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Studies on Pyrazine Derivatives. II.[1] Synthesis, Reactions, and Spectra of Pyrazine N-Oxide Derivatives[2]

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Extensive works have been made of the preparation of six sets of 2-substituted pyrazine 4-oxide and its isomeric new 1-oxide by unambiguous route, and of the reaction between substituted pyrazine mono-N-oxides and a series of halogenation reagents and acylating agents and of nuclear magnetic resonance (NMR), infrared, and ultraviolet spectral investigations in comparison with isomeric N-oxides.

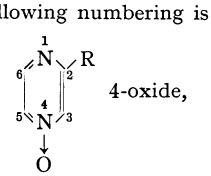
An application of NMR spectroscopy for determination of the position of the N-O function in mono-substituted pyrazine N-oxides and the analysis of N-oxidation reaction mixture are described.

Much interest has been taken in the chemistry of aromatic amine oxides in recent years.[4] Among the diazine N-oxides, pyridazine N-oxide derivatives have been chemically and physico-chemically studied in detail.[5,6] In the case of pyrimidine N-oxides and pyrazine N-oxides, however, systematic investigations have been relatively limited so far.

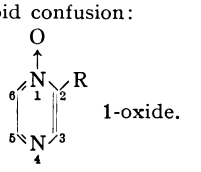
In the previous paper of this series[1] we reported the synthesis of substituted pyrazine mono-N-oxides and also reported the usefulness of these N-oxides for the synthesis of di-substituted pyrazines. However, determination of the position of N-O group in some of these N-oxides still remains unsettled. Further, it was reported that the reactions of 2-carbomethoxy- and 2-(4-morpholinocarbonyl)pyrazine 4-oxides with phosphoryl chloride afforded 2-carbomethoxy- and 2-(4-morpholinocarbonyl)-6-chloropyrazines, instead of expected 3- or 5-chloro derivatives. The position of the chloro group in 6-chloro derivatives was confirmed by converting methyl 6-chloro-2-pyrazinecarboxylate to the known 2-amino-6-chloropyrazine.

The present paper describes the synthesis of 2-substituted pyrazine 4-oxides[7] and their isomeric 1-oxides[7] by unambiguous routes, and the reactions of these N-oxides with a series of halogenation reagents and acylating agents. Spectral investigations are carried out in comparison with isomeric N-oxides. The application of nuclear magnetic resonance (NMR) spectroscopy for determination of the position of the N-O function in mono-substituted pyrazine N-oxides and the analysis of N-oxidation reaction mixture are also described.

1) Part I: F. Uchimaru, S. Okada, A. Kosasayama, and T. Konno, *Chem. Pharm. Bull.* (Tokyo), **19**, 1337 (1971).
2) This work was presented at The 2nd Symposium on Heterocyclic Chemistry (Japan), Nagasaki, November 1969.
3) Location: *Minamifunaboricho, Edogawa-ku, Tokyo.*
4) For example, E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Company, Amsterdam, 1967.
5) A. R. Katritzky and A. J. Boulton, "Advances in Heterocyclic Chemistry," Vol. 9, Academio Press, New York, London, 1968, p. 285.
6) K. Tori, M. Ogata, and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 235 (1963).
7) In this paper the following numbering is adopted to avoid confusion:



4-oxide,



1-oxide.

Synthesis of 2-Substituted Pyrazine Mono-N-oxides

In our study of N-oxidation reaction of 2-(4-morpholinocarbonyl)pyrazine (I) with hydrogen peroxide in hot acetic acid, pure mono-N-oxide (II) has been isolated as the main product, which was expected to be the 4-oxide on the basis of the data already published.[8]

We now wish to report the chemical determination of the position of oxygen atom. The acid hydrolysis of this mono-N-oxide (II) yielded a product, melting at 188—188.5° (decomp.) which was proved to be a pyrazinoic acid N-oxide from the data of elemental analysis and infrared (IR) spectrum. Foks and Sawlewicz[9] synthesized 2-pyrazinoic acid 4-oxide (III) and reported the melting point of this compound as 213—214°.[9a] Thus it seemed necessary to clarify whether the hydrolysate was 4-oxide (III), or its isomeric new 1-oxide (XVII). The carboxylic acid and also various derivatives of both N-oxides were prepared to compare their chemical and physical properties.

2-Chloropyrazine 4-oxide (IV) was synthesized from 2-chloropyrazine with hydrogen peroxide in hot acetic acid according to the method of Klein, *et al.*[10] and Bernardi, *et al.*[11] The N-oxide (IV) was shown to be free from contamination with its isomeric 1-oxide (XII) by gas chromatography.

2-Pyrazinecarboxamide 4-oxide (VI) was obtained from 2-chloro compound (IV) by substitution of chlor atom with sulfonyl group followed by subsequent replacement of the sulfonyl group with cyano group. Both attempts to convert the chloro compound (IV) to the cyano derivative (VI) by cuprous cyanide in N-methylpyrrolidone or dimethylformamide, or to obtain the cyano derivative (VI) from the amino compound (IX) by Sandmeyer reaction were failed.[12]

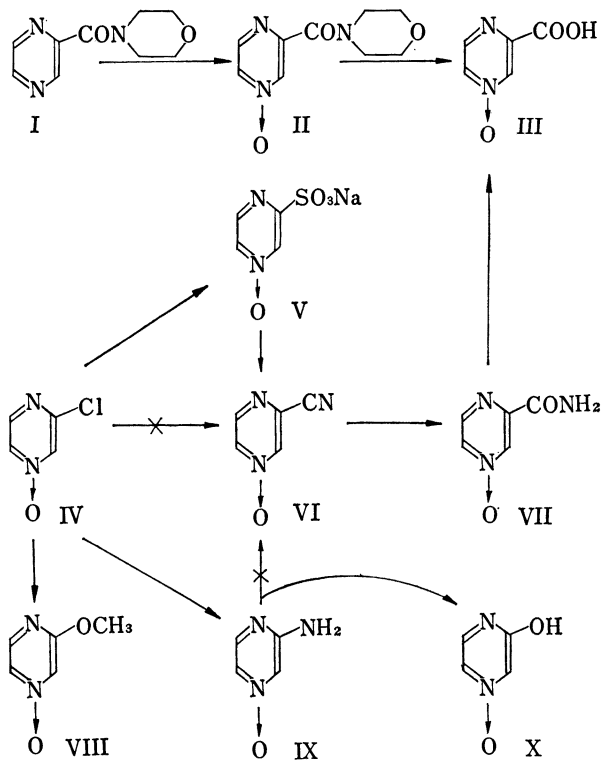


Chart 1

8) For example, ref. 4) pp. 41—49.

9) H. Foks and J. Sawlewicz, *Acta Pol. Pharm.*, **21**, 429 (1964) [*Chem. Abstr.*, **62**, 7754[f] (1965)]; *a*) See ref. 14) in Part I.

10) B. Klein, N.E. Hetman, and M.E. O'Donnell, *J. Org. Chem.*, **28**, 1682 (1963).

11) L. Bernardi, G. Palamidessi, A. Leone, and G. Larini, *Gazz. Chim. Ital.*, **91**, 1431 (1961) [*Chem. Abstr.*, **57**, 2223[e] (1962)].

12) Ochiai and Teshigawara [*Yakugaku Zasshi*, **65**, 435 (1945)] showed that the diazonium salt of 4-aminopyridine 1-oxide can be substituted by a cyano group (65%) by Sandmeyer reaction. Ochiai and Naito [*Yakugaku Zasshi*, **65**, 441 (1945)] similary converted 4-aminoquinoline 1-oxide to cyano dreivative (13%).

In the case of 2-aminopyrazine 4-oxide (IX), however,its diazonium salt is considerably unstable even at a low temperature (−10°) to be converted to 2-hydroxypyrazine 4-oxide (X);[12a,b] *a*) G. Palamidessi and L. Bernardi, *Gazz. Chim. Ital.*, **93**, 339 (1963) [*Chem. Abstr.*, **59**, 13975[d] (1963)]; *b*) M. Terao, *J. Antibiotics*, Series A, **16**, 182 (1963).

