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182. Hiroshi Igeta, Mutsumi Yamada,*1 Yuko Yoshioka, and Yutaka Kawazoe*2 : Syntheses of Pyridazine Derivatives. Ⅶ.*3 Reactivity of 3-Hydroxypyridazine 1-Oxide. (1).*4

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The reactivities of 3-hydroxypyridazine 1-oxide (I) were examined in bromination and acid- and base-catalyzed deuteration reactions. The electronic effects of 3-hydroxy and N-oxide groups were discussed in comparison of the reactivities of I with 3-hydroxypyridazine and pyridazine 1-oxide.

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It has been suggested that the reactivities of nitrogen-containing heteroaromatic compounds toward both nucleophiles and electrophiles are increased by N-oxygenation of thier aromatic nitrogens. Although many studies have been made on the effect of the N-oxide group in pyridine, quinoline, and six-membered diazine derivatives, detailes on each of a variety of the reactions and/or compounds are still open to further investigations. On the other hand, α-hydroxylated azines such as 2-pyridone, 2-quinolone, and isoquinolone, etc., are well known to readily undergo electrophilic reactions such as nitration, halogenation, deuteration, etc., just as the phenolic compounds.

The present paper describes several reactions of 3-hydroxypyridazine 1-oxide, which has both an N-oxide group and an α-hydroxyl group next to the other ring nitrogen in its molecule. Discussion will be made on comparison of the reactivities of this compound with those of other monoazine derivatives.

Results and Discussion

The structure of 3-hydroxypyridazine 1-oxide (I) was proved by Igeta[1] to be in an enol form, whereas its non-oxygenated base (Ⅱ) has 2-oxo structure in both solid state and in solution. A marked difference in the reactivity between these compounds, I and Ⅱ, was observed in halogenation reactions. The oxide (I) reacted readily with bromine in water to afford a dibromo derivative, whereas the non-oxygenated base (Ⅱ) never consumed any bromine even at 100° and was recovered from the reaction mixture. The structure of the dibromo derivative of I was determined as follows. 4,6-Dideuterio-3-hydroxypyridazine 1-oxide, the synthesis of which is described in the latter part of this paper, was brominated under the same reaction condition. The nuclear magnetic resonace spectrum of the dibromo derivative thus produced showed the presence of one hydrogen atom on the aromatic ring, indicating that 4- and 6-positions, where deuterium had been substituted, were brominated (Chart 1).

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*3 Part Ⅵ : This Bulletin, **8**, 559 (1960).
*4 This paper constitutes Part Ⅶ of a series entitled "Studies on Hydrogen Exchange" by Y. Kawazoe. Part Ⅵ : This Bulletin, **15**, 1225 (1967).
1) H. Igeta : This Bulletin, **7**, 938 (1959).

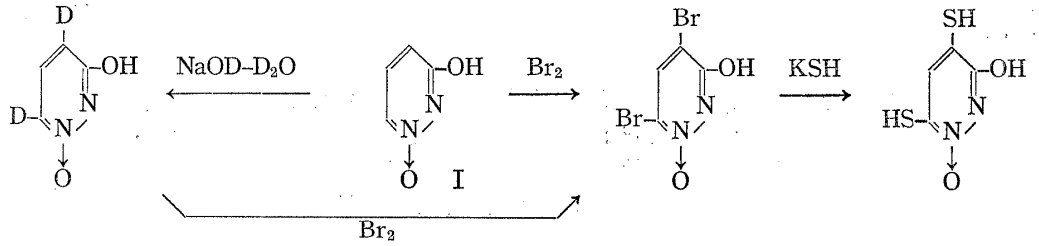

Chart 1.

This result seems to be a notable example which indicates that N-oxygenation enhanced the reactivity of positions α and γ to the N-oxide group toward an electrophile compared with that of the non-oxygenated base. Among electrophilic reactions, nitration had been the only one example that was definitely demonstrated to be accelerated by N-oxygenation.

