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Studies on Pyridazines. XI.[1] Reactivity of 3-Hydroxypyridazine 1-Oxides. (3).[2] Nuclear Magnetic Resonance Studies of 3-Hydroxypyridazine 1-Oxide and Its Derivatives

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NMR spectra of 3-hydroxypyridazine 1-oxides and their monomethylated derivatives were examined and structural propriety of their nitrated and halogenated products was confirmed by the analyses of the NMR spectra. Furthermore, in 3-hydroxypyridazine 1-oxides, predominance of enol form tautomer was proved by NMR data. The conclusion was also drawn by other spectral data (UV and IR).

Many works[4] on nuclear magnetic resonance spectra of pyridazine N-oxides have been reported, but only a few were revealed on hydroxypyridazine N-oxides, namely on C-alkylaminomethylation products[5] of 3-hydroxy- and 5-hydroxy-pyridazine 1-oxides.

In a preceding paper,[1] authors have reported on electrophilic substitution reactions of 3-hydroxypyridazine 1-oxide (I) and its mono methyl homologs (II, III and IV), affording halogeno- and nitro-derivatives whose structures were elucidated mainly by chemical method. The present paper deals with the NMR spectra of 3-hydroxypyridazine 1-oxide derivatives obtained in a preceding paper.[1]

Experimental

All the spectra were measured at 60 Mc by JNM-3H-60 spectrometer (Japan Electron Optics Lab. Co., Ltd.) in DMSO-d_6, using tetramethylsilane as an internal reference. The materials were prepared as indicated in a preceding paper,[1] which are shown in Chart 1.

Results and Discussion

The NMR spectra of 3-hydroxypyridazine 1-oxide and its methylated derivatives (I—IV) and assignment of their signals are shown in Fig. 1. Spectrum of I exhibits a set of two doublets at 3.35 τ (1H) and 2.06 τ (1H), and a quartet at 2.33 τ (1H). In the case of II, in which H_4-proton of I is replaced by methyl group, the signal corresponding to 3.35 τ disappears and only two signals at 2.49 τ and 2.13 τ due to ring protons are observed. The compound (III), in which H_5-proton of I is replaced by methyl group, exhibits signals at 3.51 τ and 2.12 τ, missing a signal corresponding to that of 2.33 τ in the spectrum of I. The compound

1) Part X: H. Igeta, T. Tsuchiya, M. Nakajima (née Yamada), T. Sekiya (née Nogami), Y. Kumaki, T. Nakai and T. Nojima, *Chem. Pharm. Bull.* (Tokyo), **17**, 756 (1969).
2) Part (2): see 1)
3) Location: *Hatanodai, Shinagawa-ku, Tokyo.*
4) *a*) K. Tori, M. Ogata and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 235 (1963); *b*) Y. Kawazoe and S. Natsume, *Yakugaku Zasshi*, **83**, 523 (1963).
5) *a*) G. Okusa, S. Kamiya and T. Itai, *Chem. Pharm. Bull.* (Tokyo), **15**, 1172 (1967); *b*) G. Okusa and M. Osada, *ibid.*, **15**, 1736 (1967); *c*) S. Kamiya, G. Okusa, M. Osada, M. Kumagai, A. Nakamura and K. Koshinuma, *ibid.*, **16**, 939 (1968).

(IV), in which H_6-proton of I is replaced by methyl group, exhibits two doublets centered at 3.38 τ and 2.42 τ, but no peak at around 2.1 τ.