Table I. Comparison of Melting Points of 2-Substituted Pyrazine N-Oxides

R		
Cl	97 — 98°	133 —134.5°
OCH_3	80 — 81.5°	159.5—160.5°
SO_3H	235 —237° (decomp.)	152.5—153° (decomp.)
CN	153.5—154.5°	156 —157°
$CONH_2$	300° (decomp.)	205 —206.5°
COOH	188 —188.5° (decomp.)	138.5—139.5°

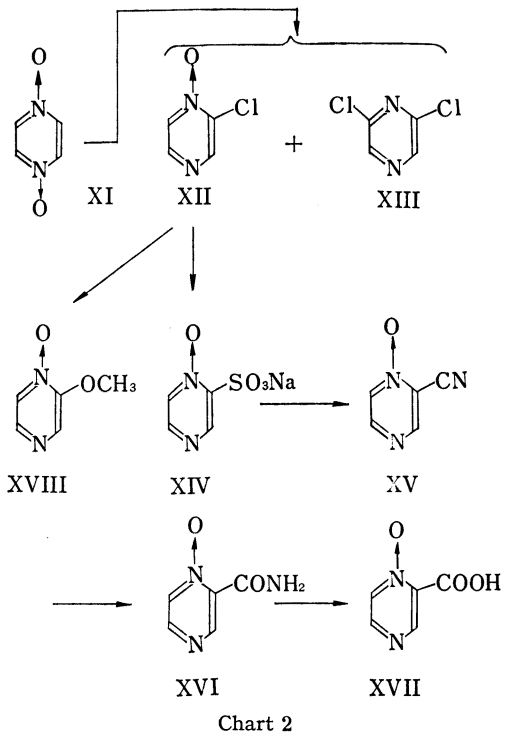


Chart 2

2-Carbamoylpyrazine 4-oxide (VII) was obtained by the reaction of 2-cyanopyrazine 4-oxide (VI) with hydrogen peroxide in alkaline solution at 50° in a moderate yield and the alkaline hydrolysis of the amide (VII) yielded 2-pyrazinoic acid 4-oxide (III) melting at 188—188.5° (decomp.).

Similarly, several new 2-substituted pyrazine 1-oxides (XIV, XV, XVI, XVII, XXIII) were synthesized from 2-chloropyrazine 1-oxide (XII).[12a] These new 1-oxides showed the melting points and physicochemical properties different from those of the isomeric 4-oxides as shown in Table I.

In view of these findings, we conclude that in the reaction of 2-(4-morpholinocarbonyl) pyrazine (I) with hydrogen peroxide, oxydation occured at the position 4.

Reaction of 2-Substituted Pyrazine Mono-N-oxides with Halogenation Reagents and Acylating Agents

We reported that the reaction between 2-carbomethoxypyrazine 4-oxide (XXIII) and phosphoryl chloride yielded methyl 6-chloro-2-pyrazinecarboxylate (XXIV), and 2-(4-morpholinocarbonyl)pyrazine 4-oxide (II) on treatment with the same reagent gave mainly 6-chloro-2-(4-morpholinocarbonyl)pyrazine (XIX) along with a small amount of 3-chloro derivative (XX).[1]

2-Pyrazinecarboxamide 4-oxide has been shown to form 6-chloro-2-pyrazinecarbonitrile when treated with phosphoryl chloride, whereas, in the case of 2-chloropyrazine 4-oxide and 2-amino derivative, 2,3- and 2,6-dichloropyrazines and 2-amino-3-chloropyrazine were obtained respectively as reported by Bernardi and his associates.[11,12a] 2-Carbomethoxypyrazine 4-oxide (XXIII) yields methyl 6-acetoxy-2-pyrazinecarboxylate (XXVII) by heating with acetic anhydride according to Foks and Sawlewicz.[13] These facts that chlorine

13) H. Foks and J. Sawlewicz, *Acta Pol. Pharm.*, **23**, 437 (1966) [*Chem. Abstr.*, **66**, 94996^s (1967)].

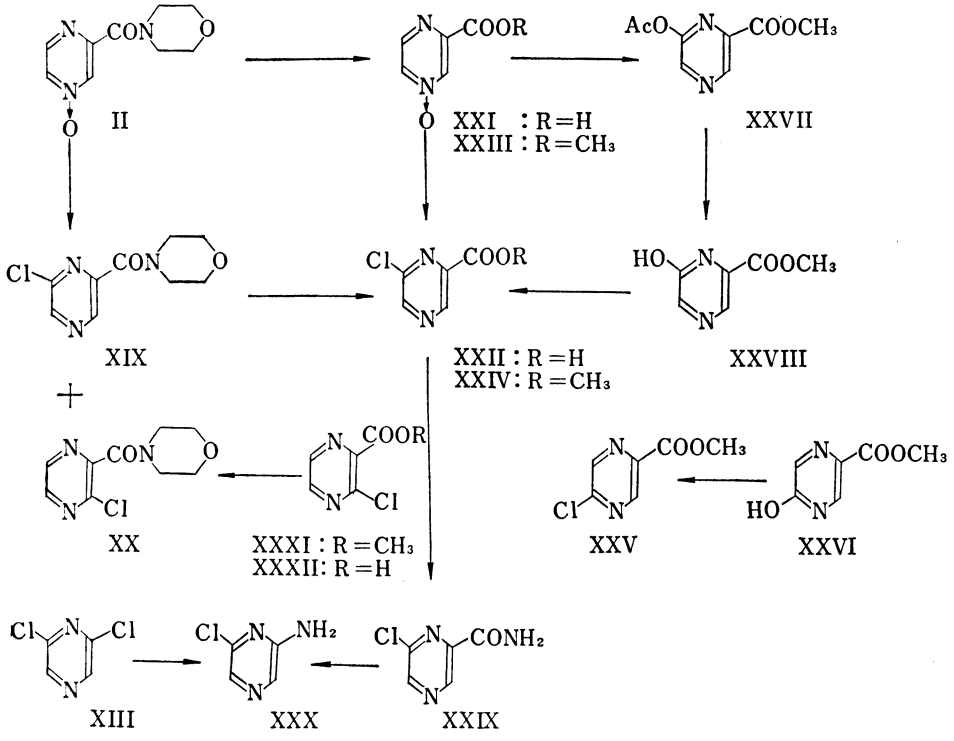


Chart 3

and acetoxy groups enter to β-position of N-oxide have been very interesting examples in contrast to the case of the pyridine N-oxide derivatives.[14] Thus, it seemed desirable to investigate the reactions of 2-substituted pyrazine mono-N-oxides with a series of halogenation reagents[15] in detail using the technique of gas chromatography.

It was found that treatment of 2-(4-morpholinocarbonyl) derivative (II) with thionyl or sulfuryl chloride yielded 6-chloride (XIX) and 3-chloride (XX) under reflux conditions. The latter chloride was identified with the authentic sample (XX) prepared from the known methyl 3-chloro-2-pyrazinecarboxylate (XXXI)[16] by mixed melting point, by ultraviolet (UV), infrared and NMR spectra and by gas chromatography.

We found that the reaction of 2-carbomethoxypyrazine 4-oxide (XXIII) with phosphoryl or thionyl chloride at refluxing temperature gave the 6-chloride (XXIV) as a sole product. This result was confirmed by using gas chromatography in comparison with the authentic 3-, 5-, and 6-chlorides.

Treatment of 2-carbomethoxypyrazine 4-oxide (XXIII) with excess or equimolar acetyl chloride yielded the 6-chloride (XXIV) but no 3- or 5-chloride (XXXI, XXV), nor 6-acetoxypyrazine (XXVII). In the case of acetic anhydride, only 6-acetoxypyrazine (XXVII) was obtained which was converted to 6-chloride (XXIV) and identified with an authentic sample. The result agreed with an earlier observation by Foks and Sawlewicz.[13]

When 2-aminopyrazine 4-oxide (XXXIII) was heated with excess phosphoryl chloide, only 3-chloride (XXXV) was obtained and no other isomeric chlorides (XXX, XXXVII) were detected.

14) *e.g.*, E.C. Taylor and A.J. Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).
15) The reaction of these N-oxides with tosyl chloride in the presence of pyridine will be reported in a forthcoming paper.
16) A. Alberts, D.J. Brown, and H.C.S. Wood, *J. Chem. Soc.*, **1956**, 2066.

