[Chem. Pharm. Bull. 20(10)2204—2208(1972)]

UDC 547.861.03 : 543.422.25

Studies on Pyrazine Derivatives. IV.[1] Coupling Constants and Chemical Shifts in Disubstituted Pyrazines[2]

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(Received April 12, 1972)

The nuclear magnetic resonance parameter of disubstituted pyrazines have been correlated with the chemical structure.

The coupling constants of 2,3-, 2,5-, 2,6-disubstituted pyrazines are 2.5—3.0, 1.1—1.4, 0 Hz respectively, and these values are not influenced by the kind of the substituents.

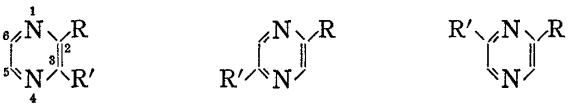
The calculated chemical shifts which are obtained from the additivity rule of the shielding parameter of the substituents are well agreed with the observed ones.

In a previous paper of this series[4] dealing with the reaction of monosubstituted pyrazine N-oxides with various reactive halides, it was desirable to correlate the structures and nuclear magnetic resonance (NMR) parameters of disubstituted pyrazines. In the present study to indicate the usefulness of the application of these correlation to the structure elucidation, we have obtained coupling constants and chemical shift values for a number of compounds most of which have not been investigated previously.[5]

In this paper, the correlation between coupling constants and structures and subsequently, the simple additivity of the substituent shielding parameter for the estimation of the ring proton chemical shifts in the disubstituted pyrazines will be described.

I. Correlation between Coupling Constants and Structures

Several reports concerning the coupling constants of pyrazine derivatives have been published so far.[6-8] There is no systematic study, however, on the correlation between coupling constants and structures in disubstituted pyrazines bearing various substituents. In the present study, the coupling constants of 2,3-, 2,5-, and 2,6-disubstituted pyrazines shown in Table I—III were determined by inspection of the expanded spectra.



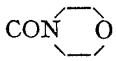
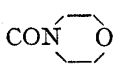
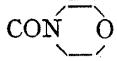
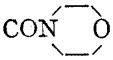
type I $J_{5,6}=2.5$—3.0 Hz | type II $J_{3,6}=1.1$—1.4 Hz | type III $J_{3,5}=\fallingdotseq 0$ Hz

Chart 1

It is apparent that these values are principally influenced by the position of substituents and not by the kind of substituents. The differences of values among three types are greater than 1.0 Hz as shown in Chart 1. From the above findings, it is assumed that the determination of the structure of a certain disubstituted pyrazine is possible by measuring its coupling constant.

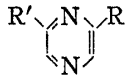
1) Part III: F. Uchimaru, S. Okada, A. Kosasayama and T. Konno, *J. Het. Chem.*, **8**, 99 (1971).
2) This work was presented to the 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July 1970.
3) Location: *2810, Minamifunabori-cho, Edogawa-ku, Tokyo.*
4) S. Okada, A. Kosasayama, T. Konno and F. Uchimaru, *Chem. Pharm. Bull.* (Tokyo), **19**, 1344 (1971).
5) R.H. Cox and A.A. Bothner-By, *J. Phys. Chem.*, **72**, 1642 (1968).
6) K. Tori and M. Ogata, *Chem. Pharm. Bull.* (Tokyo), **12**, 272 (1964).
7) Ref. 5).
8) S. Sugiura, S. Inoue, Y. Kishi, and T. Goto, *Yakugaku Zasshi*, **89**, 1646 (1969).

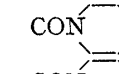
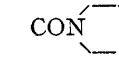
TABLE I. 2,3-Disubstituted Pyrazines

