

**Huang-Minlon Reduction of *trans*-2-Oxo-9-decalincarboxylic Acid (XI)**—A mixture of XI (300.8 mg.), 80%  $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$  (1.5 ml.), KOH (1.03 g.) and 12 ml. of triethylene glycol was worked up as above. There were obtained 35.5 mg. of an oil and 246 mg. (88.5 %) of *trans*-9-decalincarboxylic acid (XII), m.p. 130~134°, as needles (ref. m.p. 133~134°,<sup>5a</sup>) m.p. 133~134°<sup>5c</sup>). IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3625, 3465, 3020 (broad), 2675~2615 (broad), 2695. Anal. Calcd. for  $\text{C}_{11}\text{H}_{18}\text{O}_2$ : C, 72.49; H, 9.96. Found: C, 72.55; H, 10.08.

We are very grateful to Dr. K. Takeda, Director of this laboratory for his constant encouragement. Our thanks are also due to the members of the analytical and the physico chemical department of this laboratory for analytical and optical data.

### Summary

Cyanation at the angular position of  $\Delta^{1,9}$ -2-octalone (I) was conducted with potassium cyanide in the presence of ammonium chloride in polar solvent, or with hydrogen cyanide and triethyl aluminum in tetrahydrofuran. In the latter case, high stereospecificity of the reaction was observed and the formation of *trans*-2-oxo-9-decalincarbonitrile (IIa) to its *cis*-isomer IIIa was in a ratio of 24:1. The structures and the configurations of the products were determined by conversion into the known *trans*- XII and *cis*-9-decalincarboxylic acid (XIII). Moreover the stereochemistry of this cyanation reaction was discussed.

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### 42. Kazuo Tori, Masaru Ogata, and Hideo Kano: Pyridazines. IV.\*<sup>1</sup> Nuclear Magnetic Resonance Studies of Pyridazine N-Oxide and Its Derivatives.

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In recent years, the syntheses of pyridazine N-oxide derivatives has been reported by many authors. In this field, determination of the position of the N-O group in these N-oxides is of great importance. In the previous paper of this series,<sup>\*1</sup> the authors reported the location of the N-O group in monomethylpyridazine N-oxides determined by means of dipole moment studies. Among the newer techniques which can be applied to structural studies on pyridazine N-oxide derivatives, nuclear magnetic resonance (NMR) spectroscopy may give more detailed information on this problem.

The present paper describes the application of NMR spectroscopy for determination of the position of the N-O group in pyridazine N-oxide derivatives and the analysis of N-oxidation reaction mixture. The electronic structures of pyridazine N-oxide and its derivatives will be discussed briefly in connection with the chemical shifts.

### Experimental

All the spectra were taken with a Varian A-60 analytical NMR spectrometer system on 10% (w/v) deuteriochloroform solutions containing about 1% of tetramethylsilane as an internal reference. However, as 4-nitropyridazine 1-oxide (II) and pyrazine di-N-oxide are slightly soluble in the solvent,

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saturated solutions were used in these cases. Chemical shifts are expressed in p.p.m. on  $\tau$ -scale. The materials were prepared according to the already known procedures,<sup>1)</sup> except for 6-methyl-3,4-dichloropyridazine 1-oxide (XXVI), as shown in Chart 1.

**6-Methyl-3,4-dichloropyridazine 1-Oxide (XXVI)**—3-chloro-4-nitro-6-methylpyridazine 1-oxide (XXI) (200 mg.) was slowly added to 2 ml. of concentrated hydrochloric acid and heated on a water bath for 2 hr. The mixture was poured onto ice, extracted with  $\text{CHCl}_3$  and after evaporating the solvent the residue was recrystallized from benzene to colorless prisms, m.p. 165~166°, yield, 140 mg. *Anal.* Calcd. for  $\text{C}_5\text{H}_4\text{ON}_2\text{Cl}_2$ : C, 33.52; H, 2.25; N, 15.64. Found: C, 33.48; H, 2.53; N, 15.24.

## Results

All the spectra of pyridazine N-oxide derivatives were simple first order patterns which made it possible to compute all the chemical shifts and coupling constants with sufficient accuracy by a first order analysis. As an example, the spectrum of pyridazine N-oxide (I) is shown in Fig. 1. In order to obtain a complete assignment of the ring proton signals of I, a number of its derivatives were examined. Chemical shifts and spin-spin coupling constants for the individual protons of pyridazine N-oxide derivatives are shown with the structure assignments in Table I and Fig. 2.

