Mass Spectra of Pyrazine *N*-Oxides. Studies on Pyrazine Derivatives. III (1)

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The mass spectra of pyrazine 4- and 1-oxides, their di-*N*-oxides and corresponding pyrazines have been determined. The fragmentations induced by electron impact were examined by means of deuterium labeling and high-resolution measurements. The most pronounced feature of the spectra was the appearance of M-16 ion peaks. In the case of the methyl and methoxy derivatives of 1-oxides, the intensity ratio of M-17/M-16 was larger than in the 4-oxides.

Numerous papers concerning the mass spectra of aza-aromatic systems have been reported during the past decade. The studies of mass spectrometry of their *N*-oxides, however, are relatively limited. Mass spectral studies have been reported for pyridines- (2), quinolines and isoquinolines- (3), benzimidazoles and quinoxalines- (4), *as*-triazines- (5), naphthyridines and pyridazines N-oxides (6).

Generally speaking, the characteristic peak of aromatic *N*-oxides is that due to the M-16 ion. However, compounds having an alkyl group in the position *ortho* to the *N*-oxide group show a M-17 ion peak due to the loss of an OH radical. While the representative fragmentation of pyridazine *N*-oxides is observed at M-30 (M-NO) (6).

In the course of our studies on pyrazine derivatives, we synthesized two series of pyrazine *N*-oxide derivatives (1), and determined the mass spectra of these two series of *N*-oxides.

To interpret the genesis of the principal fragments, several deuterium-labeled compounds were also prepared. Methoxy-d_3-pyrazine 4-oxide (XV) was prepared by selective 4-*N*-oxidation of methoxy-d_3-pyrazine (XXIV) which had been obtained by the reaction of chloropyrazine with sodium methoxide-d_3. The structure of this compound was confirmed by nmr, ir and mass spectra as well as its elemental analysis. The same reaction of 2-chloropyrazine 4-oxide (XI) with sodium methoxide-d_3 caused partial deuterium exchange of the ring protons *alpha* to the *N*-oxide group. This was also revealed by the nmr and mass spectra. The corresponding 1-oxide (II) also showed similar ring proton exchanges.

In addition, accurate mass measurements established the elemental composition of all of the principal fragments.

The main fragmentation of 2-methylpyrazine 1-oxide (IV) is shown in Chart II. The M-17 ion peak appeared in an abundance of 43% relative to the base peak. The one-step elimination of the OH radical was confirmed by the presence of an appropriate metastable ion peak. Elimination of HCN from the diazatropylium ion gave the pyrryl ion. An alternative course is loss of an oxygen atom followed by the formation of ions *d* or *e* due to the expulsion of HCN or CH_3CN. In the case of the 4-oxide, the M-17 ion peak was weak (2%) and the formation of the pyrrole ion *d* or ion *e* *via* the M-16 ion was predominant. The loss of a stable neutral molecule such as HCN or CH_3CN is a driving force for fragmentation from the M-16 or M-17 ion.