This observation on the effect of the N-oxide group prompted us to examine the acid-catalyzed deuteration reaction of these compounds, which must involve an electrophilic attack of the reagent, D^+ or D_3O^+. This kind of deuteration has been already studied in N-oxidized[2] and α-hydroxylated[3] derivatives of monoazines in connection with their reactivity toward other electrophiles. The α-hydroxylated compounds, such as 2-pyridone, 2-quinolone, and isoquinolone, were succesively deuterated at one position to another and the order of the reactivity was well correlated with those of the reactivity in other electrophilic reactions.[3] N-Oxidized monoazines, on the other hand, which can readily react with nitronium ion, strongly resisted deuteration under acidic conditions.[2] Deuteration of I and II was carried out under various acidic conditions but no successful result was obtained. Thus, deutration of II did not progress even in 98% D_2SO_4 at 200°. Deuteration of I did not start in 98% D_2SO_4 at 200°, while decomposition took place in 10% D_2SO_4 at above 120°. As a conclusion, both compounds, I and II, exhibited no reactivity in the acid-catalyzed deuterium exchange reaction although the bromination of I readily proceeded.

Accordingly, the reactivity of I was examined from those in nucleophilic reactions. Nucleophilic replacement of bromine atoms in 4,6-dibromo-3-hydroxypyridazine 1-oxide was first examined. Contrary to halogeno pyridazine 1-oxides,[4] it did not react with amines such as piperidine under the usual reaction conditions chosen for chloro derivatives of pyridazines and monoazines, whereas it reacted with a more potent nucleophilic reagent of potassium hydrogen sulfide when refluxed in dimethyl formamide to afford a dimercapto derivative in a good yield. It can, therefore, be concluded that the halogen atoms were clearly inactivated toward nucleophiles by the effect of 3-hydroxyl group.

Subsequently, as one of nucleophilic reactions, the base-catalyzed deuterium exchage reaction was taken up, which has already been studied in detail with pyridines, pyridazines, and thier N-oxides,[5] although the reaction mechanism is not completley clear. The deutration was carried out by dissolving the compounds to be examined in 1% NaOD-D_2O solvent in a concentration of about 5%. The reaction mixture was sealed in an NMR sample tube and heated at an appropriate temperature for an appropriate period. The nuclear magnetic resonance (NMR) spectrum of the sample thus prepared was measured every an appropriate intervals to know how the deuteration had proceeded. The results are summarized in Chart 2, which includes the data for pyridazine and its 1-oxide[5] for comparison. The positions deuterated was readily determined from the analysis of

2) Y. Kawazoe, M. Ohnishi: This Bulletin, **15**, 826 (1967).
3) Y. Kawazoe, Y. Yoshioka: *Ibid.*, in press.
4) S. Sako: *Ibid.*, **14**, 269 (1966).
5) Y. Kawazoe, M. Ohnishi, Y. Yoshioka: *Ibid.*, **12**, 1384 (1964).

