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Yutaka Kawazoe,[*1] Yuko Yoshioka,[*1] Mutsumi Yamada,[*2] and Hiroshi Igeta[*2] : Studies on Hydrogen Exchange. Ⅷ.[*3] The Base-catalysed Hydrogen Exchange of Methyl Hydrogens of Methylpyridazines and Their N-Oxides.[*4]

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Many studies have been reported on the electrophilic and nucleophilic reactions of pyridazine 1-oxide derivatives.[1~8] They appear to be very similar to those of pyridine N-oxides in many reactions such as nitration,[1~5] rearrangement of N-oxide group with acetic anhydride,[9~12] etc. A marked difference, however,, was found by Sako between the chloro derivatives of pyridazine 1-oxides and pyridine 1-oxides in the reactivities toward nucleophiles such as amines and methoxide ion.[13] Thus, the kinetic study on the replacement reaction of monochloropyridazine 1-oxides with piperidine indicated that the reactivity decreased in the order of positions 5, 3, 6, and 4; the position β to the N-oxide group was more reactive than α- and γ-positions, whereas it is well known, based on the Okamoto's work[14] that the chlorine atoms at α- and γ-position in pyridine and quinoline N-oxides are much more reactive than those at β-position. The nuclear magnetic resonance studies on this class of compounds[15] have shown that the electron-releasing effect of N-oxide group contributed to the resonance hybridization of this molecule to a considerable extent (Ⅱ in Chart 1), since 4-proton (γ-position to the N-oxide) became more shielded by N-oxygenation and 4-proton of the N-oxide resonated at a higher field than that of 5-position (β-position to N-oxide) in neutral organic solvents.

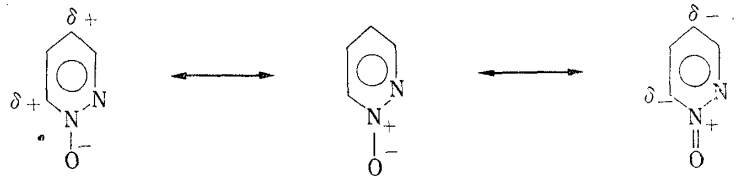

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Chart 1.

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*3 Part Ⅶ : This Bulletin, **15**, 1411 (1967).
*4 This paper constitutes Part Ⅷ of a series entitled "Syntheses of Pyridazine Derivatives" by H. Igeta. Part Ⅶ : This Bulletin, **15**, 1411 (1967).

1) T. Itai, H. Igeta : Yakugaku Zasshi, **75**, 966 (1955).
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3) H. Igeta : *Ibid.*, **8**, 550 (1960).
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13) S. Sako : *Ibid.*, **14**, 269 (1966).
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15) Y. Kawazoe, S. Natsume : Yakugaku Zasshi, **83**, 523 (1963).

In the present paper, the π-electronic structure of pyridazine and its N-oxide will be considered from the base-catalysed hydrogen-deuterium exchange reactivity of the methyl hydrogens of monomethylpyridazines and their N-oxides. Thus, this type of hydrogen exchange can be considered to be initiated by a nucleophilic attack of the base on hydrogen, followed by cleavage of C-H bond to yield a carbanion (the reaction intermediate in Chart 2) and a proton as reaction intermediate, as previously discussed for pyridine and quinoline derivatives.[16] In other words, these molecules can be regarded as a weak acid to dissociate an acidic proton. As a result, the exchange reactivity should be directly related to the π-electronic structure of this aromatic ring, as shown in Chart 2.

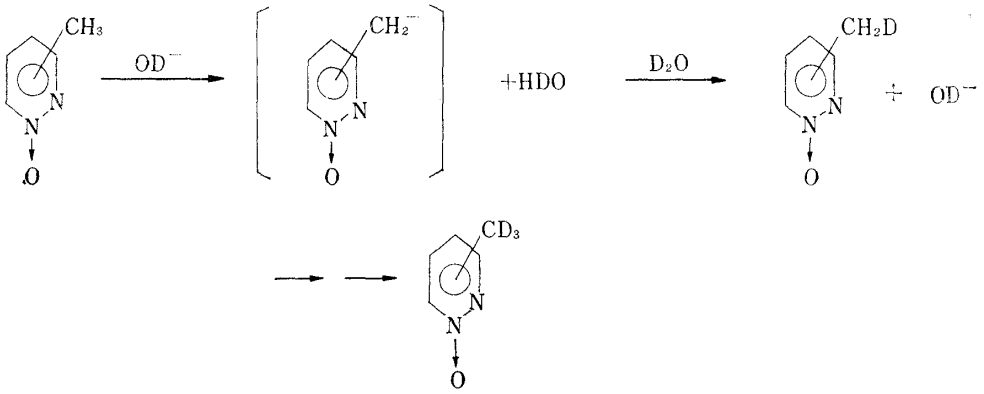

Chart 2.

Hydrogen exchange reactions were carried out as follows. The compounds examined were 3- and 4-methylpyridazines and 3-, 4-, 5-, and 6-methylpyridazine 1-oxides. They were dissolved to 5% concentration in heavy water (99 D-atom %) containing 1% NaOD and sealed in an NMR sample tube. Each of the reaction tubes thus prepared was heated to an appropriate temperature for an appropriate period. The relative exchange reactivities of these isomeric methyl hydrogens were determined by NMR spectroscopy, *i.e.*, by qualitative comparison of the remaining signal of the methyl hydrogens concerned. The results obtained are summarized in Table I and the reaction conditions for preparation of deuterated derivatives are shown in Chart 3.