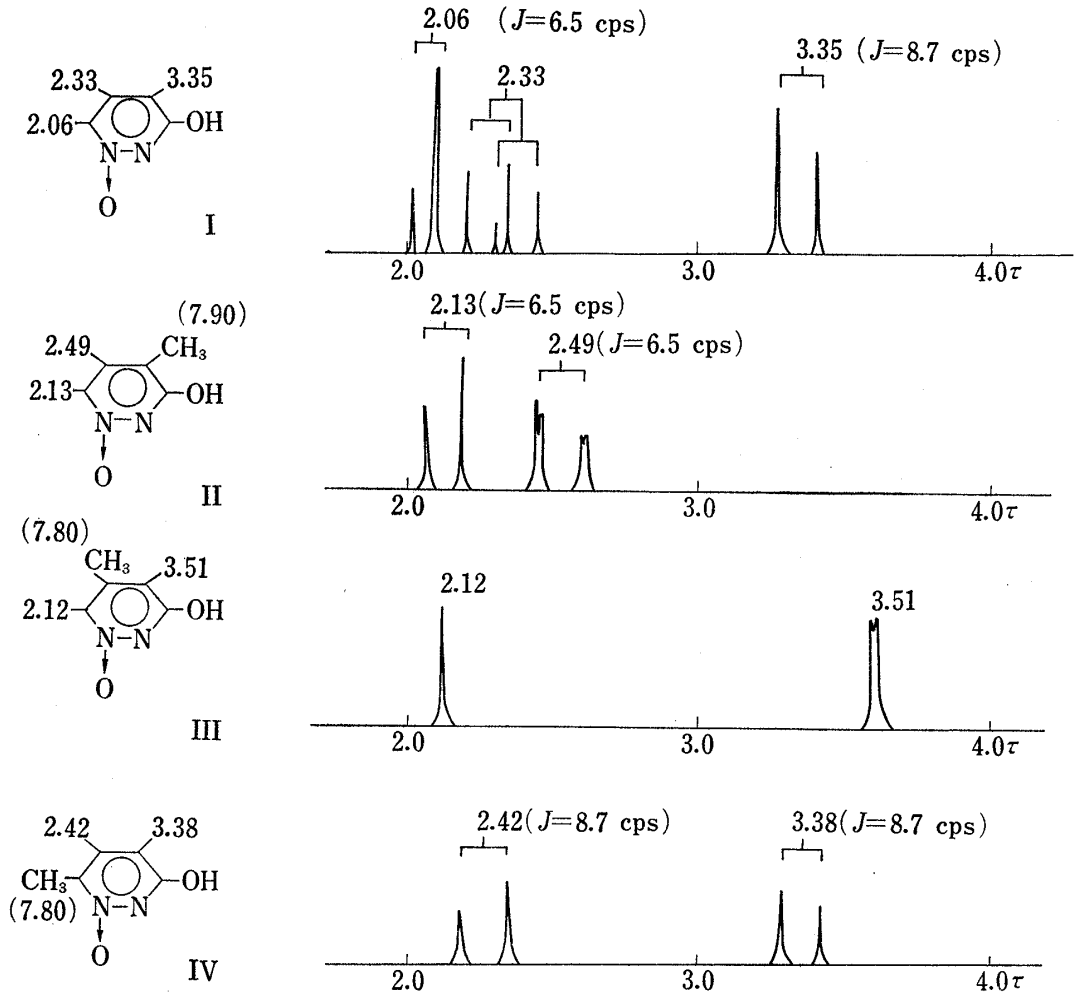


Fig. 1. Nuclear Mgagnetic Resonance Spectra of 3-Hydroxypyridazine 1-Oxides (in DMSO-d_6)

From these results, the signals at 3.35 τ, 2.33 τ, and 2.06 τ in the spectrum of I are assigned to the protons H_4, H_5 and H_6, respectively.

Tori, *et al.*[4a] examined the NMR spectra of CH_3–, Cl– CH_3O–, and NO_2–substituted, pyridazine N-oxides in $CDCl_3$ and concluded that the chemical shift of ring protons appeared in an order H_4 (τ: 2.77—3.33)>H_5 (τ: 2.10—2.48)>H_6 (τ: 1.78—1.90). Bearing this in mind, chemical shifts and the assignment of each proton in the spectra of I—IV shown in Fig. 1, are reasonable in consideration of the effect of hydroxyl group on the ring. Itai, *et al.* [5a] also reported that, in D_2O, the chemical shifts of H_4,H_5 and H_6–protons of I were 2.92 τ (d), 2.16 τ (q), and 1.77 τ (d), respectively, which are almost coincide with our data.

