines as follows.

R_4=H: Commercially available.

R_4=N,N-Me_2,[9,14] NH_2,[10] OMe[12] and Me:[8] Dechlorination of the corresponding 3,6-dichloro derivatives with H_2+Pd/C.

R_4=COOMe: Esterification of pyridazine-4-carboxylic acid with methanol[15] after dechlorination of 3,6-dichloro-pyridazine-4-carboxylic acid.[13] Yield 36%. mp 61—62°. *Anal.* Calcd. for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.68; H, 4.52; N, 19.66.

2-Substituted Pyrazines——R_2=NH_2, Me, H, Cl and COOH: Commercially available.

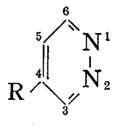
R_2=N,N-Me_2:[16] Methylamination of 2-chloropyrazine.
R_2=OMe:[17] Methoxylation of 2-chloropyrazine with NaOMe.
R_2=COOMe:[18] Esterification of pyrazine carboxylic acid with methanol.

TABLE I. Chemical Shifts (δ)[a] and SCS[b] —^{13}C and ^{1}H— of 4-Substituted Pyridazines[c]

Position R_4	C-3		C-4		C-5		C-6	
	δ	SCS	δ	SCS	δ	SCS	δ	SCS
NMe_2	138.87	−12.76	145.76	19.42	105.69	−20.65	149.68	−1.95
NH_2[d]	141.39	−10.24	146.13	19.79	107.16	−19.18	149.85	−1.78
OMe	143.87	−7.76	157.86	31.52	108.40	−17.94	151.54	−0.09
Me	153.13	1.50	137.73	11.39	126.76	0.42	150.67	−0.96
H	151.63	0.0	126.34	0.0	126.34	0.0	151.63	0.0
COOMe	152.15	0.52	127.82	1.48	125.49	−0.85	149.68	−1.95

Position R_4	H-3		H-5		H-6	
	δ	SCS	δ	SCS	δ	SCS
NMe_2	8.67	0.54	6.50	1.02	8.60	0.61
NH_2[d]	8.52	0.69	6.57	0.95	8.45	0.76
OMe	8.90	0.31	6.93	0.59	8.96	0.25
Me	9.04	0.17	7.28	0.24	9.00	0.21
H	9.21	0.0	7.52	0.0	9.21	0.0
COOMe	9.67	−0.46	7.99	−0.47	7.44	−0.23

a) δ: In ppm downfield from internal TMS.
b) SCS=δ(X-R)−δ(X-H) [CMR]
=δ(X-H)−δ(X-R) [PMR]
c) The numbering is as follows:



d) Solv.: d_6-DMSO.

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[9] I. Crossland and H. Kofod, *Acta Chem. Scand.*, **21**, 2131 (1967).
[10] T. Kuraishi, *Chem. Pharm. Bull.* (Tokyo), **4**, 137 (1956).
[11] T. Itai and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **11**, 1059 (1963).
[12] K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta*, **39**, 1755 (1956).
[13] G. Heinisch, *Monatsh. Chem.*, **104**, 953 (1973).
[14] R.S. Fenton, J.K. Landquist, and S.E. Meek, *J. Chem. Soc.*, **1971**, 1536.
[15] L. DiStefano and R.N. Castle, *J. Heterocycl. Chem.*, **5**, 53 (1968).
[16] G.W.H. Cheeseman, *J. Chem. Soc.*, **1960**, 242.
[17] A. Albert and J.N. Phillips, *J. Chem. Soc.*, **1956**, 1294.
[18] S.A. Hall and P.E. Spoerri, *J. Am. Chem. Soc.*, **62**, 664 (1940).

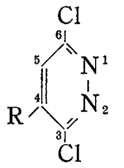
Results and Discussion

Observed ^{13}C and ^{1}H or substituent chemical shifts (SCS) of 4-substituted pyridazines (I) and 3,6-dichloro-4-substituted pyridazines (II) are summarized in Tables I and II.