Table I. Relative Rate of Deuterium Exchange of Methyl Hydrogens of Monomethylpyridazines and Their 1-Oxides in 1% NaOD-D_2O Solution[a]

	Reaction condition (%)				
	20°, 22 hr.	50°, 1 hr.	100°, 1 hr.	125°, 1hr.	140°, 1 hr.
3-CH_3-pyridazine			40	90	completed
4-CH_3-pyridazine			>90	completed	
3-CH_3-pyridazine 1-oxide	<20	40	completed		
4-CH_3-pyridazine 1-oxide	20	40	completed		
5-CH_3-pyridazine 1-oxide	40	70	completed		
6-CH_3-pyridazine 1-oxide	50	>90	completed		

a) Percentages shown in this table were evaluated for qualitative comparisons in the reactivity and may include a considerable experimental error in the magnitude.

In pyridazine free bases, the fact that 4-methyl hydrogens (β to one nitrogen and γ to the other) are more readily replaced by deuterium than the 3-methyl ones (α to one

16) Y. Kawazoe, M. Ohnishi, Y. Yoshioka: This Bulletin, **15**, 1225 (1967).

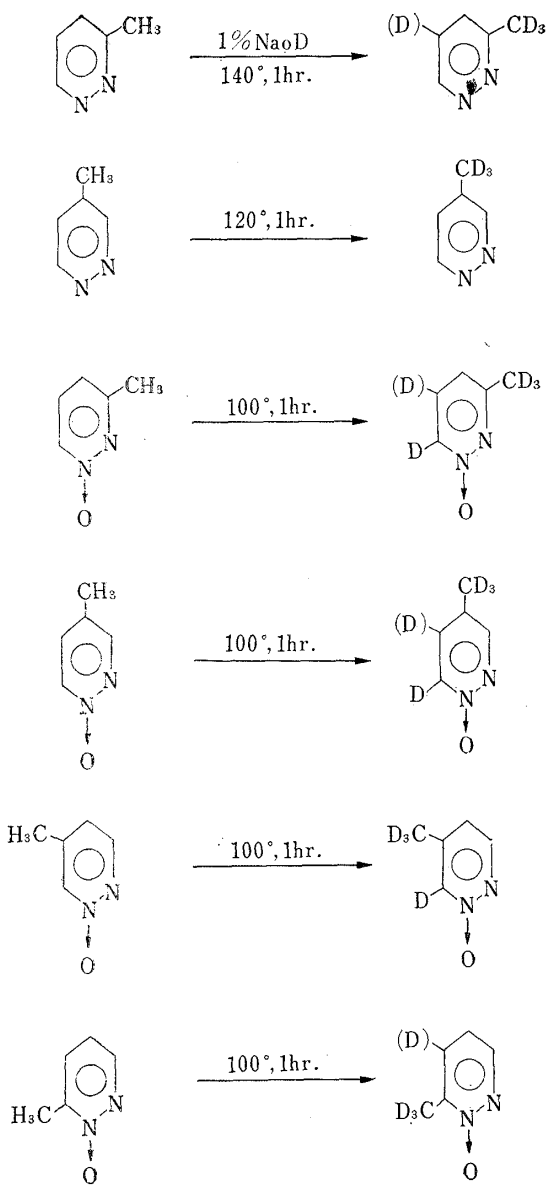

Chart 3. Deuteration Reactions in 1% NaOD-D_2O Solutions of Methyl Pyridazines and Their 1-Oxides

* Deuterium in parentheses, (D), means "partly deuterated" under the condition described.

nitrogen and β to the other) seems to agree with the fact that γ-methyl of pyridine is more reactive than the α one.[16] Contrary to this, an unexpected order of the exchange reactivity was found in a series of monomethylpyridazine 1-oxides as follows:

$$6\text{-}CH_3 > 5\text{-}CH_3 > 4\text{-}CH_3 \approx 3\text{-}CH_3$$

It is notable that the 5-methyl, which is a substituent in the position β to the N-oxide group, instead of 4-methyl in the γ-position, follows the most reactive 6-methyl in the exchange reactivity. If one assumes that both the N-oxide group and free nitrogen affected the electron system independent of each other, the reactivity could be expected to decrease in the order of 6, 4, 5, and 3. Since it can be considered that the ease of the exchange reactivity reported in this paper should be explained in principle from the delocalization energies of the carbanions as the reaction intermediate (in Chart 2), the molecular orbital calculations may be of a great help for elucidation of the exchange reactivity and of other chemical reactivities. Thus, such basic parameters as coulomb and resonance integrals in the molecular orbital treatment should be evaluated so as to be consistent with the order of the exchange reactivities obtained here. Furthermore, to be worth noting, the order obtained from deuterium exchange agreed with that of the reactivity in the base-catalysed hydrogen exchange of the ring hydrogens of pyridazine and its N-oxide,[17] although this order seriously disagrees with that of the relative reactivities of the chlorine atoms of pyridazine 1-oxides in the nucleophilic replacement reaction with piperidine.[13] Molecular orbital calculations are now in progress in connection with these reactivities of this class of compounds.

Experimental

Compounds——Methylpyridazines and their N-oxides were synthesized by the authentic preparative methods.[18]

NMR Measurements——The spectra were obtained with a JNM-3H-60 spectrometer (Japan Electron Optics Lab. Co.), operating at 60 Mc.p.s. at room temperature.

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17) Y. Kawazoe, M. Ohnishi, Y. Yoshioka: This Bulletin, **12**. 1384 (1964).
18) M. Ogata, H. Kano: This Bulletin, **1**, 29 (1953). T. Nakagome: Yakugaku Zasshi, **82**, 249 (1962). M. Ogata, H. Kano: This Bulletin, **11**, 35 (1963).