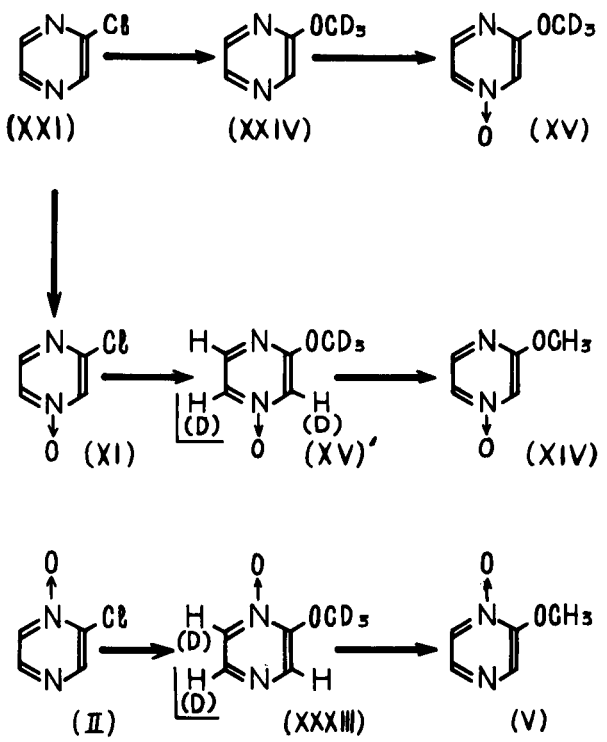


Chart I

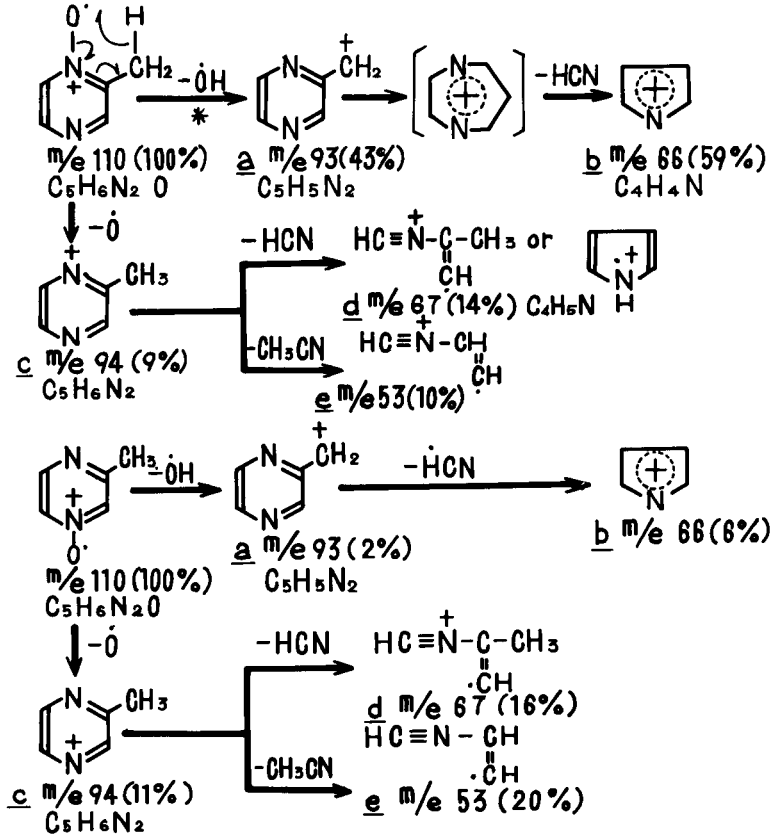


Chart II

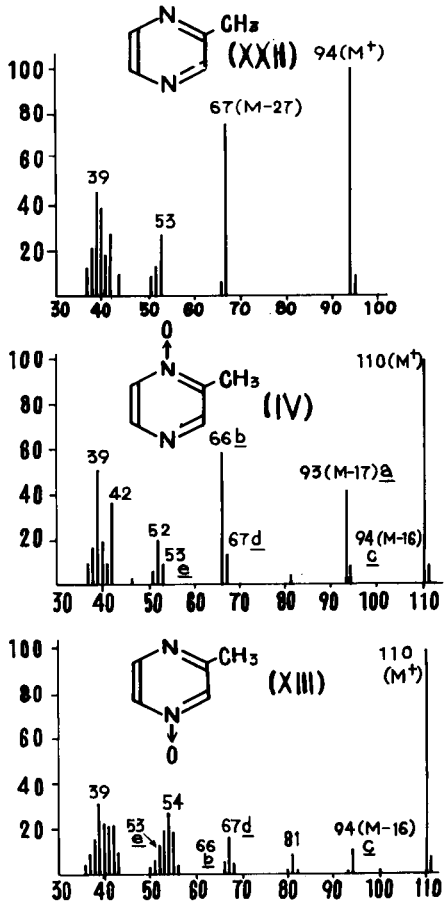


Figure I

*The occurence of this process is supported by the presence of an appropriate metastable ion in the mass spectrum.

Since an M-1 peak was observed for both of the methoxy *N*-oxides and their parent methoxypyrazine, three pathways, M-1-16, M-16-1 and M-17 are possible for the origin of the M-17 ion. Among them, the fragmentation by one-step elimination of OH was confirmed by the presence of a metastable ion peak in the 1-oxide (V). The relative abundance of the M-16 ion was less than half compared to that of the M-17 ion peak. High-resolution measurement proved that the course of the m/e 95 ion formation involves the transformation $h \rightarrow i$ and not by loss of NO from ion *g*.