TABLE II. Chemical Shifts (δ)[a] and SCS[b] —^{13}C and ^{1}H— of 3,6-Dichloro-4-substituted Pyridazines[c]

Position R_4	C-3		C-4		C-5		C-6		H-5	
	δ	SCS	δ	SCS	δ	SCS	δ	SCS	δ	SCS
NMe$_2$	146.24	−9.76	148.93	18.70	112.49	−17.74	155.11	−0.89	6.72	0.79
NH$_2$	143.72	−12.28	145.22	14.99	108.84	−21.39	154.87	−1.13	6.76	0.75
OMe	138.26	−17.74	156.06	25.83	109.50	−20.73	155.64	−0.36	6.96	0.55
Me	157.20	1.20	140.66	10.43	129.99	−0.24	155.59	−0.41	7.40	0.11
H	156.00	−0.0	130.23	0.0	130.23	0.0	156.00	0.0	7.51	0.0
Cl	154.75	−1.25	138.86	8.63	129.45	−0.78	155.17	−0.83	7.66	−0.15

[a] δ: In ppm downfield from internal TMS.
[b] SCS=δ(X-R)−δ(X-H) [CMR]
=δ(X-H)−δ(X-R) [PMR]
[c] The numbering is as follows:



^{13}C and ^{1}H chemical shifts of I and II were estimated from the additivity of the SCS determined in the previous work.[1] In the assignment of the ring carbons and protons of I and II, SCS of monosubstituted benzenes are added to the chemical shifts of the corresponding ring carbons and protons of pyridazines, and the estimated values thus obtained are compared with the observed shifts, considering the peak height and multiplicity.

TABLE III. Differences between Observed and Calculated Chemical Shifts —|Δ|— of 4-Substituted Pyridazines (ppm)

	C-3	C-4	C-5	C-6	H-3	H-5	H-6
NMe$_2$	2.88	2.94	5.01	2.67	0.12	0.36	0.44
NH$_2$	3.00	1.75	5.94	2.68	0.07	0.19	0.52
OMe	6.56	0.17	3.62	1.17	0.17	0.11	0.16
Me	0.78	1.86	0.30	0.88	0.04	0.03	0.08
H	0.0	0.0	0.0	0.0	0.0	0.0	0.0
COOMe	0.74	0.50	2.11	1.95	0.26	0.25	0.12

TABLE IV. Differences between Observed and Calculated Chemical Shifts —|Δ|— of 3,6-Dichloro-4-substituted Pyridazines (ppm)

	C-3	C-4	C-5	C-6	H-5
NMe$_2$	6.18	1.45	0.11	1.31	0.12
NH$_2$	1.26	0.84	5.94	1.73	0.02
OMe	3.12	3.31	4.20	1.14	0.06
Me	0.78	3.11	1.25	0.03	0.11
H	0.30	2.21	2.21	0.30	0.01
Cl	1.25	4.85	1.13	1.91	0.14