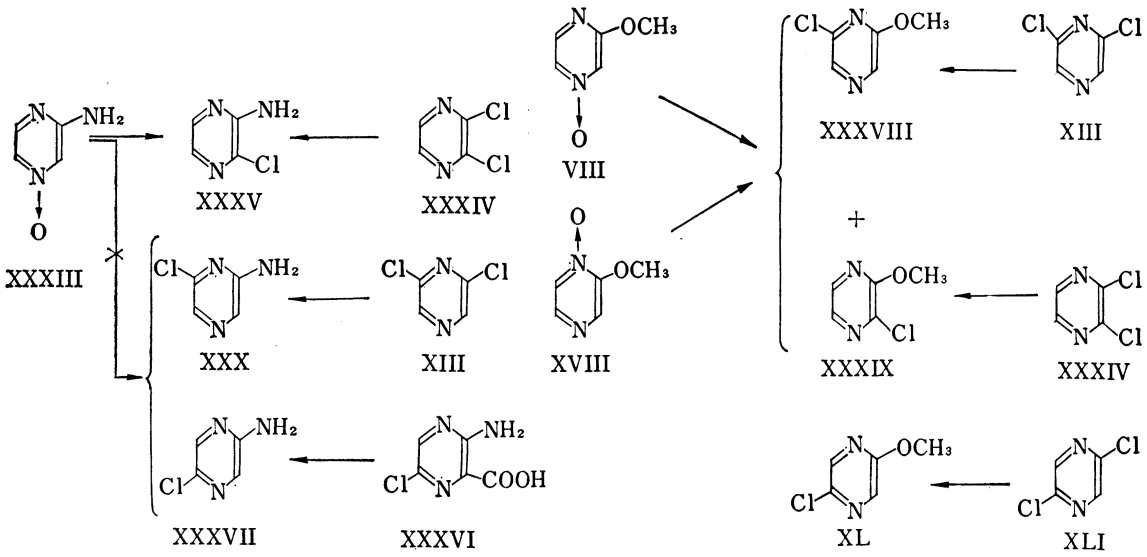


Chart 4 Chart 5

Both methoxypyrazine N-oxides (VIII, XVIII) reacted with phosphoryl chloride, yielding 3-chloride (XXXIX) and 6-chloride (XXXVIII) but not 5-chloride (XL).

In view of these findings, it was concluded that, in the reaction of substituted pyrazine N-oxides with halogenation reagents, when the substituent was an electron-withdrawing group (*e.g.*, carbomethoxy), the product would be the 6-chloride, while the 3-chloride would be obtained when the substituent is an electron-donating group (*e.g.*, amino). In the case of weak electron-donating group (*e. g.*, methoxy) both the 3- and 6-chloride would be formed. On the contrary, the 5-chloride could not be detected in all the cases. This conclusion is essentially the same with the consideration of Bernardi and associates.[12a]

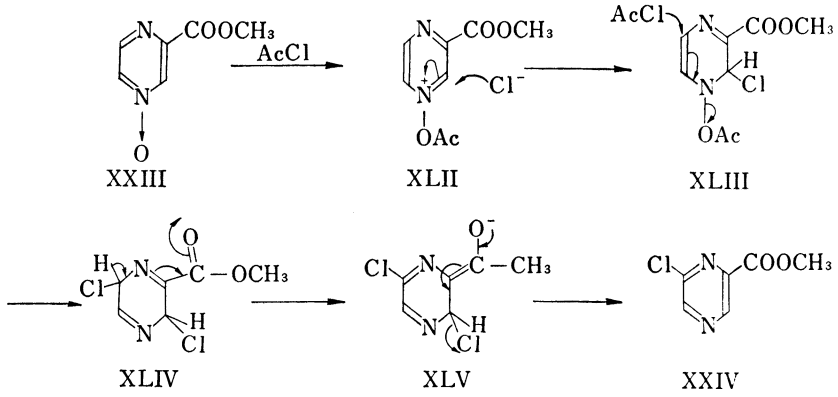


Chart 6

A general mechanism of substitution in the β-position of heterocyclic N-oxides has been suggested by Ochiai and his associates.[17] As applied to the reaction of 2-carbomethoxypyrazine 4-oxide (XXIII) with acetyl chloride, this would involve initial formation of an inter-

17) *e.g.*, ref. 4), pp. 310—325; M. Hamana, *Farumashia*, **10**, 639 (1966).

mediary adduct (XLIII) by attack of chloride ion to the electron defficient α-carbon atom, followed by nucleophilic attack by other molecule of acetyl chloride and removal of the O-acetyl group to form intermediary diazacyclohexadiene (XLIV). In the final step, the intermediate (XLIV) is led to methyl 6-chloro-2-pyrazinecarboxylate (XXIV) simply by mesomeric effect of the carbomethoxy group. Althrough the mechanism of this reaction has not been elucidated thoroughly, the scheme outlined in Chart 6 appears to offer one possible rationalization. It seems reasonable that the reaction pathway in the case of pyrazine N-oxides and acetic anhydride is much more complex.

NMR, IR, and UV Spectral Studies of 2-Substituted Pyrazine Mono-N-oxides[18]

NMR Spectra.——Proton magnetic resonance study of pyrazine mono-N-oxide itself has been already established completely by Ohtsuru and Tori.[19] However, little is known about the NMR of substituted pyrazine mono-N-oxides other than 2-methylpyrazine N-oxide.[20]

In the field of the syntheses of pyrazine N-oxide derivatives, determination of the position of N-O group in these N-oxides is of great interest. Among the physico-chemical techniques which can be applied to structural problems on pyrazine N-oxides, NMR spectroscopy will give more detailed information on this subject. This part deals with NMR spectral study of both 2-substituted pyrazine N-oxides together with the spectra of corresponding pyrazine derivatives for comparison. All the spectra of these derivatives taken in 9×1/5 sweep width gave simple patterns which made it possible to compute all the chemical shifts on the basis of coupling constants reported by Tori and Ohtsuru,[19] with sufficient accuracy for a first order analysis. As an example, the spectra of pyrazinecarbonitrile and its N-oxides are shown in Fig. 1. Chemical shifts of both series of N-oxides, the deviation from the parent base, and coupling constants are listed in Table II.

The N-oxide group in 2-substituted pyrazine 4-oxides gives a magnetic anisotropy effect on the *ortho* protons (H_3, H_5), causing substantial shielding (0.12—0.72 ppm), on the *meta*

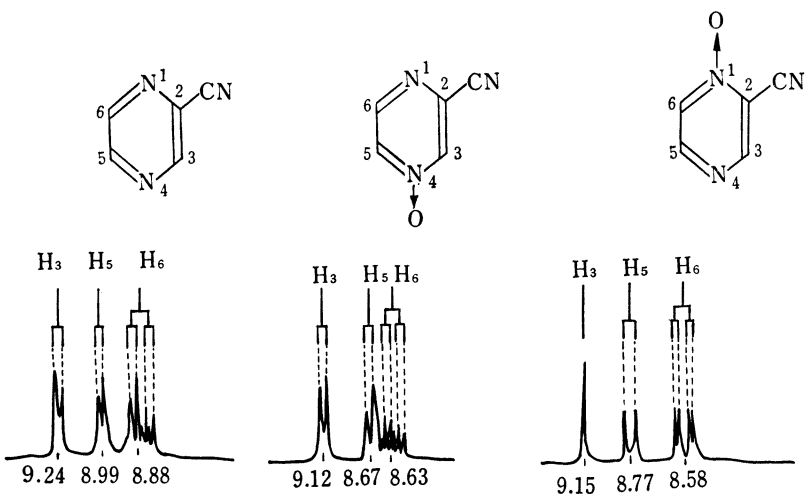


Fig. 1. Nuclear Magnetic Resonance Spectra of Pyrazinecarbonitrile and Both Cyanopyrazine N-Oxides at 100 MHz in 9×1/5 Sweep Width in DMSO-d_6

18) Mass spectra of pyrazine N-oxides (as Part III): F. Uchimaru, S. Okada, A. Kosasayama, and T. Konno, *J. Heterocyclic Chem.*, **8**, 99 (1971).
19) M. Ohtsuru and K. Tori, The 20th Meeting of Chemical Society of Japan, Abstract I-149 (1967).
20) W.H. Gumprecht, T.E. Beukelman, and R. Paju, *J. Org. Chem.*, **29**, 2477 (1964).