No.	R	R′	mp (°C) bp (°C/mm Hg)	Solvent[a]	Chemical shift (δ ppm) H_5	Chemical shift (δ ppm) H_6	$J_{5,6}$ (Hz)
I	$COOCH_3$	Cl	87 —89/2[b]	C(10)	8.65	8.59	2.5
II	$COOCH_3$	OCH_3	58 —60	C(8)	8.33	8.26	2.5
				D(8)	8.48	8.33	2.5
III	$COOCH_3$	OH	151 —153[b]	C(6)	8.24	8.11	2.5
IV	$COOCH_3$	NH_2	170.5—171.5[c]	C(6)	8.21	8.00	2.5
V	$COOCH_3$	$COOCH_3$	57.5[d]	C(10)	8.68	8.68	
VI	COOH	Cl	116.5—118.5	C(6)	8.72	8.69	
				D(8)	8.75	8.68	2.5
VII		OCH_3	142 —144/0.05	C(10)	8.18	8.18	
				D(10)	8.36	8.28	2.7
VIII		Cl	108.5—109.5	C(10)	8.56	8.46	2.7
IX			109.5—111.0	C(10)	8.58	8.58	
X	OCH_3	Cl	31.5— 32.0 (92—93/40)	C(10)	8.00	7.90	3.0
XI	NH_2	Cl	167 —168[e]	C(10)	7.92	8.59	2.5

a) C: $CDCl_3$ D: DMSO-d_6 ( ): concentration % (W/V)
b) A. Albert, D.J. Brown and H.C.S. Wood, *J. Chem. Soc.*, **1956**, 2066
c) R.C. Ellingson, R.L. Henry and F.G. McDonald, *J. Am. Chem.*, **67**, 1711 (1945)
d) R.C. Ellingson, R.L. Henry and F.G. McDonald, *J. Am. Chem. Soc.*, **71**, 2798 (1949)
e) G. Palamidessi and L. Bernardi, *Gazz. Chim. Ital.*, **93**, (4) 339 (1963) [*C. A.*, **59**, 13975d (1963)]

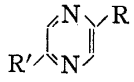
TABLE II. 2,6-Disubstituted Pyrazines



No.	R	R′	mp (°C) bp (°C/mmHg)	Solvent	Chemical shift (δ ppm) H_3	Chemical shift (δ ppm) H_5	$J_{3,5}$ (Hz)
XII	$COOCH_3$	Cl	43.5— 44.5	C(10)	9.20	8.79	0
XIII	$COOCH_3$	OCH_3	74.5— 75.5	C(6)	8.81	8.37	0
XIV	$COOCH_3$	OH	196 —197[a]	D[b]	8.45	8.29	0
XV	$COOCH_3$	$COOCH_3$	128.5—129.5[c]	C(10)	9.46	9.46	
XVI	$COOCH_3$	Br	59.0— 59.5 (115—120/5)	C(10)	9.22	8.89	0
XVII	COOH	COOH	218 —220[d] (decomp.)	D(10)	7.34	7.34	
XVIII	OCH_3	Cl	27.5— 28.5	C(10)	8.15	8.15	
XIX		Cl	93.5— 94.5	C(10)	8.84	8.63	0
XX		OCH_3	109.5—110	C(10)	8.47	8.29	0
				D(10)	8.40	8.40	

a) H. Foks and J. Sawlewicz, *Acta Pol. Pharm.*, **23**, 411 (1966)
b) saturated solution
c) H.I.X. Magner and W. Berends, *Rec. Trav. Chim.*, **77**, 827 (1958) [*C.A.*, **53**, 10240[i] (1959)]
d) K.H. Schaef and P.E. Spoerri, *J. Am. Chem. Soc.*, **71**, 2043 (1949)

Table III. 2,5-Disubstituted Pyrazines



No.	R	R′	mp (°C) bp (°C/mmHg)	Solvent	Chemical shift (δ ppm) H_3	Chemical shift (δ ppm) H_6	$J_{3,6}$ (Hz)
XXI	$COOCH_3$	Cl	90.5— 91.5	C(10)	9.08	8.71	1.4
XXII	$COOCH_3$	OCH_3	98.5— 99.5	C(10)	8.86	8.26	1.3
				D(10)	9.03	8.93	1.3
XXIII	$COOCH_3$	OH	183 —185[a]	C(1.4)	8.23	8.23	
				D(4)	8.09	7.98	1.1
XXIV	COOH	OCH_3	197.5—199.5	D(10)	8.71	8.29	1.3
XXV	COOH	NH_2	282.5—283.5[b]	D(10)	8.57	7.94	1.3
XXVI	COOH	COOH	260.0—265.0[c]	D(10)	9.30	9.30	
XXVII	CH_2OAc	CH_2OAc	77.0— 77.5	C(10)	8.63	8.63	
XXVIII	CH_3	CH_3	67 —69/35[d]	C(10)	8.33	8.33	

a) Ref. Table II *c*)
b) Ref. Table I *e*)
c) W.J. Schut, H.I.X. Magner and W. Beremds, *Receueil*, **80**, 391 (1961)
d) S. Gabriel and G.Pinkus, *Ber.*, **26**, 2197 (1893)