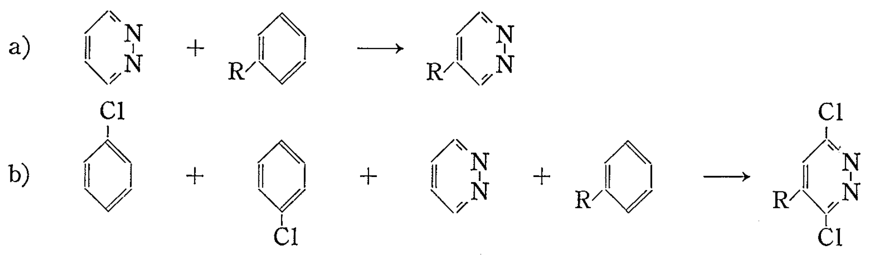


Chart 1

TABLE V. Correlation Coefficients of Chemical Shifts with Various Parameters

Position	Correlation for	I	II
C-3	δ_{ortho}a)	0.973	0.923
	δ_{3C-2}b)	0.982	0.972
	δ_{4C-3}c)	0.996	1.000
	σ_{π}	0.920	0.735
C-4	δ_{ipso}a)	0.990	0.987
	δ_{3C-3}b)	0.996	0.991
	δ_{4C-4}c)	0.997	0.999
	σ_{π}	0.755	0.711
C-5	δ_{ortho}a)	0.994	0.978
	δ_{3C-4}b)	0.994	0.998
	δ_{4C-3}c)	0.999	0.998
	σ_{π}	0.896	0.882
C-6	δ_{3C-5}b)	0.704	
	δ_{4C-2}c)	0.711	
	σ_{π}	0.177	

a) SCS of monosubstituted benzenes.
b) SCS of 3-substituted pyridines.
c) SCS of 4-substituted pyridines.
I : 4-Substituted pyridazines.
II: 3,6-dichloro-4-substituted pyridazines.

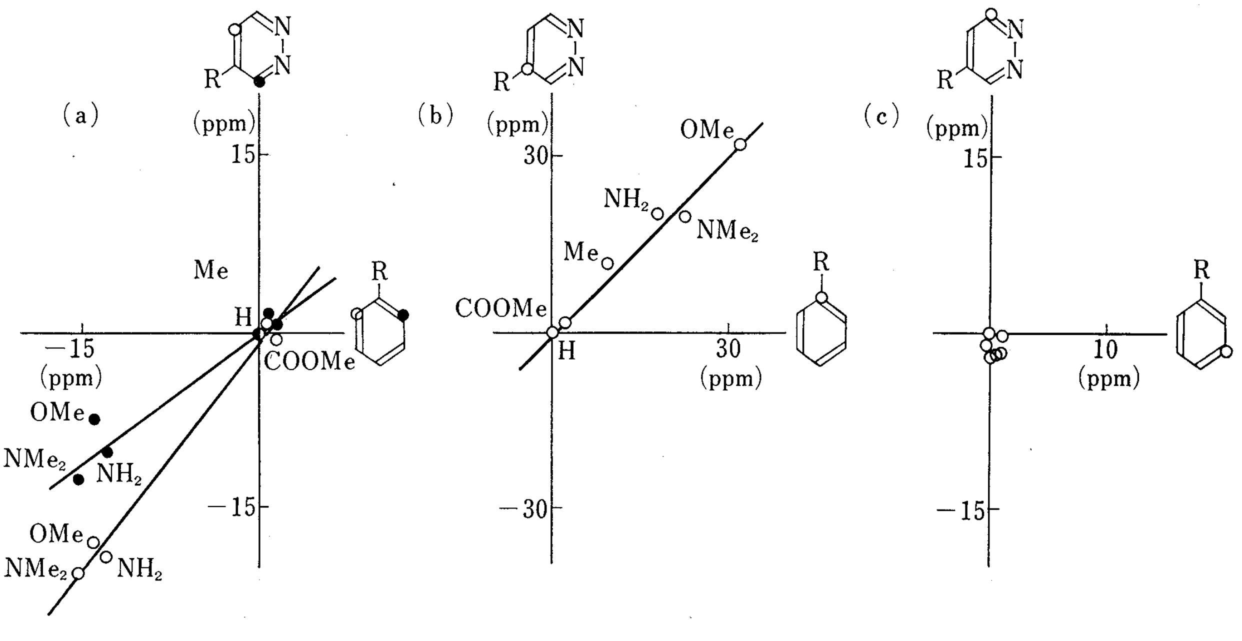


Fig. 1. Plots of ^{13}C SCS at (a) *ortho*, (b) *ipso* and (c) *meta* Positions of 4-Substituted Pyridazines *vs.* Those of Monosubstituted Benzenes

The results summarized in Tables III and IV show the difference between the observed and calculated $|\Delta|$ values (*cf.* Chart 1). The means of values at C-3, -4, -5, -6, H-3, -5 and -6 of I are 2.3, 1.2, 2.8, 1.6, 0.11, 0.16 and 0.22 ppm, respectively. Those at C-3, -4, -5, -6 and H-5 of II are 2.2, 2.6, 2.5, 1.1 and 0.08 ppm, respectively. These deviations are larger than those obtained in the case of substituted pyrimidines.[1)] However, linear relationships of SCS in the two series I and II *vs.* monosubstituted benzenes are apparent ($r > 0.9$).