TABLE II. Chemical Shifts and Coupling Constants of 2-Substituted Pyrazine 4-Oxides and 1-Oxides in 10% Solution in DMSO-d_6 at 100 MHz

Substituent	Chemical shifts δppm			Coupling constants J Hz	
	H_3	H_5	H_6	J_{56}	J_{35}
4-Oxide					
i) CN	9.12 (0.12)[a]	8.61 (0.38)	8.69 (0.19)		1.5
ii) $COOCH_3$	8.78 (0.44)	8.62 (0.31)	8.67 (0.08)	4.2	2.0
iii) COOH	8.64 (0.59)	8.51 (0.39)	8.64 (0.20)		
iv) SO_3H	8.51 (0.38)	8.33 (0.27)	8.33 (0.27)		
v) $CONH_2$	8.55 (0.72)	8.47 (0.44)	8.59 (0.18)	4.2	
vi) Cl	8.70 (0.13)	8.38 (0.33)	8.44 (0.13)	4.1	1.0
vii) OCH_3	8.06 (0.26)	7.97 (0.26)	8.16 (0.07)	4.2	1.8
1-Oxide					
i) CN	9.15 (0.07)	8.77 (−0.22)	8.58 (0.30)		
ii) $COOCH_3$	—	—	—	—	—
iii) COOH	9.17 (0.06)	8.85 (0.05)	8.60 (0.24)	4.8	
iv) SO_3H	8.95 (−0.06)	8.60 (0.00)	8.43 (0.17)		
v) $CONH_2$	9.17 (0.10)	8.68 (0.23)	8.48 (0.29)	4.7	
vi) Cl	8.90 (−0.07)	8.58 (0.13)	8.51 (0.06)	4.1	
vii) OCH_3	8.50 (−0.18)	8.36 (−0.13)	8.18 (0.05)		

a) ( ) = $\delta_{H\ base} - \delta_{H\ N\text{-}oxide}$

protons resulting in minor upfield shift (0.07—0.27 ppm). In 2-substituted pyrazine 1-oxides, the N-oxide function causes comparatively small shielding (0.05—0.30 ppm) on the *ortho* protons (H_6), and considerably small shielding or rather deshielding effect (−0.18—0.23 ppm) on the *meta* protons (H_3, H_5). Similar observations have been obtained in other aromatic amine oxides.[19,21-23]

With regard to spin–spin coupling constants, the values of *ortho* coupling ($J_{5,6}$) and *meta* coupling ($J_{3,5}$) shown in Table II are reasonable in comparison with pyrazine mono-N-oxide itself.[19]

Every spectrum of 2-substituted pyrazine 1-oxide listed in Table II is composed of a singlet peak and two doublet peaks in aromatic region, and shows simple pattern in comparison with the corresponding 4-oxide. The differences between the spectrum of 2-substituted pyrazine 1-oxide and that of 4-oxide are apparent as shown in Fig. 1. It is noteworthy that two series of isomeric N-oxides are easily discernible by comparing their NMR spectra. For example, the structure of the simple N-oxide, mp 88—89.5°, obtained by the reaction between methylpyrazine and hydrogen peroxide in hot acetic acid, is assumed to be 1-oxide by means of NMR spectroscopy and this result is consistent with the chemical proof by Gumprecht, *et al.*[20] It is also shown by NMR technique that the crude methoxypyrazine N-oxide by the N-oxidation of methoxypyrazine is composed of corresponding 4-oxide alone.[24]

In the NMR spectra of 2-substituted pyrazine N-oxides shown in Table II, the signal of H_3 of the 1-oxide can always be seen apart from the other signals of the 1-oxide and the corresponding 4-oxide (0.12—0.47 ppm) other than cyano derivative (0.03 ppm) as a singlet in the lowest field. From the observation mentioned above, it is apparent that NMR spectroscopy will be

21) Y. Kawazoe and S. Natsume, *Yakugaku Zasshi*, **83**, 523 (1963).
22) K. Tori and M. Ogata, *Chem. Pharm. Bull.* (Tokyo), **12**, 272 (1964).
23) R.A. Abramovitch and J.B. Davis, *J. Chem. Soc.* (*B*), **1966**, 1137.
24) H. Otomasu, R. Yamaguchi, K. Ishigo-oka, and H. Takahashi [*Yakugaku Zasshi*, **82**, 1434 (1964)] obtained 2-methoxyquinoxaline 4-oxide by N-oxi dation of the parent base and assumed that the reason for this phenomenon is owing to the fact that the methoxy group exerts a great steric hindrance towards the adjacent ring-nitrogen.

useful in analysis of a reaction mixture obtained in the N-oxidation of 2-substituted pyrazine derivatives. In fact, analysis of standard samples prepared from each authentic N-oxide or a reaction mixture gave the values shown in Table III. These results are consistent with the values obtained by gas chromatographic analysis. As already mentioned, the fact that methoxypyrazine yields only the 1-oxide is also demonstrated by checking its NMR spectrum.

Table III. Methylpyrazine 1-Oxide (%) in the Mixture of Methylpyrazine 1-Oxide and 4-Oxide

	Standard sample (%)				Reaction
	I	Error	II	Error	mixture
	42.9	—	58.4	—	
NMR ring proton (DMSO-d_6)[a]	42.9	0.0	55.9	−2.5	54.6
CH_3 ($CDCl_3$)[a]	40.3	−2.6	56.1	−2.3	54.3
GLC[b]	44.7	+1.8	59.3	+0.9	60.5

a) 10% solution *b*) 5% PEG succinate (2m) at 140°

IR Spectra——The infrared spectra of 2-substituted pyrazine 4-oxides and 2-methylpyrazine 1-oxide have been well investigated by Shindo.[25] Little is known, however, about the infrared spectra of 2-substituted pyrazine 1-oxides other than the 2-methyl derivative. In the present study, the infrared spectra of five sets of substituted pyrazine and its both 1- and 4- oxides are examined.

It has been established that the N-O stretching frequencies in substituted pyrazine N-oxides appear as a strong absorption band in the region of 1350—1260 cm^{-1}. The observed N-O stretching frequencies in solid state which are absent in the spectra of corresponding pyrazines are listed in Table IV. These values of six 4-oxide derivatives are in good agreement with those reported by Sindo.

On the other hand, the 1-oxide derivatives exhibit their N-O frequencies in the region of 1339—1292 cm^{-1}, which show a deviation to lower frequencies to some extent than the corresponding 4-oxides except for pyrazinoic acid N-oxides and these behaviors are just the same as that shown by methylpyrazine N-oxides.[25]

Table IV. N-O Stretching Frequencies of Pyrazine N-Oxides (KBr Tablet)

Substituent	4-Oxide N-O cm^{-1}	1-Oxide N-O cm^{-1}	$\Delta\nu$ cm^{-1}
CN	1333	1320	13
$COOCH_3$	1337		
COOH	1303	1315	−12
Cl	1323	1313	10
$CONH_2$	1307	1295	12
OCH_3	1343	1339	4
CH_3	1325	1292	33

UV Spectra——Pyrazine and alkylpyrazines exhibit an absorption at about 260—270 mμ in water while their mono-N-oxides show two peaks, one about 215 mμ, and the other about 260 mμ which are characteristic of the N-O function.[26]

25) H. Shindo, *Chem. Pharm. Bull.* (Tokyo), **8**, 33 (1960).
26) B. Klein and J. Berkowitz, *J. Am. Chem. Soc.*, **81**, 5160 (1959).

Seven sets of both pyrazaine N-oxides examined in water exhibit ultraviolet absorption spectra characteristic of N-oxides as shown in Table V. Nearly all N-oxides show peaks at about 220—230 mμ and another at about 260—270 mμ. However the difference between two isomeric N-oxides is not discernible.