The values of spin–spin coupling constant between H_4 and H_5–protons of I and IV are 8.7 cps and $J_{5,6}$ of I and II are 6.5 cps, indicating that these values are reasonable compared with that of ortho coupling of ring protons in aromatic system.[6]

Concerning to the coupling between methyl group and ring protons, the values between C_4–CH_3 and H_5, C_5–CH_3 and H_4 are found to be 0.3—0.6 cps. On the other hand, the value

6) J.A. Pople, W.G. Schneider and H.G. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co. Inc., N.Y., 1959, p. 193.

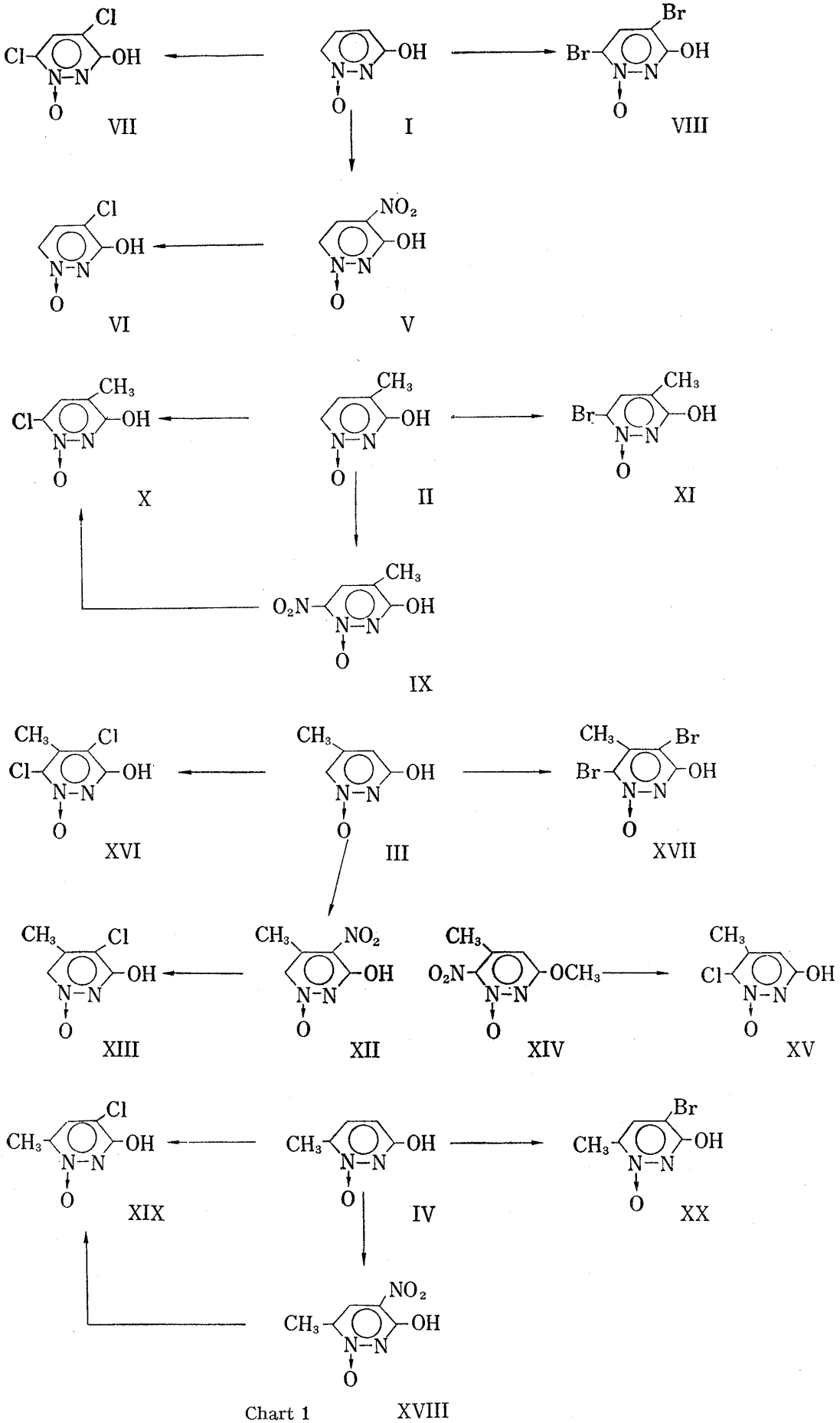


Chart 1

of coupling constant between C_{5or6}-CH_3 and H_{6or5} is nearly zero. Owing to the effect of methyl group, a proton signal adjacent to CH_3 group appears higher field by approximately 0.15 ppm when both methyl group and hydrogen are located at 4- and 5-positions, and shows less higher field shift (0.06—0.09 ppm) when located at 5- and 6-positions. These magnitude of higher shift and almost coincide with that reported by Ohtsuru, *et al.*[7]

From these points of view, in the case of 3-hydroxypyridazine N-oxides, the bond C_4–C_5 might have stronger double bond character than that of C_5–C_6. The details on this point would be discussed later.