TABLE Ia. Nuclear Magnetic Resonance Spectral Parameters for Pyridazine N-Oxide Derivatives

Substituent	$\tau_3$	$\tau_4$	$\tau_5$	$\tau_6$	$\tau_{\text{CH}_3}$	$J_{3,4}$	$J_{3,5}$	$J_{3,6}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$
None (I)	1.46	2.78	2.17	1.74	—	5.3	2.5	1.0	8.0	1.0	6.5
3-Cl (IV)	—	2.77	2.25	1.82	—	—	—	—	8.3	0.6	6.2
3-CH <sub>3</sub> (XVII)	—	3.02	2.42	1.90	7.48	$\sim 0^a$	$\sim 0^a$	$\sim 0^a$	8.2	0.5	6.1
4-CH <sub>3</sub> (XXXII)	1.65	—	2.43	1.83	7.64	0.2 <sup>b</sup>	2.8	0.5	0.5 <sup>b</sup>	0.2 <sup>b</sup>	6.2
5-CH <sub>3</sub> (XXXIII)	1.62	3.01	—	1.92	7.63	5.6	$\sim 0.2^c$	0.5	0.7 <sup>c</sup>	0.7	0.7 <sup>c</sup>
6-CH <sub>3</sub> (XVI)	1.63	2.88	2.27	—	7.49	5.6	2.5	$\sim 0^d$	8.2	$\sim 0^d$	$\sim 0^d$
3-Cl, 6-Cl (X)	—	2.78	2.10	—	—	—	—	—	8.4	—	—
3-Cl, 4-CH <sub>3</sub> (XXXI)	—	—	2.41	1.90	7.61	—	—	—	0.5 <sup>b</sup>	0.2 <sup>b</sup>	6.2
3-Cl, 5-CH <sub>3</sub> (XXXIV)	—	2.95	—	2.01	7.64	—	—	—	0.7 <sup>c</sup>	0.7	0.7 <sup>c</sup>
3-Cl, 6-CH <sub>3</sub> (XIII)	—	2.83	2.27	—	7.51	—	—	—	8.3	$\sim 0^d$	$\sim 0^d$
4-Cl, 6-CH <sub>3</sub> (XXVII)	1.61	—	2.32	—	7.49	—	3.0	$\sim 0^d$	—	—	$\sim 0^d$
3-Cl, 4-Cl, 6-CH <sub>3</sub> (XXVI)	—	—	2.23	—	7.50	—	—	—	—	—	$\sim 0^d$

a) 3-CH<sub>3</sub>-H coupling, b) 4-CH<sub>3</sub>-H coupling, c) 5-CH<sub>3</sub>-H coupling, d) 6-CH<sub>3</sub>-H coupling.

TABLE Ib. Nuclear Magnetic Resonance Spectral Parameters for Pyridazine N-Oxide Derivatives

Substituent	$\tau_3$	$\tau_4$	$\tau_5$	$\tau_6$	$\tau_{\text{OCH}_3}$	$\tau_{\text{CH}_3}$	$J_{3,4}$	$J_{3,5}$	$J_{3,6}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$
3-OCH <sub>3</sub> (VII)	—	3.31	2.47	2.05	5.98	—	—	—	—	8.6	0.7	5.8
3-OCH <sub>3</sub> , 6-CH <sub>3</sub> (XIX)	—	3.33	2.48	—	5.98	7.55	—	—	$\sim 0^d$	8.5	$\sim 0^d$	$\sim 0^d$
4-OCH <sub>3</sub> , 6-CH <sub>3</sub> (XXIII)	1.92	—	2.80	—	6.07	7.48	—	3.7	—	—	$\sim 0^d$	$\sim 0^d$
3-OCH <sub>3</sub> , 6-Cl (VI)	—	3.28	2.29	—	5.96	—	—	—	—	8.8	—	—
3-OCH <sub>3</sub> , 6-OCH <sub>3</sub> (XII)	—	3.27	2.64	—	{5.92 6.02}	—	—	—	—	8.7	—	—
3-OCH <sub>3</sub> , 4-Cl, 6-CH <sub>3</sub> (XXIV)	—	—	2.46	—	5.92	7.56	—	—	—	—	—	$\sim 0^d$
3-OCH <sub>3</sub> , 4-OCH <sub>3</sub> , 6-CH <sub>3</sub> (XXV)	—	—	3.05	—	{5.90 6.02}	7.51	—	—	—	—	—	$\sim 0^d$
4-NO <sub>2</sub> (II)	0.70	—	1.55	1.84	—	—	—	2~3	$\sim 0.5$	—	—	7.0
4-NO <sub>2</sub> , 6-CH <sub>3</sub> (XXII)	0.80	—	1.55	—	—	7.41	—	3.3	$\sim 0^d$	—	—	$\sim 0^d$
3-Cl, 4-NO <sub>2</sub> , 6-CH <sub>3</sub> (XXI)	—	—	1.66	—	—	7.46	—	—	—	—	—	$\sim 0^d$
3-OCH <sub>3</sub> , 4-NO <sub>2</sub> , 6-CH <sub>3</sub> (XX)	—	—	1.65	—	5.82	7.49	—	—	—	—	—	$\sim 0^d$