TABLE V. UV Spectra of Pyrazine N-Oxides (in H_2O)

Substituent	4-Oxide λ max, mμ ($\varepsilon \times 10^{-4}$)						1-Oxide λ max, mμ ($\varepsilon \times 10^{-4}$)					
CN	230	(2.26)	274	(1.70)	310 sh[a]	(0.24)	232	(2.53)	274	(1.15)	310 sh	(0.24)
$COOCH_3$	229	(2.08)	270.5	(1.21)	305 sh							
COOH	223.5	(1.45)	266.5	(1.05)	300 sh		224	(1.24)	270	(1.15)	300 sh	(0.39)
$CONH_2$	227.5	(2.00)	269	(1.10)	305 sh		228.5	(2.24)	270	(1.14)	300 sh	(0.29)
Cl	225	(1.47)	268	(1.50)	295 sh		223	(1.70)	265	(1.02)	295 sh	(0.28)
					304 sh						305 sh	(0.23)
SO_3H	224	(1.64)	270	(1.23)	300 sh	(0.26)	225	(2.21)	270.5	(1.25)	300 sh	(0.28)
OCH_3	216	(2.68)	261	(1.42)	304	(0.68)	221	(1.53)	260[b]	(0.68)	309	(0.45)
OH	222—223[c]		276[c]		330—332[c]		232[d]				330[d]	
	(1.70)		(0.67)		(0.43)		(3.89)				(3.56)	

a) shoulder b) shifts to 273.5 mμ in dioxane c) ref. 12b) d) in MeOH

Experimental[27]

All melting points are uncorrected. Thin-layer chromatography (TLC) was performed by the ascending technique using 20×5 cm precoated silica gel and the following solvent systems: solvent I, $(CH_3)_2C{=}O$–$CHCl_3$(7:3), solvent II, $CHCl_3$–EtOH(9:1), solvent III, $CHCl_3$–MeOH(1:1). Gas–liquid chromatographic works were done with Hitachi Perkin-Elmer Model 53K and Model F6 D using following columns: 3 mm×1 m, 5% polyethylene glycol succinate on Anakrom ABS 70—80 mesh (5% PEG succinate); 3 mm×1 m, 2% polyethylene glycol 20 M on Anakrom ABS 70—80 mesh (2% PEG 20 M); 0.5 mm×45 m, stainless steel capillary, coated with butanediol succinate (BDS 45).

Measurement of Spectra——IR Spectra: The Hitachi Model EPI-2, EPI-S2, and EPI-G2 infrared spectrophotometers were used. Liquid samples were measured in liquid film and KBr disc method was applied to solid state measurement. The positions of bands were calibrated with a polystyrene film.

NMR Spectra: The JEOLCO Model JNM 4H-100 high resolution NMR spectrometer was used. The spectra were observed on 10% solution (w/v) in $CDCl_3$ and in DMSO-d_6 containing tetramethylsilane as an internal reference at room temperature. Chemical shifts and coupling constants were read out on the expanded chart measured at 9 1×5 sweep width by using frequency counter installed in the spectrometer. All the chemical shifts are expressed in ppm from tetra methyl silane (TMS), and the coupling constants are in Hz.

UV Spectra: The ultraviolet spectra were obtained with the Hitachi Model EPS-2U spectrometer.

Mass Spectra: The mass spectra were measured by a Hitachi mass spectrometer RMS-4 with a direct inlet system. Heating temperature was around 205—290°. The ionization energy was kept at 70 eV.

2-Chloropyrazine 4-Oxide (IV)——The 4-oxide (IV) prepared from chloropyrazine[10,28] according to the method of Klein, *et al.*,[10] and Bernardi, *et al.*,[11] was shown to be free from contamination with 2-chloropyrazine 1-oxide (XII) by gas–liquid chromatography using a 5% PEG Succinate column at 120°. Relative retention time [t_R,2-chloropyrazine 1-oxide (XII)=1.00] of 2-chloropyrazine 4-oxide (IV) is 1.03.

2-Pyrazinesulfonic Acid 4-Oxide (V)——To an aqueous solution (10 ml) of sodium sulfite (1.26 g) was added 2-chloropyrazine 4-oxide (IV) (1.3 g) and red colored solution which turned to colorless solution immediately after reflux, was heated under reflux for 4 hr. The solution was concentrated to a small volume, *in vacuo* and chilled on an ice bath. The precipitate was filtered and washed with methanol to afford sodium salt (1.64 g, 82.8%) of (V), mp 295—300°.

The sodium salt (0.64 g) of (V) was passed through a column of "Amberlite IR 120(H^+)" (5 ml) and the solution was evaporated to dryness *in vacuo* to afford 2-pyrazinesulfonic acid 4-oxide (V) [0.533 g, 94.5%

27) Thanks are due to Messrs. I. Ito and K. Tomita for NMR spectral measurements, Mr. B. Kurihara for Mass spectral measurements, and Mr. K. Shimazaki, Miss K. Takahashi for elemental analyses.

28) B. Klein and P.E. Spoerri, *J. Am. Chem. Soc.*, **73**, 2949 (1951).

based on sodium salt of (V)], mp 230—235° (decomp.). *Anal.* Calcd. for $C_4H_4O_4N_2S$: C, 27.29; H, 2.29; N, 15.85. Found: C, 27.31; H, 2.49; N, 15.31.

2-Cyanopyrazine 4-Oxide (VI)[29]——A mixture of sodium salt (1 g) of V and potassium cyanide (0.99 g) was heated gradually on a silicon oil-bath under reduced pressure (5 mmHg) and light brown solid (0.612 g, 31%), mp 145—149°, was sublimed at 290—295°. Recrystallization from methanol gave light brown prisms, mp 153.5—154.5°. *Anal.* Calcd. for $C_5H_3ON_3$: C, 49.60; H, 2.50; N, 34.70. Found: C, 49.99; H, 2.84; N, 34.76. IR ν_{max}^{KBr} cm^{-1}: 2250 (CN).

2-Pyrazinecarboxamide 4-Oxide (VII)——A mixture of 2-cyanopyrazine 4-oxide (VI) (20 mg) in alkaline 3% hydrogen peroxide solution (0.54 ml, pH *ca.* 9) was warmed on a steam-bath at 55°. After 10 min the pH was adjusted to 9 with 1% sodium hydroxide and warmed additional 45 min. The solution was chilled and colorless deposited powder was collected by filtration. After washing with water and then methanol and drying *in vacuo* at 100°, pure (VII) (12 mg, 52.2%), mp 291—291.5° (decomp.) was obtained. IR ν_{max}^{KBr} cm^{-1}: 1685 (amide, C=O). Mass Spectrum *m/e*: 139 (M^+).

2-Pyrazinoic Acid 4-Oxide (III)——A solution of the amide (VII) (11 mg) in 1N sodium hydroxide (0.15 ml) was heated under reflux for 12 hr. The solution was passed through a column of "Amberlite IR 120 (H^+)" (1 ml), and the solution was evaporated to dryness *in vacuo*. Recrystallization of the residue from water afforded the acid (III) as colorless prisms (1 mg, 9%), mp 189—189.5° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3110—2320 (COOH), 1733 (COOH). Mass Spectrum *m/e*: 140 (M^+).

2-Aminopyrazine 4-Oxide (IX)——This material was prepared from 2-chloropyrazine 4-oxide (IV) by a method similar to that described by Klein, *et al.*[30]

Sandmeyer Reaction of 2-Aminopyrazine 4-Oxide (IX)——2-Aminopyrazine 4-oxide (IX) (0.15 g) was dissolved in a solution of conc. sulfuric acid (0.54 g) and water (1.5 ml) on heating on a steam-bath. The solution was cooled in a dry ice-acetone bath and diazotized with a solution of sodium nitrite (0.101 g) in water (0.6 ml) with stirring at −10°——20° for 1 hr to produce a paste of a reaction mixture. Separately, potassium cuprous cyanide solution was made from copper sulfate crystals ($CuSO_4 \cdot 5H_2O$) (0.338 g) and potassium cyanide (0.365 g) according to the metod of Ochiai and Teshigawara.[12]

To the potassium cuprous cyanide solution the diazonium salt solution was added with stirring at 5—10°. The reaction mixture was allowed to stand overnight at room temperature and the precipitate was removed by filtration. The filtrate was made strongly alkaline with aqueous sodium hydroxide, evaporated to dryness *in vacuo* and the residue was extracted with hot methanol (80 ml). The extract was re-dissolved in water (10 ml) and the solution (pH, 10.3) was neutralized to pH 5.5 with hydrochloric acid, concentrated to dryness *in vacuo* to afford a crystalline residue [53 mg, 35% as (X)], mp 170—185° (decomp.), which was recrystallized from ethanol using active charcoal, to give 2-hydroxypyrazine 4-oxide (17 mg), mp 225°. IR ν_{max}^{KBr} cm^{-1}: 3100, 3040 (ν_{CH}), 2950—2500 (bonded OH), 1640 (lactam C=O). UV $\lambda_{max}^{H_2O}$ $m\mu$: 221—222, 272—275, 328—334. TLC: solvent I, *Rf* 0.5.