II. Simple Additivity of Shielding Parameter to the Ring Proton Chemical Shifts

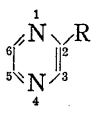
The substituent shielding parameter in the benzene derivatives was determined independently by Diehl,[9] Spiesecke, *et al.*[10] nad Martin, *et al.*[11] It was also reported by Gutowsky, *et al.*[12] that the additivity rules of the substituted shielding parameter could be applied for the estimation of the ring proton chemical shifts in polysubstituted benzene derivatives.

The substituent shielding parameter in Table IV were estimated from monosubstituted pyrazines as shown in Chart 2.

Table IV. Substituent Shielding Parameter[a]

R	d_o	d_m	d_p
$COOCH_3$	+0.74	+0.13	+0.19
CN	+0.37	+0.18	+0.25
OCH_3	−0.35	−0.48	−0.48
Cl	−0.04	−0.20	−0.08
CH_3	−0.12	−0.12	−0.20

a) The d_o, d_m, d_p represents *ortho, meta, para* shielding parameter respectively. The plus sign shows lower shift relative to pyrazine (8.59 ppm) in $CDCl_3$.



R=$COOCH_3$, Cl, OCH_3, CN, CH_3
$d_o=\delta_3-8.59$, $d_m=\delta_6-8.59$, $d_p=\delta_5-8.59$

Chart 2

d_o, d_m, and d_p represent *ortho, meta,* and *para* shielding parameter for substituent R, respectively δ_3, δ_5, δ_6, and 8.59 represent ring proton chemical shifts in monosubstituted pyrazines and pyrazine itself in deuteriochloroform solution.[13] Calculated chemical shifts using the simple additivity of the

9) P. Diehl, *Helv. Chim. Acta*, **44**, 829 (1961).
10) H. Spiesecke and W.G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).
11) J.S. Martin and B.P. Dailey, *J. Chem. Phys.*, **39**, 1722 (1963).
12) H.S. Gutowsky, D.W. McCall, B.R. McGarvey and L.H. Meyer, *J. Am. Chem. Soc.*, **74**, 4809 (1952).
13) Strictly speaking, spectra should be determined in dilute cyclohexane solution. However, the substituted pyrazines synthesized in the present study are hardly soluble in cyclohexane.

Table V. Observed and Calculated Chemical Shifts

R	R′		Obs.	Cal.	$\Delta^{a)}$
2-$COOCH_3$	3-Cl	H_5	8.65	8.58	+0.07
		H_6	8.59	8.64	−0.05
2-$COOCH_3$	3-OCH_3	H_5	8.33	8.30	+0.03
		H_6	8.26	8.24	+0.02
2-OCH_3	3-Cl	H_5	7.90	7.91	−0.01
		H_6	8.00	8.03	−0.03
2-$COOCH_3$	3-$COOCH_3$	H_5	8.68	8.91	−0.23
		H_6	8.68	8.91	−0.23
2-$COOCH_3$	6-Cl	H_3	9.20	9.25	−0.05
		H_5	8.79	8.82	−0.03
2-$COOCH_3$	6-OCH_3	H_3	8.81	8.85	−0.04
		H_5	8.37	8.43	−0.06
2-$COOCH_3$	6-$COOCH_3$	H_3	9.46	9.52	−0.06
		H_5	9.46	9.52	−0.06
2-OCH_3	6-Cl	H_3	8.15	8.16	−0.01
		H_5	8.15	8.15	0
2-$COOH_3$	5-Cl	H_3	9.08	9.13	−0.05
		H_6	8.71	8.76	−0.05
2-$COOCH_3$	5-OCH_3	H_3	8.86	8.85	+0.01
		H_6	8.26	8.37	−0.01
2-CH_3	5-CH_3	H_3	8.33	8.35	−0.02
		H_6	8.33	8.35	−0.02
2-$COOCH_3$	5-$COOCH_3$	H_3	9.38	9.46	−0.08
		H_6	9.38	9.46	−0.08

a) Δ=Obs. −Cal.

substituent shielding parameter showed good agreement with observed ones as shown in Table V.