Table I. Nuclear Magnetic Resonance Spectral Parameters for 3-Hydroxypyridazine 1-Oxide Derivatives

Substituent	τ_{H4}	τ_{H5}	τ_{H6}	τ_{CH3}	$J_{4,5}$	$J_{5,6}$
None (I)	3.35	2.33	2.06	—	8.7	6.5
4-NO_2 (V)	—	1.55	2.00	—	—	6.5
4-Cl (VI)	—	2.11	1.89	—	—	6.5
4-Cl, 6-Cl (VII)	—	2.08	—	—	—	—
4-Br, 6-Br (VIII)	—	2.08	—	—	—	—
4-CH_3 (II)	—	2.48	2.13	7.90	0.3[a]	6.5
4-CH_3, 6-NO_2 (IX)	—	1.65	—	7.85	0.9[a]	—
4-CH_3, 6-Cl (X)	—	2.12	—	7.91	0.6[a]	—
4-CH_3, 6-Br (XI)	—	2.12	—	7.91	0.6[a]	—
5-CH_3 (III)	3.51	—	2.12	7.80	0.3[a]	~0[a]
5-CH_3, 4-Cl (XIII)	—	—	1.95	7.73	—	~0[a]
5-CH_3, 6-Cl (XV)	3.36	—	—	7.75	0.3[a]	—
5-CH_3, 4-Cl, 6-Cl (XVI)	—	—	—	7.57	—	—
5-CH_3, 4-Br, 6-Br (XVII)	—	—	—	7.57	—	—
6-CH_3 (IV)	3.38	2.42	—	7.80	8.7	0[a]
6-CH_3, 4-NO_2 (XVIII)	—	1.35	—	7.67	—	0[a]
6-CH_3, 4-Cl (XIX)	—	1.98	—	7.76	—	0[a]
6-CH_3, 4-Br (XX)	—	1.98	—	7.76	—	0[a]

(in DMSO-d_6)
a) CH_3-H coupling

Table I gives chemical shifts and values of coupling constant of the compounds prepared in a preceeding paper.[1] The nitro compound (V), obtained by nitration of I, exhibits two doublet signals centered at 1.55 τ and 2.00 τ and their coupling constant is 6.5 cps, suggesting that the nitro group is not located at 6-position, but 4-position. This is also supported by examining the spectrum of monochloro compound (VI) derived from V by reaction with hydrochloric acid.