The correlations of ^{13}C and ^{1}H SCS of series I and II with some empirical parameters such as SCS of monosubstituted benzenes, as well as the substituent constants σ_π are summarized in Table V; C-3, -4, -5, H-3, -5 and -6 showed good linear relations with SCS, but none of them was linear with respect to the chemical shifts of C-6. However, the mean deviation of the additivity is within 1.6 ppm. So it can be concluded that the additivity of chemical shift holds satisfactorily at this position.

In addition, we attempted to correlate all ^{13}C and ^{1}H SCS of series I and II with those of 3-substituted or 4-substituted pyridines.[5a,19)] The results indicated a high degree of linearity at all positions; the order of correlation coefficient is 4-substituted pyridines > 3-substituted pyridines > monosubstituted benzenes. The finding that the correlation coefficient between 4-substituted pyridines was highest indicates that an additional nitrogen is more effective at the *para* position than at the *meta* position in controlling the substituent effect.[5a,20)]

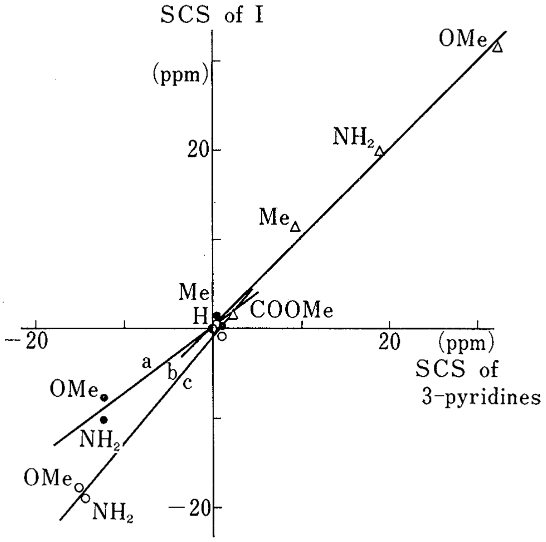


Fig. 2. Plots of SCS of 4-Substituted Pyridazines (I) *vs.* Those of 3-Substituted Pyridines

a) ●, correlation between C-3 of (I) and C-2 of 3-pyridines.

b) △, correlation between C-4 of (I) and C-3 of 3-pyridines.

c) ○, correlation between C-5 of (I) and C-4 of 3-pyridines.

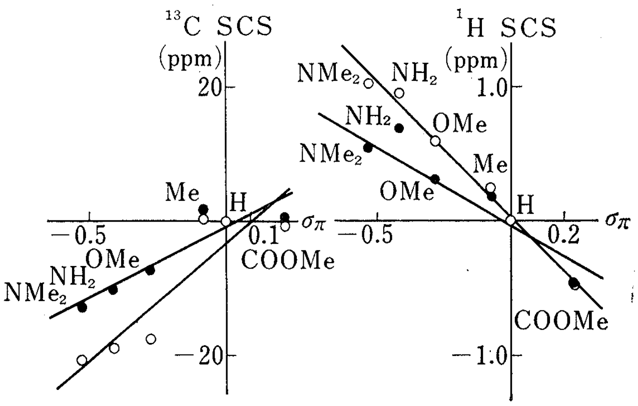


Fig. 3. Plots of SCS at C-3 and -5 or H-3 and -5 of 4-Substituted Pyridazines *vs.* Substituents Constants σ_π

●: C-3 or H-3 SCS *vs.* σ_π.