2-Methoxypyrazine 4-Oxide (VIII)——To a cold solution of sodium methoxide made from sodium (0.506 g) and absolute methanol (10 ml) was added 2-chloropyrazine 4-oxide (IV) (2.6 g) with stirring and cooling, and then the reaction mixture was kept at room temperature for 1 hr. The solvent was evaporated *in vacuo* and the residue was extracted with hot chloroform, decolorized with active charcoal. Evaporation of the solvent *in vacuo* afforded crystals (2.06 g, 81%), mp 55.5—64.5°. Several recrystallization from ether gave methoxypyrazine 4-oxide (VIII) as colorless needles, mp 80—81.5°. *Anal.* Calcd. for $C_5H_6O_2N_2$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.68; H, 4.93; N, 21.91.

2-Chloropyrazine 1-Oxide (XII)——Bernardi's method[11] was modified for the preparation of the 2-chloropyrazine 1-oxide. To phosphoryl chloride (1.83 ml) powdered pyrazine-1, 4-dioxide[26] (0.56 g) was added and the suspension was heated with stirring. The vigorous reaction occured at 102—107°. After 4 min the dark mixture was cooled and poured on ice with stirring. After the decomposition of the excess reagent was complete, the solution in which 2,6-dichloropyrazine (XIII) was separated out, was extracted with three portions of ether (each 30 ml) and from the ether layer 2,6-dichloropyrazine (0.435 g, 58.5%), mp 52.5—54°, was obtained. The aqueous layer was made alkaline (pH 8—9) with 20% sodium hydroxide on cooling, extracted with chloroform (total 150 ml), and the extract was washed with water, dried over anhydrous sodium sulfate and the solvent was stripped *in vacuo* to afford crystals (XII) (0.166 g, 25.4%), mp 127.5—131.5°. The crystals were analyzed by gas chromatography and no 2-chloropyrazine 4-oxide (IV) was detected. Recrystallization from acetone gave a pure sample of XII, mp 133—134.5° (Lit,[11] mp 140—146°), as colorless prisms. *Anal.* Calcd. for $C_4H_3ON_2Cl$: C, 36.82; H, 2.32; O, 12.27; N, 21.47; Cl, 27.17. Found: C, 37.02; H, 2.77; O, 12.34; N, 21.73; Cl, 27.63. TLC: solvent I, *Rf* 0.5, solvent II, *Rf* 0.59.

2-Pyrazinesulfonic Acid 1-Oxide (XIV)——To a solution of sodium sulfite (1.52 g) in water (22 ml) 2-chloropyrazine 1-oxide (XII) (1.57 g) was added and the mixture was heated under reflux for 5 hr. The solution was concentrated to about one-fifth volume to give sodium salt (2.15 g, 90.5%) of (XIV), mp 280—281° (decomp.). The sodium salt was dissolved in water (20 ml) and passed through a column of "Amberlite

29) The mp of this compound (VI) was reported, without experimental details, as 153° by H. Shindo.[25]
30) B. Klein, E. O'Donnel, and J. Auerbach, *J. Org. Chem.*, **32**, 2412 (1967).

IR120(H^+)" (18 ml) and the eluate and washings were evaporated to dryness *in vacuo* affording 2-pyrazinesulfonic acid 4-oxide (1.68 g, 88.5%), mp 152—154°. Several recrystallization from water gave a pure sample as colorless powder, mp 252.5—253° (decomp.). *Anal.* Calcd. for $C_4H_4O_4N_2S$: C, 27.29; H, 2.29; N, 15.85. Found: C, 26.86; H, 2.35; N, 15.92.

2-Cyanopyrazine 1-Oxide (XV)——A mixture of sodium salt (0.677 g) of (XIV) and dried potassium cyanide (0.67 g) was heated under reduced pressure (1 mmHg). Light yellow solid (0.21 g, 50.6%), mp 135—145°, was sublimed at 290—310°. The crude product was recrystallized from methanol to afford colorless prisms, mp 156—157°. The infrared spectrum did not show the absorption band characteristic for nitrile group in the region 2200—2300 cm^{-1}. *Anal.* Calcd. for $C_5H_3ON_3$: C, 49.60; H, 2.50; N, 34.70. Found: C, 49.54; H, 2.59; N, 34.54. TLC: solvent II, *Rf* 0.54.

2-Pyrazinecarboxamide 1-Oxide (XVI)——2-Cyanopyrazine 1-oxide (XV) (0.974 g) was dissolved in alkaline 3% hydrogen peroxide solution (23.2 ml, pH 9) and the solution was heated on a steam bath at 55°. After 15 min the pH of the solution was adjusted to 9 with 1% sodium hydroxide and heating at 55° was continued for an additional 3.75 hr. The solution was allowed to stand overnight at room temperature to precipitate light yellow prisms (0.563 g, 50.3%), mp 198—200°. Concentration of the mother liquors to dryness *in vacuo* and recrystallization of the residue from water yielded an additional product (0.118 g, 10.5%), mp 194—197°. Recrystallization from water gave colorless prisms, mp 205—206.5°. *Anal.* Calcd. for $C_5H_5O_2N_3$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.19; H, 3.83; N, 30.48. IR ν_{max}^{KBr} cm^{-1}: 3330—3010 (amide NH_2), 1690—1650 (amide C=O).

2-Pyrazinoic Acid 1-Oxide (XVII)——A solution of the amide (XVI) (0.425 g) in 10% sodium hydroxide (2.44 ml) was heated under reflux for 12 hr. The resulting light red-brown solution was made acidic with conc. hydrochloric acid (0.53 ml) and cooled. The precipitate (0.214 g, 50%) was collected by filtration. After several recrystallization from water a pure sample was obtained as colorless prisms, mp 138.5—139.5°. *Anal.* Calcd. for $C_5H_4O_3N_2$: C, 42.85; H, 2.88; N, 20.00. Found: C, 42.98; H, 3.11; N, 20.41. IR ν_{max}^{KBr} cm^{-1}: 3080—2140 (COOH), 1780 (COOH).

3-Chloro-2-pyrazinoic Acid (XXXII)——To an aqueous solution (5 ml) of potassium carbonate (0.22 g) methyl 3-chloro-2-pyrazinecarboxylate (XXXI) (0.5 g), which was prepared from methyl 3-hydroxypyrazinecarboxylate by the method of Alberts, *et al.*[16] was added and the mixture was heated under reflux. The solution was made strongly acidic with conc. hydrochloric acid, extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent left a residue (0.4 g, 87%), mp 103—107°, which was recrystallized from ether–petroleum ether to afford colorless powdered crystals, mp 116.5—118.5°. IR ν_{max}^{KBr} cm^{-1}: 3000—2300 (COOH), 1710 (COOH). UV λ_{max}^{MeOH} $m\mu$ (log ε): 277.5 (3.83).

The hydrolysis of the ester (XXXI) with aqueous sodium hydroxide gave the same product (80.5%, mp 103—107°) as yielded above.

3-Chloro-2-(4-morpholinocarbonyl)pyrazine (XX)——To a solution of thionyl chloride (1.5 ml) in absolute benzene (15 ml) 3-chloro-2-pyrazinoic acid (XXXII) (0.5 g) was added and the suspension was heated under reflux with stirring for 2 hr. After all the excess reagent and solvent was removed *in vacuo*, the residue was taken up in benzene (15 ml). To the benzene solution a solution of morpholine (0.55 g) in benzene (15 ml) was added dropwise with stirring and cooling (below 15°). The mixture was stirred on cooling in an ice bath for 1 hr and the precipitated morpholine hydrochloride was removed by filtration. The filtrate was concentrated to dryness *in vacuo* and the resulting red-brown crystals (0.74 g) dissolved in chloroform was chromatographed on silica gel and eluated with chlaoroform. The eluate was recrystallized from isopropyl alcohol affording colorless prisms (0.53 g, 73%), mp 108.5—109.5°. *Anal.* Calcd. for $C_9H_{10}O_2N_3Cl$: C, 47.48; H, 4.42; N, 18.45; Cl, 15.57. Found: C, 47.90; H, 4.86; N, 18.68; Cl, 15.76. IR ν_{max}^{KBr} cm^{-1}: 1643 (amide C=O). UV λ_{max}^{MeOH} $m\mu$ (log ε): 278.1 (3.83).

Methyl 5-Hydroxy-2-pyrazinecarboxylate (XXVI)——The suspension of 5-hydroxy-2-pyrazinoic acid[31] (0.18 g) in absolute methanol (7 ml) containing a few drops of thionyl chloride was heated at 80° in a sealed tube for 1.5 hr.[32] The solution was concentrated to dryness *in vacuo* and the oily residue crystallized in needles which was triturated with a small volume of methanol. The crude product (0.135 g, 68.2%), mp 172—173°, was collected by filtration.