The dihalogeno compounds (VII and VIII), exhibit only one singlet signal at 2.08 τ, indicating these are 4,6-dihalogeno compounds.

The mononitro compound (IX) obtained from II, shows a signal of H_5 at 1.65 τ, shifted lower field by 0.85 ppm than that of II and the halogenation products (X and XI), exhibit also somewhat downwards shifted signal at 2.12 τ. Further, the signals in question exhibited a coupling of 0.6 cps with the methyl group and therefore, these compounds, IX—XI, can be assigned as 6-substituted compounds.

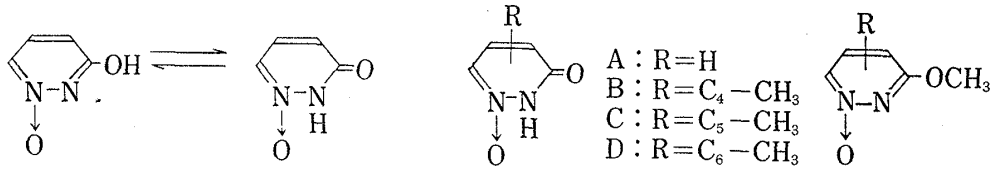
The NMR spectra of two monochloro derivatives of III seems to be worthy to note. The compound (XIII) obtained from XII, shows a signal at 1.95 τ (1H, singlet) and the compound (XV) derived from XIV, exhibits a signal at 3.36 τ (1H, unresolved quartet). Furthermore, signals of methyl group appear at 7.73 τ (singlet) in XIII, and at 7.75 τ (doublet, J=0.3 cps) in XV. From these facts, both isomers are proved to be 4-chloro compound (XIII) and

7) M. Ohtsuru, K. Tori and H. Watanabe, *Chem. Pharm. Bull.* (Tokyo), **15**, 1015 (1967).

6-chloro compound (XV), respectively. These conclusions are in good accord with the chemical proof given in a preceeding paper.[1)]

As for the nitration product (XVIII) and two halogenation products (XIX and XX), obtained from IV, the reasonable chemical shifts of H_5 protons as well as almost negligible coupling between these protons and C_6–CH_3 group leads to the conclusion that all of these are 4-substituted compounds.

Concerning to 3-hydroxypyridazine 1-oxide, one (Igeta[8)]) of the present authors, has already pointed out that, among the two possible tautomers (Ia and Ib), the phenolic structure (Ia) has a larger contribution from the data of UV spectrum and pKa' value.



Ia Ib XXI XXII

In order to provide a further assuarance of this conclusion, we examined the NMR spectra of N–CH_3 compounds (XXI_{A-D})[9)] and O–CH_3 compounds ($XXII_{A-D}$) of 3-hydroxypyridazine 1-oxide and its monomethyl derivatives (I—IV)

An order of chemical shift of ring protons of these compounds is $H_4>H_5>H_6$ with no exception and is the same as that of 3-hydroxy compounds. The assignment shown in Table II is confirmed by the comparison of chemical shift of ring protons among the ring methylated isomers.

Table II. Nuclear Magnetic Resonance Spectral Parameters for Pyridazine 1-Oxide Derivatives