It is noteworthy that the structure of a certain disubstituted pyrazine is easily determined by measuring the coupling constants and ring proton chemical shifts.

Experimental

All melting points are uncorrected. NMR spectra were taken with the JEOLCO model JNM 4H-100 high resolution spectrometer in $CDCl_3$ or DMSO-d_6 containing tetramethylsilane as internal reference.[14] All chemical shifts are expressed in δ values and coupling constants in Hz, which are observed on expanded charts measured at $9\times1/5$ sweep width.

Methyl 3-Methoxypyrazine-2-carboxylate (II)——To a solution of sodium methoxide prepared from sodium (250 mg) and absolute methanol (16 ml) was added below 5° methyl 3-chloropyrazine-2-carboxylate[15] with stirring. Immediately NaCl precipitated. The solution was kept at room tempareture for 4.5 hr and left overnight. After filtration of NaCl absolute ether was added. White mass was separated and washed with ether. The combined solution was concentrated *in vacuo* and distilled. bp 83—85 (2 mmHg), mp 56—59°. Yield, 750 mg (53.0%). Recrystallization from petroleum ether gave colorless needles, mp 58—60°. UV λ_{max}^{EtOH} mμ(log ε): 221.2 (3.99), 297.5 (3.90). NMR (8% solution in $CDCl_3$) δ: 8.26 (1H, doublet, J=2.5 Hz, ring proton), 8.33 (1H, doublet, J=2.5 Hz, ring proton), 4.00 (3H, singlet, $COOCH_3$ or OCH_3), 4.08 (3H, singlet, $COOCH_3$ or OCH_3). IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O), 1563, 1535 (pyrazine), 1150, 1270 (CO). *Anal.* Calcd. for $C_7H_8O_3N_2$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.67; H, 4.88; N, 16.65. Another white mass (430 mg) was dissolved in a small portion of water and acidified with conc. HCl and

14) Thanks are due to Messrs. I. Suyama and K. Tomita for NMR spectral measurements.
15) A. Albert, D.J. Brown and H.C.S. Wood, *J. Chem. Soc.*, **1956**, 2066.

extracted with $CHCl_3$. 3-Methoxy-2-pyrazinoic acid, mp 165—167° (decomp.) was obtained. Recrystallization from water gave colorless needles, mp 169—171°. IR ν_{max}^{KBr} cm^{-1}: 1710 (COOH), 1570, 1540 (pyrazine). *Anal.* Calcd. for $C_6H_6O_3N_2$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.55; H, 3.95; N, 17.92.

3-Methoxy-2-(4-morpholinocarbonyl)pyrazine (VII)——A mixture of 3-methoxy-2-pyrazinoic acid[16] (1.77 g), absolute benzene (10 ml) and $SOCl_2$ (0.5 ml) was refluxed for 2 hr with stirring. Benzene and excess $SOCl_2$ was removed *in vacuo*. The residue was dissolved in absolute benzene (20 ml). To ice-cold solution of morpholine (3.6 g) in absolute benzene (20 ml), the acid-chloride was added gradually with stirring. The solution was kept for 2 hr at room temperature and left overnight. The precipitated morpholine hydrochloride was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography and a pale yellow oil was obtained. Yield. 2.39 g (93.5%). bp 142—144° (0.05 mmHg). UV λ_{max}^{MeOH} $m\mu(\log \varepsilon)$: 213.0 (4.08), 284.7 (3.87). NMR (10% solution in $CDCl_3$) δ: 8.18 (2H, singlet, ring proton), 4.03 (3H, singlet, OCH_3); (10% solution in DMSO-d_6) δ: 8.28 (1H, doublet, $J=2.7$ Hz, ring proton), 8.37 (1H, doublet, $J=2.7$ Hz, ring proton), 3.98 (3H, singlet, OCH_3). IR $\nu_{max}^{liq.\ film}$ cm^{-1}: 2860 (OCH_3), 1640 (CON$\langle$), 1570 1540 (pyrazine), 1110, 1020 (C-O). *Anal.* Calcd. for $C_{10}H_{13}O_3N_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.82; H, 6.11; N, 18.08.