d) 6-CH<sub>3</sub>-H coupling

1) T. Itai, H. Igeta: *Yakugaku Zasshi*, **75**, 996 (1955); H. Igeta: *This Bulletin*, **7**, 938 (1959); **8**, 559 (1960); T. Nakagome: *Yakugaku Zasshi*, **81**, 554, 1048 (1961); **82**, 244, 253 (1962); M. Ogata, H. Kano: *This Bulletin*, **11**, 29, 35 (1963).

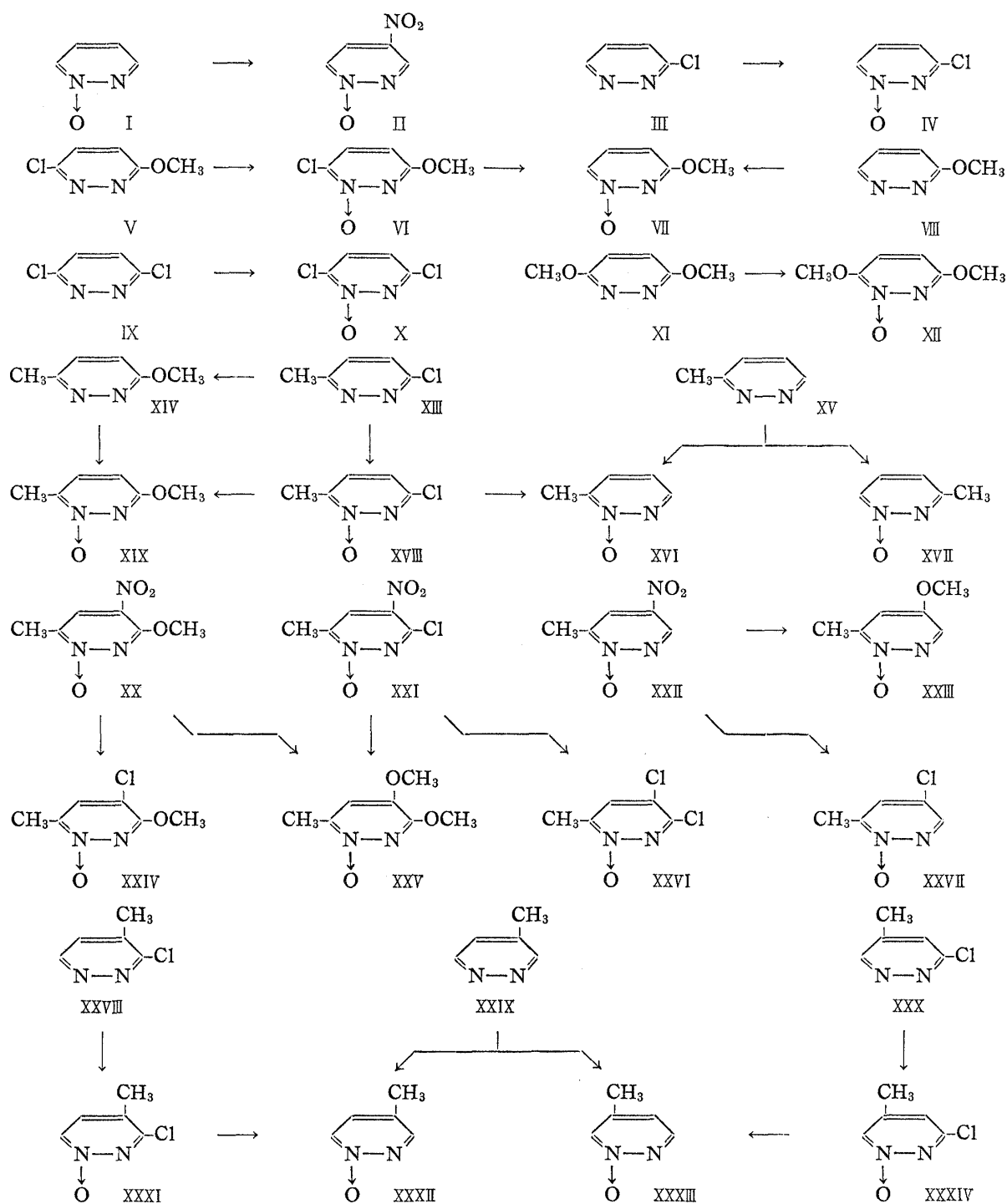


Chart 1.

In general, a substituted chlorine gives little or no effect on the chemical shifts of the ring protons in aromatic compounds; a substituted methyl group does a little effect.<sup>2,3)</sup> Therefore, chlorine and methyl substituted pyridazine N-oxide were used to assign the ring proton signals. The NMR spectrum of 3,6-dichloropyridazine N-oxide (X) is composed of two doublet peaks at 2.10  $\tau$  and 2.78  $\tau$ , corresponding to the peaks