The fact that the M-17 ion had about the same intensity compared to the M-16 ion in the 4-oxide (XIV) in which the *ortho* effect has difficulty in existing, is explained by the contribution of the M-1-16 or/and M-16-1 pathway. Although the peak at m/e 96 could be produced both by loss of NO or HCHO, high-resolution measurement and examination of the deuterium-labeled compound (XV) showed that this ion is generated mainly by loss of HCHO from the molecular ion.

The relative intensity of the M-16 and M-17 ion peaks of the corresponding parent pyrazines, 1-oxides and 4-oxides having different substituents are summarized in Table I together with that of other main peaks. The M-16 ion peaks are characteristic in the mass spectra of both pyrazine 1-, and 4-oxides as in the case of ordinary aromatic amine *N*-oxides reported earlier. The 1-oxides of methyl and methoxy pyrazines showed stronger M-17 ion peaks presumably due to the so-called *ortho* effect (2), (4), (7). The ratio of the M-17/M-16 fragments was 2.7-4.7 compared to 0.2-1.0 observed in the 4-oxides.

In the mass spectrum of dimethylpyrazine mono-*N*-oxide (X), a strong M-17 ion peak (46%) was observed. This peak is also assumed to be formed by a one-step

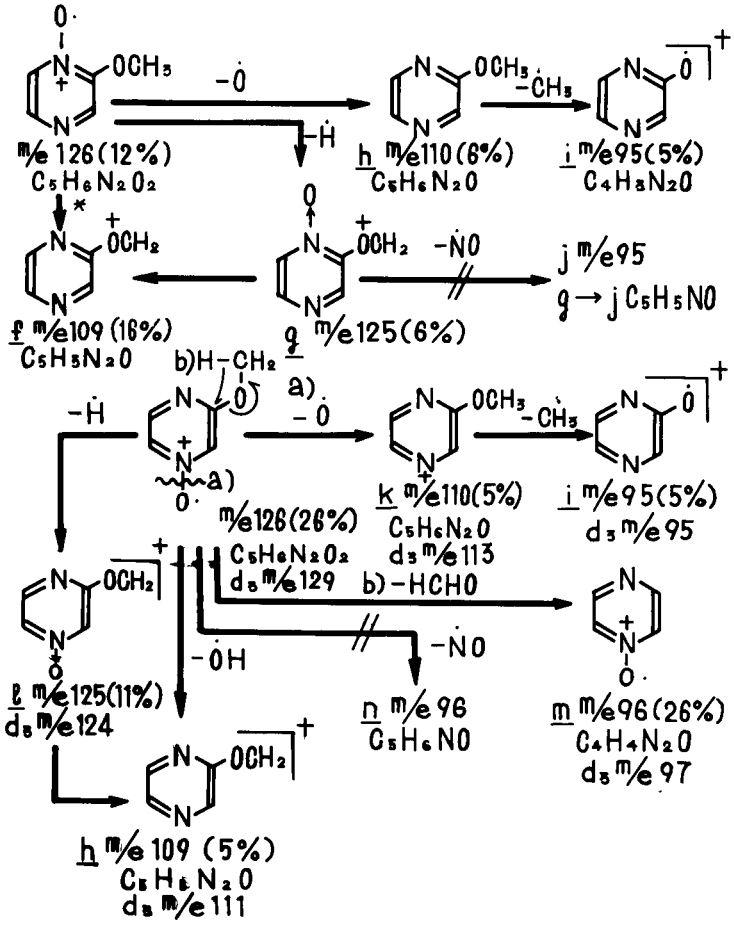


Chart II

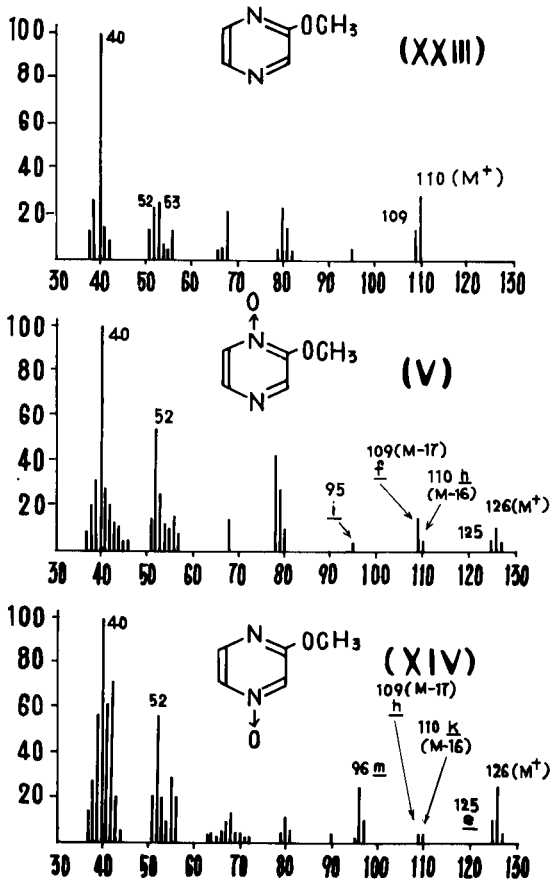


Figure II

elimination of an OH radical since the parent pyrazine did not show the M-1 ion peak.

The mass spectra of the di-*N*-oxides also showed the characteristic fragmentation of aromatic amine *N*-oxides. In the spectrum of pyrazine di-*N*-oxide (XXX), the molecular ion constituted the base peak and only weak M-16 and M-17 ion peaks were detectable. On the other hand, in the case of methylpyrazine di-*N*-oxide (XXXI), the M-16 ion constituted the base peak and the M-17 ion peak was observed in an abundance of only 5% showing the preferred elimination of an oxygen atom. The mass spectrum of dimethylpyrazine di-*N*-oxide (XXXII) showed molecular ion (base peak), M-16 and M-17 ion peaks. In addition, M-33 and M-34 ions were observed in an abundance of 24 and 51%, respectively. Two pathways, M → (M-17) → (M-34), and (M-16) → (M-33) were established by metastable ion peaks.