Group	Substituent	τ_{H_4}	τ_{H_5}	τ_{H_6}	τ_{C-CH_3}	τ_{O-CH_3}	τ_{N-CH_3}	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$
A	3-OH (I)	3.35	2.33	2.06	—	—	—	8.7	~0	6.5
	3-OCH_3 (XXII-A)	3.05	2.12	1.79	—	6.03	—	8.7	~0	6.3
	2-CH_3, 3=O (XXI-A)	3.32	2.46	2.12	—	—	6.43	9.9	1.5	6.3
B	3-OH, 4-CH_3 (II)	—	2.49	2.13	7.90	—	—	0.3[a)]	—	6.5
	3-OCH_3, 4-CH_3 (XXII-B)	—	2.29	1.89	7.89	6.02	—	~0 [a)]	—	6.6
	2-CH_3, 3=O, 4-CH_3 (XXI-B)	—	2.54	2.16	7.92	—	6.38	1.2[a)]	—	6.0
C	3-OH, 5-CH_3 (III)	3.51	—	2.12	7.80	—	—	0.3[a)]	~0	~0[a)]
	3-OCH_3, 5-CH_3 (XXII-C)	3.17	—	1.86	7.73	6.08	—	0.3[a)]	~0	~0[a)]
	2-CH_3, 3=O, 5-CH_3 (XXI-C)	3.42	—	2.11	7.85	—	6.43	0.6[a)]	1.5	~0[a)]
D	3-OH, 6-CH_3 (IV)	3.38	2.42	—	7.80	—	—	8.7	—	~0[a)]
	3-OCH_3, 6-CH_3 (XXII-D)	3.09	2.18	—	7.71	6.02	—	9.0	—	~0[a)]
	2-CH_3, 3=O, 6-CH_3(XXI-D)	3.25	2.45	—	7.75	—	6.34	9.9	—	~0[a)]

(in DMSO-d_6)
a) CH_3–H coupling

It is noteworthy that the coupling constants of a series of compounds, where R=H (abbreviated as A group), have, $J_{4,5}$ (8.7—9.9 cps)>$J_{5,6}$ (6.3—6.5 cps) and the magnitude of these coupling constants are almost the same as those of the isomers which have CH_3 group on the ring. For instance, $J_{4,5}$ in D group compounds is 8.7—9.9 cps and $J_{5,6}$ in B group

8) H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **7**, 938 (1959).
9) H. Igeta, T. Tsuchiya, M. Yamada and H. Yokogawa, Presented at the 88th Annual Meeting of Pharmaceutical Society of Japan, Abstracts of Papers, p. 103 (Apr. 1968, Tokyo). The details will be published soon.

compounds is 6.0—6.6 cps. The larger magnitude of $J_{4,5}$ to $J_{5,6}$ is also observed in the coupling between CH_3 and the ring proton, and thus, $J_{CH3,H4}$ (0.3—1.2 cps)$>J_{CH3,H5}$ ($\approx$0) in C group are found.

On the other hand, meta-coupling ($J_{4,6}$), having a magnitude of 1.5 cps, are commonly observed in N-CH_3 compounds (XXI). On the contrary, the corresponding coupling are almost negligible in both OH and O-CH_3 compounds. For example, H_6-proton of III or $XXII_C$ shows a sharp singlet peak, and that of XXI_C exhibits a doublet (J=1.5 cps). This phenomenon might be useful in distinguishing between O-CH_3 and N-CH_3 compounds in some 3-hydroxypyridazine 1-oxide derivatives.

From the above mentioned informations, it is interesting to clarify the reason of an order, $J_{4,5}>J_{5,6}$ in 3-hydroxypyridazine 1-oxide derivatives. There may be two possible explanations.

(1) In 3-hydroxypyridazine 1-oxides, as Igeta has already refered, a-type predominates over b-type, and if this conclusion is correct, then the NMR spectra of 3-hydroxypyridazine 1-oxides should be essentially the same as that of pyridazine 1-oxides. The NMR spectra of pyridazine 1-oxides, having no probability of any tautomerism, has been reported,[4a] pointing out the order, $J_{4,5}>J_{5,6}$. The order as well as the magnitude of each coupling constant reported by these authors are in accord with those obtained in the present study.

(2) All the N-CH_3 compounds (XXI) having apparently the structure of 3 (2H)-pyridazinone and consequently have different electronic structure from those of ordinary pyridazine 1-oxides, are measured in the present work and they exhibit the order, $J_{4,5}>J_{5,6}$, and so data of (1) can be explained, even if b-type tautomer has a larger contribution in 3-hydroxypyridazine 1-oxides.

Of the two explanations, the supposition (1) seems to be more reasonable from the following considerations.