2) J. A. Pople, W. G. Schneider, H. J. Bernstein: "High-resolution Nuclear Magnetic Resonance," 259 (1959). McGraw-Hill Book Co., Inc., New York, N. Y.

3) K. Tori, M. Ogata, H. Kano: to be published.

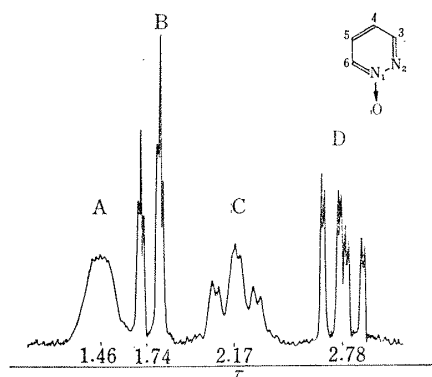


Fig. 1.  
Nuclear Magnetic Resonance Spectrum  
of Pyridazine N-Oxide at 60 Mc.p.s.  
in Deuteriochloroform

A, proton 3; B, proton 6  
C, proton 5; D, proton 4

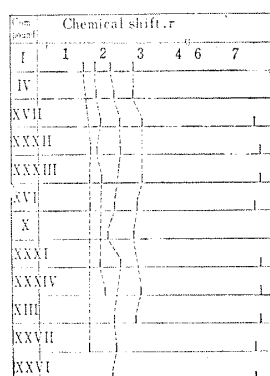


Fig. 2a. Nuclear Magnetic Resonance  
Spectra of Pyridazine N-Oxide  
Derivatives

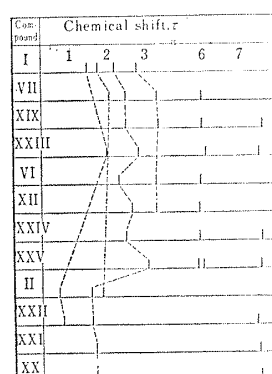


Fig. 2b. Nuclear Magnetic Resonance  
Spectra of Pyridazine N-Oxide  
Derivatives