EXPERIMENTAL

Spectra were obtained with a Hitachi mass spectrometer RMS-4 using a heated inlet system and an ionizing voltage of 70 eV. The source temperature was about 200°.

Exact mass measurements were made with a Japan Electron Optics JMS-01S high resolution mass spectrometer with a direct inlet system; perfluorokerosene was used to provide reference masses. The ionizing energy was kept at 75 eV and the ionizing current at 200 μA.

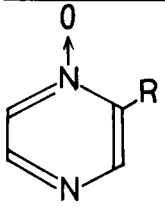
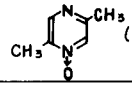
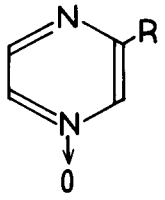
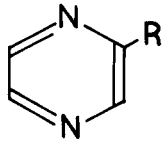
Materials.

The *N*-oxides used in the present work were prepared according to the methods reported in the preceeding paper (1). Methylpyrazine di-*N*-oxide was prepared by a method similar to that described by Gumprecht *et al.* (8). 2,5-Dimethylpyrazine mono- and di-*N*-oxides were synthesized according to the method of Klein and Berkowitz (9).

Methoxy-d_3-pyrazine.

To a solution of 0.424 g. (18.4 mmole) of sodium metal in 5 ml. of perdeuteriomethanol was added 2 g. (17.5 mmole) of chloropyrazine with stirring. The reaction mixture was kept below 20° by external cooling for an hour and allowed to stand for 48 hours at room temperature. The resulting sodium chloride was removed by filtration and the filtrate was neutralized with dry ice. The solvents were evaporated under vacuum and the residue was extracted with methylene chloride. The methylene chloride solution was washed with water, dried and evaporated. Distillation of the residue yielded 1.4 g. (69%) of a liquid, b.p. 148-150°. It gave

Table I. Relative intensity (%)