○: C-5 or H-5 SCS *vs.* σ_π.

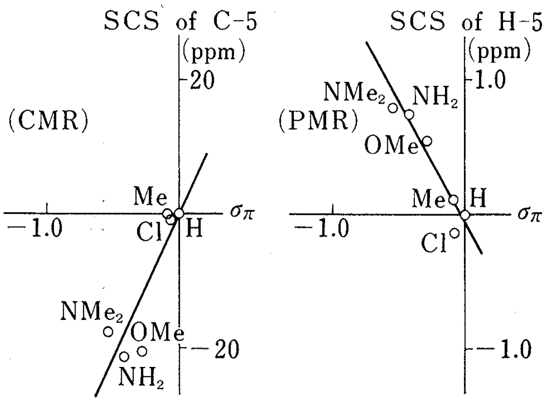


Fig. 4. Plots of SCS at C-5 and H-5 of 3,6-Dichloro-4-substituted Pyridazines *vs.* Substituent Constants σ_π

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19) *a*) Y. Sasaki, M. Suzuki, and M. Hattori, *Chem. Pharm. Bull.* (Tokyo), **17**, 1515 (1969); *b*) H. Takai and Y. Sasaki, unpublished data.

20) J. Elguero, C. Marzin, A.R. Katritzky, and P. Linda, "The Tautomerism of Hetrocycles," Academic Press, Inc., New York, 1976, Chapter 2.

Table VI. ^{13}C Chemical Shifts (δ)[a] and SCS[b] of 2-Substituted Pyrazines[c]

Position R_4	C-2		C-3		C-5		C-6	
	δ	SCS	δ	SCS	δ	SCS	δ	SCS
NMe_2	155.03	9.99	130.03	−15.01	131.57	−13.47	141.71	−3.33
NH_2	154.85	9.81	132.75	−12.29	134.18	−10.86	142.01	−3.03
OMe	160.71	15.67	136.05	−8.99	136.53	−8.51	140.59	−4.45
Me	153.97	8.93	144.74	−0.30	141.74	−3.30	143.78	−1.26
H	145.04	0.0	145.04	0.0	145.04	0.0	145.04	0.0
Cl	149.90	4.86	142.62	−2.42	145.21	0.17	144.00	−1.04
COOMe	143.24	−1.80	146.11	1.07	147.67	2.63	144.32	−0.72

a) δ: In ppm downfield from internal TMS.
b) SCS $=\delta(\text{X-R})-\delta(\text{X-H})$
c) The numbering is as follows:

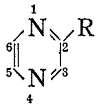

Table VII. Differences between Observed and Calculated Chemical Shifts —$|\Delta|$— of 2-Substituted Pyrazines (ppm)

	C-2	C-3	C-5	C-6
NMe_2	12.37	0.63	1.78	4.05
NH_2	8.23	0.95	1.03	3.93
OMe	15.68	5.33	0.81	5.53
Me	0.60	1.02	0.30	1.18
H	0.0	0.0	0.0	0.0
Cl	1.13	2.72	2.09	2.42
COOMe	3.78	0.19	1.93	0.72

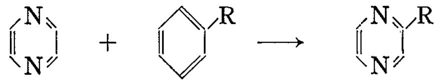

Chart 2

Table VIII. Correlation Coefficients of Chemical Shifts with Various Parameters

Position	Correlation for	III
C-2	δ_{ipso}[a]	0.933
	δ_{2C-2}[b]	0.986
	δ_{3C-3}[c]	0.935
	σ_π	0.771
C-3	δ_{ortho}[a]	0.962
	δ_{2C-3}[b]	0.973
	δ_{3C-2}[c]	0.976
	σ_π	0.956
C-5	δ_{para}[a]	0.977
	δ_{2C-5}[b]	0.983
	δ_{3C-6}[c]	0.971
	σ_π	0.972
C-6	δ_{2C-6}[b]	0.977
	σ_π	0.788

a) SCS of monosubstituted benzenes.
b) SCS of 2-substituted pyridines.
c) SCS of 3-substituted pyridines.
III: 2-Substituted pyrazines.