31) E. Felder, D. Pitre, and E.B. Grabitz, *Helv. Chim. Acta*, **47**, 873 (1964).

32) Esterification of the carboxylic acid with 20% methanolic hydrogen chloride under reflux for 1 hr afforded crude ester (XXVI) (60.6%), mp 170—172.5°. On the other hand, when the carboxylic acid (0.24 g) was esterified with refluxing methanol on bubbling with dry hydrogen chloride gas, the unknown product (0.11 g), mp 285—286° (decomp.) was obtained. A sample, mp 292.5°—293° (decomp.), colorless needles from water, showed: UV (H_2O): 274 and 307 with a shoulder at 300, 319, 338 $m\mu$, IR (KBr) cm^{-1}: 3400—2890 (OH or NH), 1725 (ester C=O), 1693, 1655 (C=O, C=N or C=C), NMR (DMSO-d_6) δ ppm: 3.77 (3H, singiet, OCH_3), 7.14 (1H, singlet, aromatic proton), 11.31—11.70 (2H, broad, OH or NH).

A portion was purified by preparative thin-layer chromatography on silica gel followed by recrystallization from methanol for analysis, mp 181.5—184°, as colorless needles. *Anal.* Calcd. for $C_6H_6O_3N_2$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.56; H, 4.18; N, 17.59. TLC: solvent III, *Rf* 0.70. IR ν_{max}^{KBr} cm^{-1}: 3470, 3050, 2945, 2850, 2650, 2500, 2330 (OH,NH,CH), 1715 (ester C=O), 1687 (lactam C=O). UV $\lambda_{max}^{H_2O}$ mμ: 259, 312.

Methyl 5-Chloro-2-pyrazinecarboxylate (XXV)——A suspension of methyl 5-hydroxy-2-pyrazinecarboxylate (XXVI) (1.27 g) in phosphoryl chloride (9.7 ml) containing a few drops of conc. hydrochloric acid was gradually heated with stirring and the exothermic reaction occurred at about 70°. Heating under reflux was continued for 1.5 hr. Most of excess reagent was removed *in vacuo* and the resulting dark mixture was poured on chopped ice with stirring. The product was isolated by extraction into chloroform (200 ml). The extract was washed with water, 5% sodium bicarbonate, again with water, and dried over sodium sulfate. After removal of the solvent *in vacuo* the residue was taken up in ether, the solvent was removed *in vacuo* and the residue was dissolved in petroleum ether. The solution was concentrated to about 20 ml at atmospheric pressure to deposit colorless needles (0.823 g), mp 87.5—90°. Recrystallization from petroleum ether gave colorless needles, mp 90.5—91.5°. *Anal.* Calcd. for $C_6H_5O_2N_2Cl$: C, 41.76; H, 2.92; N, 16.24; Cl, 20.54. Found: C, 41.99; H, 2.76; N, 15.98; Cl, 20.65. TLC: solvent I, *Rf* 0.68. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O), 1150, 1020 (C–O). UV $\lambda_{max}^{H_2O}$ mμ (log ε): 225 (4.05), 278 (3.94), 281 (3.99), 296 (inflection, 3.55). NMR (10% solution in $CDCl_3$) δ ppm: 4.07 (3H, singlet, $COOCH_3$), 8.71 and 9.08 (2H, two doublets, J= 1.4 Hz).

The Reaction of 2-Carbomethoxypyrazine 4-Oxide (XXIII) with Halogenation Reagents and Acylating Agents——i) With Phosphoryl Chloride: This reaction was performed by following exactly the same method described in Part I.[1]

ii) With Thionyl Chloride: A suspension of 2-carbomethoxypyrazine 4-oxide (XXIII) (15.4 g) in thionyl chloride (200 ml) was heated to reflux for 7 hr. After removal of the excess reagent *in vacuo* the dark residue was distilled, collecting colorless liquid (13.8 g, 87.9%), bp 97—102° (4 mmHg), which solidified on cooling. Recrystallization from cyclohexane gave methyl 6-chloro-2-pyrazinecarboxylate (XXIV) as colorless needles (5.05 g, 32%), mp 41—44.5°.

iii) With Acetyl Chloride: A suspension of the 4-oxide (XXIII) (15.4 g) in acetyl chloride (15.7 g) was refluxed 35 hr. Excess reagent was removed *in vacuo* and the black residue was taken up in chloroform (40 ml) and the chloroform solution was washed with water (40 ml), dried over sodium sulfate and evaporated to dryness *in vacuo*, leaving dark oil. This was distilled, collecting colorless liquid (1.18 g, 68%), bp 93—94° (4 mmHg), which solidified, on cooling, mp 38—39.5°. Recrystallization from cyclohexane gave methyl 6-chloro-2-pyrazinecarboxylate (XXIV) as colorless needles, mp 41—43.5°.

Equimolecular quantities of the 4-oxide (XXIII) (0.77 g) and acetyl chloride (0.39 g) in dry chloroform (10 ml) was refluxed for 35 hr. A probe sample indicated a peak of methyl 6-chloro-2-pyrazinecarboxylate (XXIV), but not that of 3-chloride (XXXI), 5-chloride (XXV) or 6-acetoxypyrazine (XXVII) by gas-liquid chromatography.

iv) With Acetic Anhydride: A solution of the 4-oxide (XXIII) (120 g) in acetic anhydride (1.5 liters) was heated under reflux for 30 hr. Following removal of solvent *in vacuo*, the black tarry residue was dissolved in chloroform (1 liter). The solution was washed with water and dried over calcium chloride and concentrated to a dark liquid. This was distilled, collecting colorless liquid (102 g, 66.6%), bp 145—150° (2 mmHg), which solidified in the receiver, mp 54—57°. Recrystallization from ether gave colorless prisms, mp 58—60°.[33] *Anal.* Calcd. for $C_6H_8O_4N_2$: C, 48.97; H, 4.11; N, 14.28. Found: C, 49.36; H, 4.06; N, 14.00. UV $\lambda_{max}^{H_2O}$ mμ (log ε): 277 (3.96). IR ν_{max}^{KBr} cm^{-1}: 1776 (acetoxy, C=O), 1736 (ester, C=O).

Table VI. Relative Retention Times [t_R, Methyl 6-Chloro-2-pyrazinecarboxylate (XXXIV)=1.00] of the Distilled Products and of the Reference Compounds

Compd.	BDS-45	PEG succinte
Product in i)	1.00	—
Product in ii)	1.00	—
Product in iii)	1.00	—
Product in iv)	—	4.65
Methyl 6-chloro-2-pyrazinecarboxylate (XXIV)	1.00	1.00
Methyl 3-chloro-2-pyrazinecarboxylate (XXXI)	0.96	—
Methyl 5-chloro-2-pyrazinecarboxylate (XXV)	0.83	—
Methyl 6-acetoxy-2-pyrazinecarboxylate (XXVII)	—	4.65

33) This is in good agreement with the mp reported by Foks and Sawlewicz.[13]

v) Gas–Liquid Chromatographic Analyses: The distilled products of i), ii), iii), and iv) were analysed using a BDS-45 column at 135° and a 5% PEG succinate column at 170°. In all cases only one peak was obtained in the chromatogram.

Methyl 6-Hydroxy-2-pyrazinecarboxylate (XXVIII)——To a solution of methyl 6-acethoxy-2-pyrazinecarboxylate (XXVII) (1.1 g) in methanol (2 ml) 22% methanolic hydrogen chloride (10 drops) was added. On standing this solution was darkened and crystals deposited gradually and allowed to stand overnight. Upon cooling a precipitated solid (0.67 g, 77.7%), mp 195—196° (decomp.), was filtered off. Recrystallization from methanol afforded colorless needles, mp 196—197° (decomp.).[34] *Anal.* Calcd. for $C_6H_6O_3N_2$: C, 46.78; H, 3.93; N, 18.19. Found: C, 46.93; H, 4.13; N, 18.05. IR ν_{max}^{KBr} cm^{-1}: 3020—2140 (OH or NH), 1718 (ester C=O), 1685—1665 (lactam, C=O). UV $\lambda_{max}^{H_2O}$ $m\mu$ (log ε): 242 (3.90), 329 (3.93).