	R		M^+	M-16	M-17	M-18(OD)	M-17/M-16	M-1	M-2	m*	transition(obsd.)
	H	(I)	54	10	4		0.4	0			
	Cl	(II)	68	6.5	2.5		0.5	0			
	CN	(III)	32	4	2		0.5	0			
	CH_3	(IV)	100	9	42		4.7	0		78.6	$110^+ \rightarrow 93^+ + 17$
	OCH_3	(V)	12	6	16		2.7	6		94.3	$126^+ \rightarrow 109^+ + 17$
	NH_2	(VI)	58	5.9	3.3		0.6	0			
	ND_2	(VII)	100	6.3	2.2	2.7		15	0		
	$CONH_2$	(VIII)	85	2.4	2.4		1.0	0			
	COOH	(IX)	4.3	3.8	0		0	0			
		(X)	100	10	46		4.6	0			
	Cl	(XI)	93	12.5	0		0	0			
	CN	(XII)	38	8.5	0		0	0			
	CH_3	(XIII)	100	11	2		0.2	0			
	OCH_3	(XIV)	26	5	5		1.0	11			
	OCD_3	(XV)		7.1		6.9	(0.97)	5.6	34		
	NH_2	(XVI)	100	9.6	3.2		0.3	0			
	ND_2	(XVII)	100	8.8	4	1.8		10.5	0		
	$CONH_2$	(XVIII)	100	3.1	0		0	0			
	COOH	(XIX)	52	2.4	4.7		1.8	0			
	H	(XX)	76	0	0			0			
	Cl	(XXI)	94	0	0			0			
	CH_3	(XXII)	100	0	0			0			
	OCH_3	(XXIII)	29	0	0			15			
	OCD_3	(XXIV)		0	0			8.4	43.8		
	NH_2	(XXV)	100	0	0			3			
	ND_2	(XXVI)	100	0	0			17	0		
	$CONH_2$	(XXVII)	72	2.1	1.1			0			
	COOH	(XXVIII)	27.2	0	4			0			
		(XXIX)	20	0	0			0			

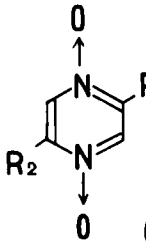
	R_1	R_2	M^+	M-16	M-17	M-32	M-33	M-34	m*	transition(obsd)
	(XXX) H	H	100	5	2	5	—	—		
	(XXXI) H	CH_3	15	100	5	20	20	—		
	(XXXII) CH_3	CH_3	100	39	26	11	24	51	108.5	$140^+ \rightarrow 123^+ + 17$
									91.5	$123^+ \rightarrow 106^+ + 17$
									92.2	$124^+ \rightarrow 107^+ + 17$