3-Morpholino-2-(4-morpholinocarbonyl)pyrazine (IX)——A mixture of 3-chloro-2-(4-morpholinocarbonyl)pyrazine[18] (250 mg), absolute morpholine (760 mg), and absolute benzene (10 ml) was refluxed for 5.5 hr with stirring and left overnight at room temperature. The precipitated morpholine hydrochloride was filtered off and the filtrate was concentrated at 100° *in vacuo*. A small portion of ether was added to the gummy residue, then white crystall (230 mg) was obtained, mp 109.5—111.0°. Recrystallization from isopropylalchol gave colorless needles, mp 109.5—111.0°. UV λ_{max}^{MeOH} $m\mu(\log \varepsilon)$: 210.0 (3.96), 341.5 (3.57). NMR (10% solution in $CDCl_3$) δ: 8.58 (2H, singlet, ring proton). IR ν_{max}^{KBr} cm^{-1}: 1633 (CON$\langle$), 1560, 1530 (pyrazine), 1112 (C-O).

Methyl 6-Bromo-2-pyrazinoate (XVI)——To a $POBr_3$ which was warmed to 60° in a 200 ml three necked flask equipped with thermometer, calcium chloride tube, and condenser was added gradually methyl 6-hydroxy-2-pyrazinoate[19] (15.4 g), then the temperature was elevated to 125° after 10 min. Acompaning violent evolution of HBr gas, the reaction mixture became pasty and cooled to room temperature. Stirring and cooling, the resulting dark solid was poured in to a 500 ml three necked flask containing ether (200 ml) and cold water (100 ml), while internal temperature was maintained below 50°. After stirring at 0—5° during 30 min, the product was extracted with $CHCl_3$ (500 ml×4) and washed with 10% Na_2CO_3 (100 ml×2), saturated solution of NaCl (150 ml×2), then dried over Na_2SO_4. The $CHCl_3$ was evaporated and the residue was again dissolved in $CHCl_3$ (100 ml). The undissolved substance was removed by filtration. After evaporation of $CHCl_3$, the residue was distilled in reduced pressure. bp 115—120° (5 mmHg), mp 55—57°. Yield, 9.07 g (41.8%). Recrystallization from petroleum ether gave colorless needles, mp 58—58.5°. UV $\lambda_{max}^{H_2O}$ $m\mu$: 225.0, 291.0. NMR (10% solution in $CDCl_3$) δ: 9.22 (1H, singlet, ring proton), 8.89 (1H, singlet, ring proton), 4.03 (3H, singlet, $COOCH_3$). IR ν_{max}^{KBr} cm^{-1}: 1735 (C=O), 1515 (pyrazine), 1153, 1115 (C-O). *Anal.* Calcd. for $C_6H_5O_2N_2Br$: C, 33.21; H, 2.32; N, 12.91. Found: C, 33.33; H, 2.28; N, 12.77.

2,5-Diacetoxymethylpyrazine(XXVII)——A mixture of dimethylpyrazine dioxide[20] (990 mg) and acetic anhydride (14 ml) was refluxed for 1 hr. Excess reagent was removed *in vacuo* and the resulting dark residue was distilled. bp 105°. (5 mmHg). Yield, 440 mg (27.0%). Recrystallization from ether gave mp 77.0—77.5°. UV $\lambda_{max}^{H_2O}$ $m\mu$: 273.5. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O), 1250, 1230, 1060 (C-O). *Anal.* Calcd. for $C_{10}H_{12}O_4N_2$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.71; H, 5.22; N, 12.06.

Acknowledgement The authors are grateful to Dr. T. Ishiguro, president of this company, Dr. M. Shimizu, Director of these Laboratories, Dr. T. Naito, Vice Director of these Laboratories and Dr. G. Ohta, Manager of Chemical Research Laboratory, for kind encouragement throughout the course of this work.

16) Ref. 3).
17) All silica gel chromatography in this paper was eluted with $CHCl_3$.
18) Ref. 3).
19) H. Foks and J. Sawlewicz, *Acta Pol. Pharm.*, 23, 411 (1966).
20) B. Klein and J. Berkowitz, *J. Am. Chem. Soc.*, **81**, 5160 (1959); G.T. Newbold and F.S. Spring, *J. Chem. Soc.*, 1947, 1183; C.F. Koelsh and W.H. Gumprecht, *J. Org. Chem.*, 23, 1603 (1958).