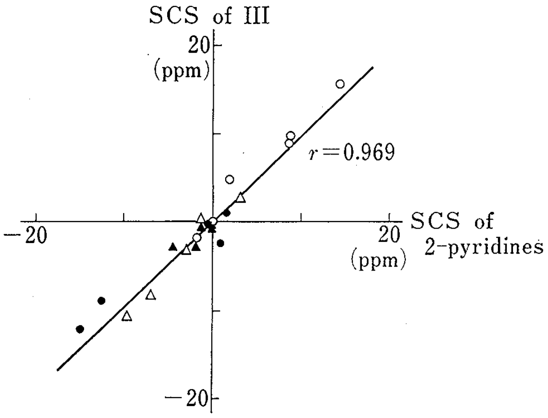

Fig. 5. Plots of ^{13}C SCS of 2-Substituted Pyrazines (III) *vs.* Those of 2-Substituted Pyridines

○: C-2 of III *vs.* 2-Pyridines.
●: C-3 of III *vs.* 2-Pyridines.
△: C-5 of III *vs.* 2-Pyridines.
▲: C-6 of III *vs.* 2-Pyridines.

As regards the correlation between SCS of I and substituent constants σ_π, the correlation coefficients (*r*) at C-3, -4 and -5 *vs.* σ_π were 0.920, 0.755 and 0.896, respectively, and that at C-6— the *meta* position—was 0.177 (*cf.* Table V). The poor correlation at this position can presumably be attributed mainly to the narrow distribution range of the chemical shifts, so that they are relatively sensitive to experimental error or to the second order effect.21) This is consistent with the results for monosubstituted benzenes.3b)

Based on these findings, we are able to predict the ^{13}C and ^{1}H chemical shifts of substituted pyridazines, and similar trends are also evident for 3,6-dichloro-4-substituted pyridazines.

The observed ^{13}C chemical shifts or SCS of 2-substituted pyrazines (III) are summarized in Table VI, and as illustrated in Chart 2, the observed shifts of III were next compared with those calculated assuming the additivity of SCS of monosubstituted benzenes.

The differences between the observed and calculated values —$|\Delta|$— are summarized in Table VII; the means of $|\Delta|$ values at C-2, -3, -5 and -6 are within 6.0, 1.6, 1.2 and 2.6 ppm, respectively. The magnitudes at C-3 and -5 are small enough to assign the shifts of related compounds using the additivity rule alone, but this is not the case at C-2 and -6.

Turner and Cheeseman22) have pointed out the correlations of ^{13}C chemical shifts between 2-substituted pyrazines and monosubstituted benzenes or 2-substituted pyridines. Their results were confirmed in this work and extended to include 3-substituted pyridines and a consideration of the substituent constants σ_π.

The results indicate a high degree of linearity at all ring carbons between ^{13}C SCS of III and 2-substituted pyridines (*cf.* Fig. 5), and high correlations in the case of III with those of monosubstituted benzenes or 3-substituted pyridines, except at C-6 (*cf.* Table VIII). In addition, a good correlation was obtained between SCS of III at C-3— the *ortho* position— and at C-5— the *para* position— and σ_π. A similar tendency was noted in 4-substituted pyridazines.

These results provide a basis for predicting the chemical shifts of substituted pyrazine derivatives.

Acknowledgement We wish to thank Dr. M. Sugiura for carrying out measurements of the ^{13}C spectra of 2-substituted pyrazines.

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21) P. Lazzeretti and F. Taddei, *Org. Magn. Reson.*, 3, 283 (1971).
22) C.J. Turner and G.W.H. Cheeseman, *Org. Magn. Reson.*, **6**, 663 (1974).