(A) The *meta*-coupling, commonly observed in N-CH_3 compounds, are not observed both in 3-OH compounds and in 3-OCH_3 compounds.

(B) The coupling constants, $J_{4,5}$, of 3-OH compounds and 3-OCH_3 compounds are 8.7 cps, while those of N-CH_3 compounds have a slightly larger magnitude (9.9 cps).

From these NMR data alone, the propriety of (1) and therefore, the conclusion that b-type tautomer has little contribution but a-type has a larger one in 3-hydroxypyridazine 1-oxides can be drawn.

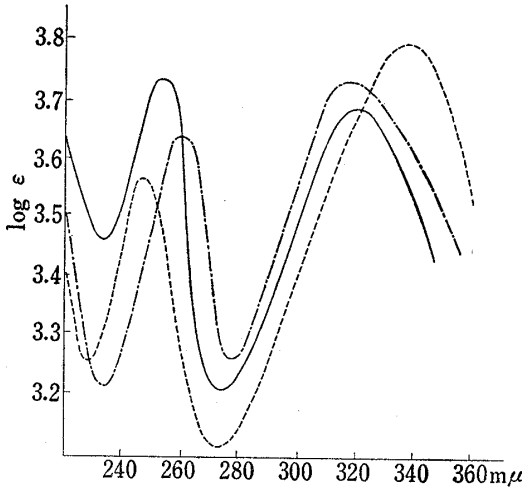


Fig. 2-1. Ultraviolet Absorption Spectra (in EtOH)

——— I ····· XXI-A
·—·—·— XXII-A

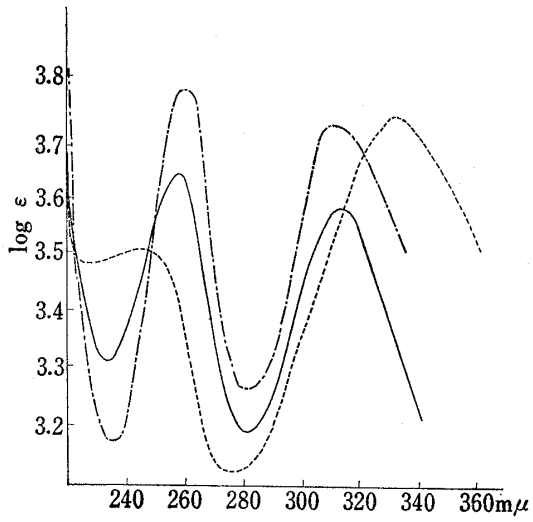


Fig. 2-2. Ultraviolet Absorption Spectra (in EtOH)

——— III ····· XXI-C
·—·—·— XXII-C

In order to obtain further support of this view, UV spectra of 3-hydroxypyridazine 1-oxide (I), 3-methoxypyridazine 1-oxide ($XXII_A$), 3 (2H)-pyridazinone 1-oxide (XXI_A), and their ring methyl derivatives were measured. (Fig. 2).

The spectra of 3-hydroxy compounds are apparently similar to those of 3-OCH_3 compounds, and not to N–CH_3 compounds. From the facts, it is concluded that a-type tautomer predominates in 3-OH compounds.

IR spectra of them were also measured, using $CHCl_3$ containing 10 v/v% MeOH as a solvent to dissolve all the samples with no exception. The absorption of lactam function, $\nu_{C=O}$ (1630—1660 cm^{-1}), observed in the spectra of all the N–CH_3 compounds is not substantially recognized in corresponding OCH_3 and OH compounds, and the spectra of the latter two are very similar.

From these spectral data, it is firmly confirmed that, in 3-hydroxypyridazine 1-oxides, a-type tautomer has a larger contribution, while b-type tautomer has little one.

The present study thus provides a correctness of the inference on the structure of 3-hydroxypyridazine 1-oxides, previously suggested by one of the present authors.

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