at  $2.17\tau$  and  $2.78\tau$  in that of I. Thus, the signal peaks at  $2.17\tau$  and  $2.78\tau$  may be assigned to the protons  $H_3$  and  $H_4$ , and those at  $1.46\tau$  and  $1.74\tau$  to the protons  $H_5$  and  $H_6$ . However, at this point it is not yet possible to distinguish  $H_4$  from  $H_5$  or  $H_3$  from  $H_6$ . In order to distinguish proton  $H_3$  from  $H_5$ , the spectra of pyrazine, pyrazine mono-N-oxide and pyrazine di-N-oxide were examined. The protons of pyrazine and pyrazine di-N-oxide show singlet peaks at  $1.37\tau$  and  $1.99\tau$ , respectively. The spectrum of pyrazine mono-N-oxide is composed of two quartets ( $A_2X_2$  type) centered at  $1.48\tau$  and  $1.82\tau$ . On this basis, it may be suggested that a proton attached to a carbon atom adjacent to the N-O group shows its signal peak at a higher field than a proton attached to a carbon atom adjacent to the nitrogen atom. Thus, it is considered that the peaks at  $1.46\tau$  and  $1.74\tau$  in the spectrum of I correspond to the protons  $H_3$  and  $H_5$ , respectively. Turning now to the isomeric 3-methylpyridazine N-oxides (XVI and XVII), it is considered that XVI is 3-methylpyridazine 2-oxide and XVII is 3-methylpyridazine 1-oxide from their proton signals.

The spectra of 3-chloro-4-methyl- and 3-chloro-5-methylpyridazine N-oxides (XXXI and XXXIV) display no signals corresponding to the proton  $H_3$ , so these compounds are considered as 1-oxides. Accordingly, the peak at  $2.41\tau$  is due to the proton  $H_5$  in XXXI, and the peak at  $2.95\tau$  to the proton  $H_4$  in XXXIV. It becomes clear that the peaks of the proton  $H_4$  appears at a lower field than that of  $H_5$ . Consequently, in the spectrum of I the peaks at  $2.17\tau$  and  $2.78\tau$  are assigned to the protons  $H_3$  and  $H_4$ , respectively. In isomeric 4-methylpyridazine N-oxides (XXXII and XXXIII), XXXII is identified as 1-oxide and XXXIII as 2-oxide, and the structures of other chloro- and/or methyl-substituted compounds are similarly identified as shown in Table Ia. The present assignments of

structures of many pyridazine derivatives are consistent with those obtained from the previous dipole moment studies.<sup>4)</sup>

The chemical shifts and spin-spin coupling constants in methoxyl and nitro derivatives of pyridazine N-oxide are summarized in Table Ib and illustrated in Fig. 2b. The authenticity of the structure of these compounds has been proven by synthesis (Chart 1). The effect of a substituted methoxyl or nitro group on the chemical shifts of the ring proton is large, as expected.

In the NMR spectra of pyridazine N-oxide derivatives, the signal of H<sub>3</sub> always can be seen, although broad, while the signal of H<sub>5</sub> is also discernible as a small broad one. These broadenings can be attributed to the nuclear quadrupole relaxation effects of the N<sup>14</sup> nucleus.

In regards to the chemical shifts of methyl groups, it is found that signals of methyl groups attached to the 3- or 6-position are in somewhat lower fields than those of methyl groups attached to the 4- or 5-position. In regards to the chemical shifts of methoxyl groups, the downfield trend is found to be in the order 3-methoxyl > 6-methoxyl > 4-methoxyl.

The values of spin-spin coupling constants,  $J_{4,5}$ ,  $J_{3,4}$  and  $J_{5,6}$ , as shown in Table I, are reasonable for *ortho* couplings of the ring protons by comparison with aromatic systems,<sup>5)</sup> and the two *meta* couplings,  $J_{3,5}$  and  $J_{4,6}$ , and *para* coupling,  $J_{3,6}$ , also fall in the normal range, whereas the coupling constant,  $J_{3,5}$ , in pyridazine has been found to have a large value of 3.5 c.p.s.<sup>5)</sup> It is noteworthy that in both 3- and 6-methyl derivatives the spin-spin coupling constants between a methyl group and a ring proton are not discernible, while in both 4- and 5-methyl derivatives these are easily discernible. Similar results were observed in 4- and 5-methylpyridazine derivatives.<sup>5)</sup>

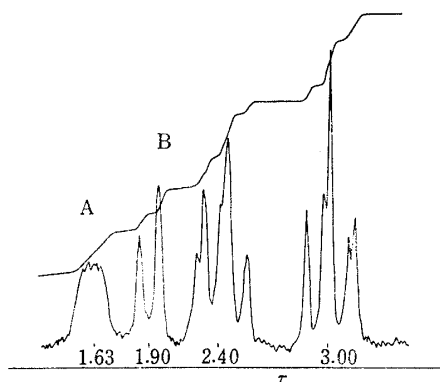


Fig. 3. Nuclear Magnetic Resonance Spectrum of a Mixture of 3-Methylpyridazine 1-Oxide and 2-Oxide at 60 Mc.p.s., in Deuteriochloroform