Structure-proof of This Compound was Done as Follows: A suspension of this hydroxy derivative (XXVII) (0.66 g) in phosphoryl chloride (3.9 ml) was refluxed for 50 min. The dark solution was concentrated *in vacuo* to about one-third volume and poured onto chopped ice with stirring. The solution was extracted with chloroform. The residue, after removal of solvent, was dissolved in ether and insoluble starting material (0.86 g, 9% recovered), mp 193—195° (decomp.) was filtered off. The dark oil from the filtrate showed only one peak (t_R, 1.00) of methyl 6-chloro-2-pyrazinecarboxylate (XXIV) by gas–liquid chromatography. This was distilled, collecting colorless liquid (0.332 g, 45.3%), bp 91° (33 mmHg), which solidified, mp 42.5—43.5°. This material did not depress the mp of authentic methyl 6-chloro-2-pyrazinecarboxylate (XXIV).

2-Amino-3-chloropyrazine (XXXV)——A mixture of 2,3-dichloropyrazine (XXXIV) (1.83 g) and conc. ammonium hydroxide (10 ml) was heated in a sealed tube at 140° for 14 hr. The solution was cooled and the crystalline mass (0.82 g, 51.2%), mp 167—168°, was filtered off. Recrystallization from methanol gave colorless prisms, mp 167—168°.[35] *Anal.* Calcd. for $C_4H_4N_3Cl$: C, 37.06; H, 3.11; N, 32.42; Cl, 27.35. Found: C, 37.16; H, 3.42; N, 32.23; Cl, 27.66. IR ν_{max}^{KBr} cm^{-1}: 3375, 3295, 3170 (NH), 1633 (NH). NMR (10% solution in $CDCl_3$) δ ppm: 7.92 and 7.70 (2H, two doublets, J=2.5 Hz), 5.05 (2H, singlet, NH_2). Mass Spectrum m/e: 129 (M^+).

2-Amino-6-chloropyrazine (XXX)——This compound (mp 152—154°) was prepared by the method of Part I of this series.[1]

2-Amino-5-chloropyrazine (XXXVII)——This material (mp 130—132°) was prepared by Palamidessi and Bernardi.[36]

The Reaction of 2-Aminopyrazine 4-Oxide (XXXIII) with Phosphoryl Chloride——A suspension of 2-aminopyrazine 4-oxide[30] (XXXIII) (0.3 g) in freshly distilled phosphoryl chloride (3 ml) was refluxed for 2 hr. A probe sample showed a main spot (*Rf* 0.62) and did not indicate that of starting material (XXX,*Rf* 0.28) or deoxygenated product (aminopyrazine, *Rf* 0.46)[30] by thin-layer chlomatogrum using solvent I. Most of excess reagent was removed *in vacuo* and poured on chopped ice. After the decomposition was complete, the solution was made strongly alkaline with 10% sodium hydroxide, extracted with chloroform. The extracts were washed with water, dried over sodium sulfate and concentrated to dryness *in vacuo* affording a solid (0.142 g, 40.6%), which was analysed by gas–liquid chromatography. This crude material was recrystallized from methanol affording colorless prisms, mp 165—166.5°, which was identified as 2-amino-3-chloropyrazine (XXXV) (mp, mixture mp and infrared spectra).

Gas–liquid chromatographic analyses of the crude material and reference substances were performed by using a 5% PEG succinate column (1 m) at 120°.

Table VII. Relative Retention Times [t_R,2-Amino-3-chloropyrazine (XXXV)=1.00]

Compd.	t_R
Crude material	1.00
2-Amino-3-chloropyrazine (XXXV)	1.00
2-Amino-5-chloropyrazine (XXXVII)	5.05
2-Amino-6-chloropyrazine (XXX)	4.88
Aminopyrazine	1.25

2-Chloro-6-methoxypyrazine (XXXVIII)——To a solution of 2,6-dichloropyrazine (XIII) (2.98 g)[11] in chloroform (3 ml) and methanol (4 ml) sodium methoxide solution made from metal sodium (0.483 g) and methanol (10 ml) was added with stirring and cooling (below 15°). After addition was complete the solution was allowed to stand overnight at room temperature. The precipitated sodium chloride was removed by

34) Foks and Sawlewicz[13] give the mp as 205—206°.
35) Bernardi, *et al.*[12a] give the mp as 169°.
36) G. Palamidessi and L. Bernardi, *J. Org. Chem.*, **29**, 2491 (1964).

filtration, the solvent was evaporated *in vacuo* and the residue was re-dissolved in chloroform, filtered. The oily residue, after removal of solvent, was distilled affording a colorless liquid (2.08 g, 72%), bp 117° (112 mmHg), which solidified, mp 27.5—28.5°. Redistillation afforded a colorless liquid, bp 105° (103 mmHg), which solidified, mp 27.5—28.5°. *Anal.* Calcd. for $C_5H_5ON_2Cl$: C, 41.56; H, 3.49; N, 19.38. Found: C, 42.00; H, 3.53; N, 19.17. IR ν_{max}^{film} cm^{-1}: 904, 860 (δ CH). UV λ_{max}^{MeOH} mμ: 219.5, 277—280 (inflection), 297.5.

2-Chloro-5-methoxypyrazine (XL)——Sodium methoxide solution (1.5 mmole/ml) was cautiously added dropwise to a solution of 2,5-dichloropyrazine (XLI) (0.56 g)[36] in a mixture of methanol (0.5 ml) and ether 1 ml) with stirring and cooling until a peak of starting material (XLI) disappeared in gas–liquid chlomatogram using a BDS 45 column at 130°. In several runs this required 2.5 ml (3.75 mmole) of the sodium methylate solution. This reaction mixture was poured on ice water (5 ml) and extracted with several portions of ether (total 100 ml). The extracts were washed with water, dried over sodium sulfate. The oily residue, after evaporation of the solvent, was chromatographed on silica gel (15 g). The column was washed with petroleum ether–dichloromethane (10:1) (100 ml), then eluated with petroleum ether–dichloromethane (1:1) (200 ml). The eluate from the later solvent system was distilled to afford light yellow liquid (0.06 g, 11%), bp 105° (105 mmHg). The product solidified on cooling at 0° and melted on standing at room temperature. IR ν_{max}^{film} cm^{-1}: 894, 839 (δ CH). UV $\lambda_{max}^{H_2O}$ mμ: 221.5, 306.

The Reaction of 2-Methoxypyrazine 4-Oxide (VIII) and 2-Methoxypyrazine 1-Oxide (XVIII) with Phosphoryl Chloride——i) The Reaction of the 4-Oxide (VIII): To phosphoryl chloride (10.45 g) 2-methoxypyrazine 4-oxide (VIII) (0.86 g) was added in several portions with stirring and gradually heated to reflux. After 30 min the excess solvent was removed *in vacuo* and the black residue was poured on chopped ice with good stirring. The product was isolated by extraction into chloroform (60 ml). The extract was washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* at low temperature and the residue was distilled, giving a smelling colorless liquid (0.3 g, 30.6%), bp 75° (110 mmHg).

ii) The Reaction of the 1-Oxide (XVIII): A suspension of the 1-oxide (XVIII) (0.64 g) in phosphoryl chloride (3.12 g) was warmed with stirring at 60° for 35 min. A probe sample at this time showed two peaks at 229 mμ and 300 mμ, indicating that the N-oxide peak at 260 mμ had disappeared. The solution was chilled and poured cautiously on to chopped ice with good stirring. After decomposition was complete the solution was extracted with chloroform (total 150 ml), the extract was washed with water and dried over sodium sulfate. After the solvent had been removed the crude product was distilled under reduced pressure. Colorless liquid (0.46 g, 63%), bp 118° (123 mmHg) was collected. A portion was re-distilled for analysis, bp 117° (123 mmHg). *Anal.* Calcd. for $C_5H_5ON_2Cl$: C, 41.56; H, 3.49; N, 19.38. Found: C, 40.20; H, 3.17; N, 18.94.

Gas–liquid chromatographic analyses of the products in i) and ii) was performed by using a 2% PEG 20 M column at 70° and a BDS 45 column at 100°.

TABLE VIII. Relative Retention Times [t_R, 2-Chloro-3-methoxypyrazine (XXXVIII)=1.00]

Compd.	PEG	BDS-45
Product in i)	1.00 and 2.19	1.00 and 7.41
Productin ii)	1.00 and 2.19	1.00 and 7.41
2-Chloro-6-methoxypyrazine (XXXVIII)	1.00	1.00
2-Chloro-5-methoxypyrazine (XL)	1.37	5.21
2-Chloro-3-methoxypyrazine (XXXIX)	2.19	7.41

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