Table II

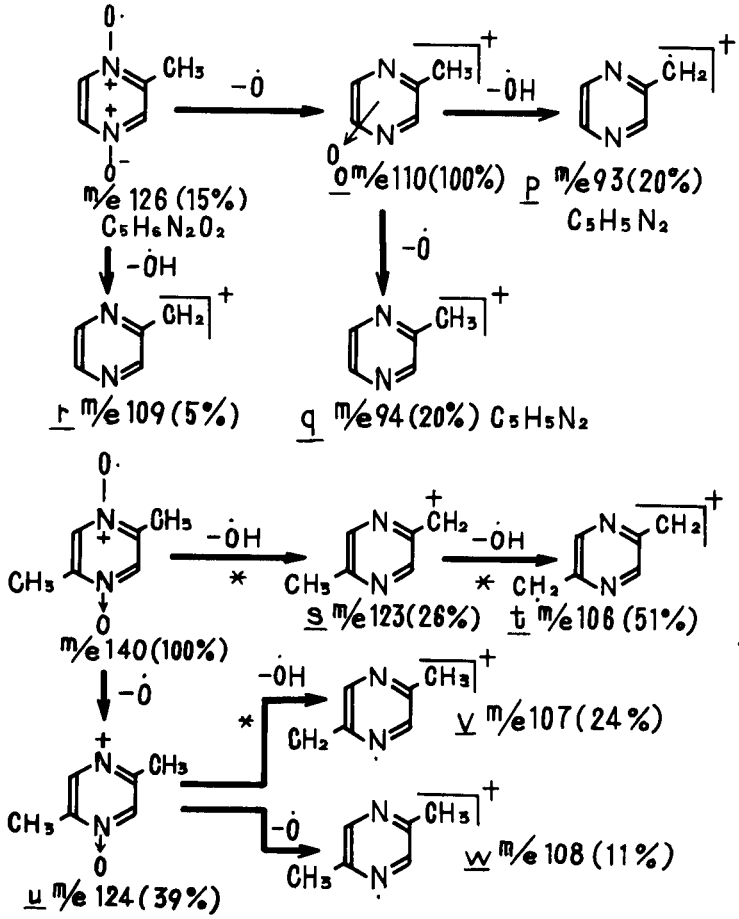


Chart IV

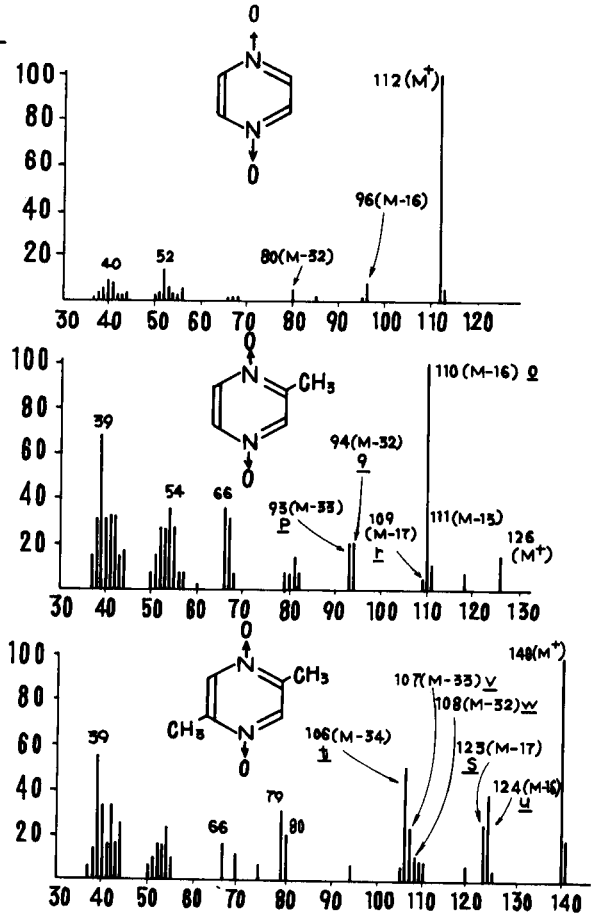


Figure III

a negative Beilstein test and its nmr spectrum in deuteriochloroform showed no signal for an *O*-methyl group and the signals in the ring proton region were exactly the same as that of methoxypyrazine.

Anal. Calcd. for $C_5H_3D_3N_2O$: C, 53.09; H, 8.03; N, 24.77; mol. wt., 113. Found: C, 53.02; H, 8.15; N, 25.00; mol. wt., 113 (mass spectrometric).

Methoxy-d_3-pyrazine 4-Oxide.

To a solution of 17.4 ml. of acetic acid and 3.4 ml. (24 mmoles) of 30% hydrogen peroxide was added 1.2 g. (10.6 mmoles) of methoxy-d_3-pyrazine and the mixture was heated at 75° for 19 hours. After addition of 3 ml. of 30% hydrogen peroxide and heating for an additional 2 hours, the reaction mixture was diluted with 3 times its volume of water and was then repeatedly evaporated under vacuum. The residue was dissolved in 20 ml. of chloroform, and the chloroform layer was dried over sodium sulfate and evaporated to give 1.03 g. (85.6%) of prisms, melting at 74-76°. Recrystallization from ether gave 0.35 g. (29.2%) of crystals, m.p. 79-80°. Its nmr spectrum showed no signal due to an *O*-methyl group; IR ν max (potassium bromide) cm^{-1}: 2270-2075 (several absorption bands characteristic for C-D stretch); molecular weight, 129 (calcd.); 129 (mass spectrometric).

Acknowledgment.

The authors are grateful to Professor H. Ogura of Kitasato University for his measurements of high-resolution mass spectra. The authors are also indebted to Dr. T. Ishiguro, President of this Company, and Dr. M. Shimizu, Director of these Laboratories, for kind encouragement throughout the course of this work.

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