A, proton 3 in 1-oxide;  
B, proton 6 in 2-oxide

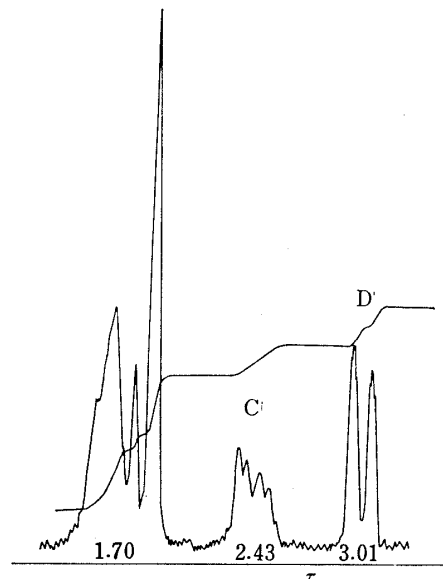


Fig. 4. Nuclear Magnetic Resonance Spectrum of a Mixture of 4-Methylpyridazine 1-Oxide and 2-Oxide at 60 Mc.p.s., in Deuteriochloroform

C, proton 5 in 1-oxide;  
D, proton 4 in 2-oxide

4) H. Kano, M. Ogata, H. Watanabe, I. Ishizuka: This Bulletin, 9, 1017 (1961); H. Watanabe, M. Ogata, H. Kano: This Bulletin, 11, 39 (1963).

5) J. A. Pople, W. G. Schneider, H. J. Bernstein: "High-resolution Nuclear Magnetic Resonance," 193 (1959). McGraw-Hill Book Co., Inc., New York, N. Y.

### Application to Analysis of Reaction Mixture Obtained by N-Oxidation

It is apparently considered from above mentioned studies that NMR spectroscopy is useful in analysis of a reaction mixture obtained in the N-oxidation of pyridazine derivatives. Analysis of a reaction mixture gave the following results: 3-chloro-, 3-methoxy-6-chloro-, 3-methoxy-, 3-chloro-6-methyl-, and 3-methoxy-6-methylpyridazine (III, V, VIII, XIII, and XIV) gave the 1-oxide alone, while 3-methyl- and 4-methylpyridazine (XV and XXIX) gave mixtures of both of 1-oxides and 2-oxides in the ratio of 1:1 and 1:3, respectively, independently of reaction times, as shown in Figs. 3 and 4. These results are not exactly consistent with the values from gas-chromatography analyses previously reported.<sup>6)</sup> However, in the latter case the results might have been influenced by the decomposition of samples.

### Discussion

#### Substituent Effects

The substituent effects on the chemical shifts in pyridazine N-oxide derivatives are discussed in the comparison with the other aromatic systems. In benzene, furan, pyrrole and thiophene, it has been found that the total effects on all ring proton shifts produced by a single methyl group was about 0.75 p.p.m.,<sup>7)</sup> whereas in thiazole, pyrimidine<sup>7)</sup> and pyridazine,<sup>8)</sup> it was about 0.6 p.p.m. This difference may be interpreted as that the migrating charge from a methyl group to the ring by hyperconjugation or an equivalent process is localized partly on the nitrogen atom in the ring. Other substituent effects may also be interpreted as the charge migration from a substituent to the ring or *vice versa* by the mesomeric effects, the inductive effects, or both. The ring proton at the *ortho*-position of a substituent may be influenced to some degree by bond-anisotropic effect of the substituent. However, it is estimated by Makisumi, *et al.*<sup>8)</sup> that the effect of a methyl or a methoxyl group will be no more than a 0.1 p.p.m. shift to upfield.

TABLE II. Substituent Effects<sup>a)</sup> in Pyridazine<sup>b)</sup> and Pyridazine N-Oxide Derivatives

Compound	Position				sum
	3	4	5	6	
3-Chloropyridazine 1-oxide (IV)	—	-0.01	+0.08	+0.08	+0.15
3-Chloropyridazine	—	-0.04	0.00	+0.07	+0.03
3-Methylpyridazine 1-oxide (VII)	—	+0.53	+0.30	+0.31	+1.14
3-Methoxypyridazine	—	+0.53	+0.14	+0.36	+1.03
3-Methylpyridazine 1-oxide (XVII)	—	+0.24	+0.25	+0.16	+0.65
3-Methylpyridazine	—	+0.17	+0.15	+0.18	+0.50
4-Methylpyridazine 1-oxide (XXXII)	+0.19	—	+0.26	+0.09	+0.54
5-Methylpyridazine 1-oxide (XXXIII)	+0.16	+0.18	—	+0.23	+0.57
4-Methylpyridazine	+0.16	—	+0.22	+0.20	+0.58
6-Methylpyridazine 1-oxide (XVI)	+0.17	+0.10	+0.10	—	+0.37
4-Nitropyridazine 1-oxide (II)	-0.76	—	-0.62	+0.10	-1.28

a) All values are the displacements of the proton shifts in p.p.m. relative to the same position in the unsubstituted ring.

b) Reference (3).

The substituent effects on the chemical shifts of pyridazine N-oxides are listed in Table II, compared with those of pyridazines.<sup>3)</sup> The magnitude of the substituent effect is much the same in pyridazines and pyridazine N-oxides, but the distribution

6) M. Ogata, H. Kano: This Bulletin, 11, 29, 35 (1963).

7) G. S. Reddy, R. T. Hobgood, Jr., J. H. Goldstein: J. Am. Chem. Soc., 84, 336 (1962).

8) Y. Makisumi, H. Watanabe, K. Tori: To be published.

of the effect is not quite the same. In any methyl substituents of methylpyridazine N-oxides, it is evident from Table II that the effects fall in the range from 0.54 p.p.m. to 0.65 p.p.m., except for the case of the 6-methyl substituent which has a significantly lower value of 0.37 p.p.m. The former values are similar to those in the case of aromatic systems containing a nitrogen atom.<sup>3,5)</sup> The anomaly of the latter is very interesting. It has a parallel relationship to the nitration reaction of methylpyridazine N-oxides,<sup>6)</sup> in which only 3-methylpyridazine 1-oxide (XVII) is nitrated easily. The order of the magnitude of the methyl effect is 3-methyl > 5-methyl > 4-methyl > 6-methyl, which fact is different from the other cases mentioned above.

The additivity of the substituent effects is easily seen from Table I. Here again, it is found that the effect of the 6-methoxyl substituent, as well as 6-methyl substituent, is very small. In order to interpret substituent effects in detail, more elaborate investigations of the electronic distribution in the ring system containing N-oxide group are necessary. Moreover, the lack of knowledge of the inductive effects of nitrogen atoms or the charge absorbed by nitrogen atoms, such as in the case of pyrimidines pointed out by Reddy, *et al.*,<sup>7)</sup> would have a large signification here. As the result, it may be confirmed that the pyridazine N-oxide ring system has an aromatic character similar to other heterocyclic compounds.

#### Electronic Distributions of Pyridazine N-oxide

There is a quantitative relationship between chemical shift and electron distributions in aromatic molecules, as reported by many authors.<sup>9)</sup> Among them, Spiesscke and Schneider<sup>9)</sup> have proposed a proportionality :

$$\delta_{H_1} = 10.6\rho \quad (A)$$

where  $\delta_{H_1}$  is the chemical shift referred to benzene (5 mol. % in cyclohexane) and  $\rho$  is the electronic charge density. However, it is doubtful whether one can apply this relationship directly to the ring systems containing some hetero atoms.<sup>8)</sup>

As shown in Fig. 2, NMR spectra of pyridazine N-oxide (I) shows an order,  $H_3 < H_6 < H_5 < H_4$ , as the magnitude of shielding of ring protons. With the exception of the C<sub>6</sub>-position, this order of shielding of ring proton is in a good agreement with a LCAO-MO calculation of the local  $\pi$ -electron densities in the pyridazine N-oxide molecule, as shown in Chart 2 (a).<sup>10)</sup> Calculation of charge density indicated that the proton attached to C<sub>6</sub> should be the most shielded one. For this anomaly, a possible explanation may be given by taking into account the diamagnetic anisotropy effect of the N-O group, which has been discussed on the pyridine N-oxide series briefly by Nakagawa, *et al.*<sup>11)</sup>

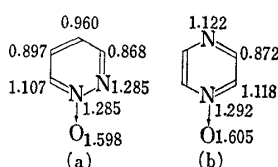


Fig. 5.  
Local  $\pi$ -Electron Distributions in (a) Pyridazine N-Oxide and (b) Pyrazine N-Oxide calculated with the LCAO-MO method<sup>10)</sup>

$$k_N = 0.4\beta; k_O = 0.8\beta; k_{N\delta+} = 1.6\beta;$$

$$\text{Inductive effect} = (\frac{1}{3})^n k_{N\delta+}; \rho_{NO} = 1.$$

- 9) J.R. Leto, F.A. Cotton, J.S. Waugh : *Nature*, **180**, 978 (1957); G. Fraenkel, R.E. Carter, A. McLachlan, J.H. Richards : *J. Am. Chem. Soc.*, **82**, 5846 (1960); I.C. Smith, W.G. Schneider : *Can. J. Chem.*, **39**, 1158 (1961); H. Spiesscke, W.G. Schneider : *Tetrahedron Letters*, 468 (1961); P.C. Lauterbur : *Tetrahedron Letters*, 274 (1961); W. Seiffert, H. Zimmermann, G. Scheibe : *Angew. Chem.*, **74**, 249 (1962).
- 10) T. Kubota, H. Watanabe, I. Tanaka : *Bull. Chem. Soc. Japan*, to be published (presented at the 15th annual meeting of the Chem. Soc. Japan in Kyoto, April, 1962).
- 11) N. Nakagawa, Y. Kawazoe, H. Hotta, M. Ito : presented at Symposium on Nuclear Magnetic Resonance (Japan), in Tokyo, November 1961.

In the present case, the chemical shifts which are roughly calculated on the basis of the calculation shown in Fig. 5 (a) and of the above proportional relationship (A) which seems to be applicable in the C<sub>4</sub>- and C<sub>5</sub>-positions, showed that the signals of protons H<sub>6</sub> and H<sub>3</sub> should be at about 4.4 $\tau$  and 1.8 $\tau$ , respectively. The differences between the calculated values and the observed ones are about 2.65 p.p.m. and about 0.35 p.p.m. for H<sub>6</sub> and H<sub>3</sub>, respectively. The former downfield shift is attributable to the effect of N-O group anisotropy, the magnitude of which is consistent with that proposed by Nakagawa, *et al.*<sup>11)</sup> The latter downfield shift is considered due to the effect of the anisotropy of lone-pair electrons of the nitrogen atom or of some analogous effect originating from the nitrogen atom. However, these downfield shifts may be overestimated, since the effects by such anisotropies as above on the *para*-positions of N-O group and nitrogen atom have been reported to cause only small upfield shifts of about 0.08 p.p.m.<sup>11)</sup> With respect to the pyrazine N-oxide molecule mentioned before, the same procedure, employing the spectral data and the calculation as shown in Fig. 5 (b),<sup>10)</sup> results in that the downfield shift by the N-O group anisotropy is about 2.7 p.p.m. and that by the nitrogen atom is about 0.35 p.p.m. A more precise investigation on the NMR spectra of diazine N-oxides will be reported in a forthcoming paper.

The chemical shift of the methyl proton may be interpreted as a reflection of charge densities on the carbon atom in an aromatic ring. In the methyl derivatives of pyridazine N-oxides, the chemical shifts of the methyl protons are in the sequence 3-methyl $\approx$ 6-methyl<5-methyl $\approx$ 4-methyl. Here again, 6-methyl shift is lower than the others. This may also be attributable to the anisotropic effect of the N-O group. The methoxyl shifts are in the order 3-methoxyl<6-methoxyl<4-methoxyl. In this case, the anisotropic effect of N-O group is somewhat reduced, because the distance between 6-methoxyl protons and the N-O group is larger than that between 6-methyl protons and the N-O group.

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### Summary

Pyridazine N-oxide derivatives have been studied by NMR spectroscopy. In all cases the spectra were simple patterns, which could be easily assigned by first order treatments. In order to obtain a complete assignment of the ring proton signals, a number of pyridazine N-oxide derivatives were examined, and the structures determined from the results are consistent with the dipole moment studies. Analysis of N-oxidation reaction mixtures of pyridazine derivatives was performed by NMR spectroscopy. Substituent effects on the chemical shifts are discussed in relation to the other aromatic ring systems. The electronic distribution of pyridazine N-oxide and diamagnetic anisotropy effect of N-O group are also discussed briefly.

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