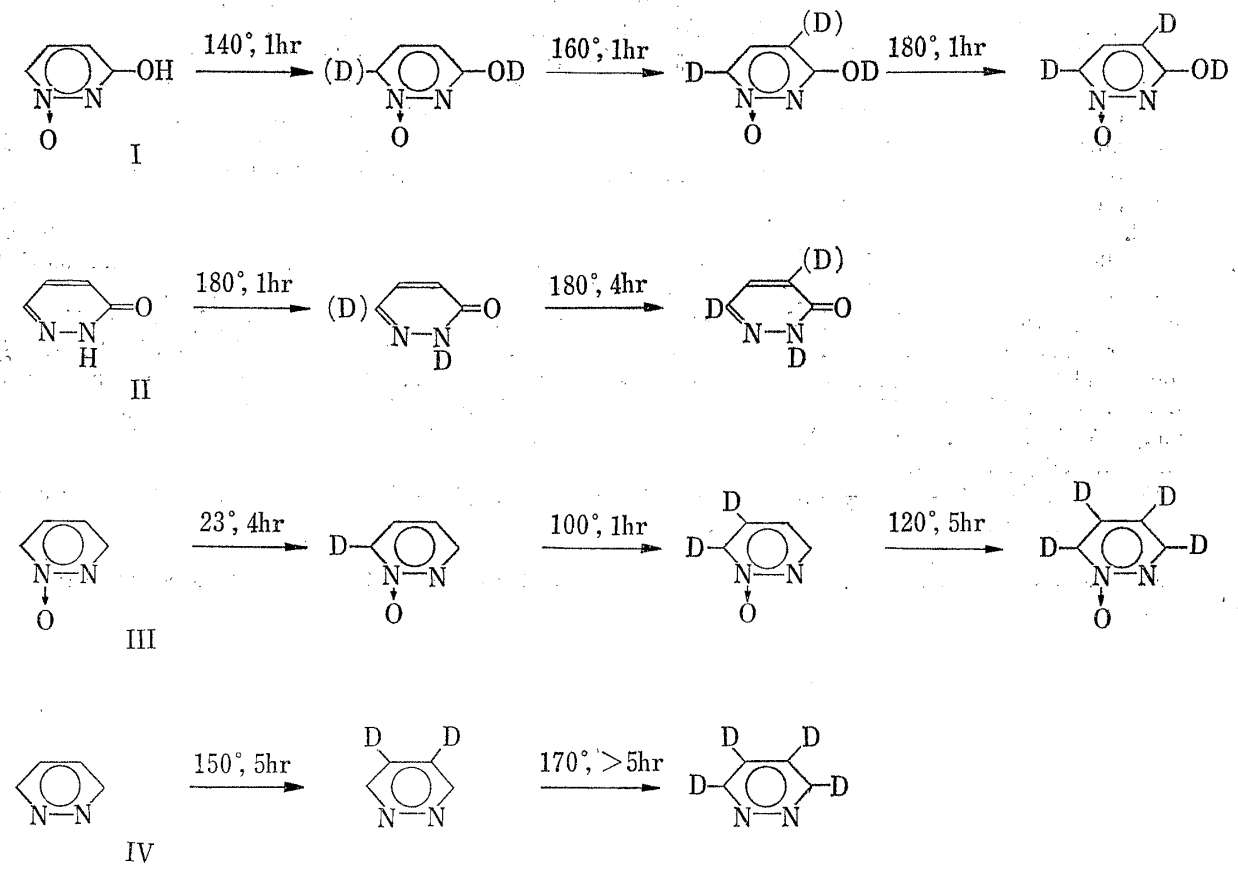

Chart. 2. The Base-Catalyzed Deuterium Exchange Reaction of Pyridazine Derivatives in 1% NaOD-D_2O Solution (Deuterium in parentheses, (D), means "partly deuterated" under the condition described.)

the NMR spectra. Thus, the deuterated positions of dideuterio derivatives of I and II were determined from the NMR data that deuteration erased a pair of doublets from the spectrum and changed the signal pattern of the other signal from a triplet to a singlet. It is reasonable to assign the lower doublet to proton-6 adjacent to nitrogen functions, the higher one to proton-4, and the triplet definitely to proton-5. It becomes evident from these data that introduction of a hydroxyl group to 3-position decreased to a great extent the base-catalyzed deuterium exchange reactivity of the aromatic ring hydrogens and that, on the other hand, N-oxygenation accelerated the exchange considerably. It can, therefore, be concluded that the N-oxygenation of II promoted not only the electrophilic substitution at 4- and 6-positions with halogen, but also the base-catalyzed hydrogen exchange, which can be regarded as a nucleophilic reaction, at the same positions 4 and 6. Furthermore, it is worth noting that the orientation of the base-catalyzed exchange reaction of I and II was directed toward ortho and para and not toward meta in regard to the hydroxyl group and that the effect of 3-hydroxyl group seems to overcome the accelerating effect of the N-oxide group.

There still remain questions about the reactivities of I in connection with the electronic effects of N-oxide and 3-hydroxyl groups. They are now being further investigated with the data from other electrophilic reactions.

Experimental

3-Hydroxy-4,6-dibromopyridazine 1-Oxide——To a solution of 200 mg. of I dissolved in 5 ml. of H_2O, bromine was added dropwise until no more precipitate was produced. The precipitate was collected and

recrystallized from MeOH to colorless needles, m.p. 220~221° (decomp.). Yield 70%. *Anal.* Calcd. for $C_4H_2O_2N_2Br_2$: C, 17.80; H, 0.75; N, 10.38. Found: C, 17.25; H, 0.98; N, 10.11.

Bromination of 3-Hydroxy-4,6-dideuteriopyridazine 1-Oxide——The mixture of 1 g. of I and 16 ml. of 1% NaOD-D_2O was heated in a sealed tube at 160° for 1 hr. and then at 180° for another one hr. Since two pairs of doublets disappeared from the NMR spectrum of this reaction mixture, it is evident that deuteration occurred exclusively at position-4 and -6. After the reaction mixture was neutralized with aq. HCl upto pH=6 and then saturated with NaCl, a large excess of EtOH was added. After the resulting precipitate was removed by filtration, aq. bromine was added to this ethanolic solution until bromination had been completed. The resulting needles were gathered and recrystallized from aq. MeOH to give colorless needles in an excellent yield. The dibromide thus obtained showed the completely same NMR spectrum as that prepared from non-labeled 3-hydroxypyridazine 1-oxide in chemical shift and signal-intensity.

3-Hydroxy-4,6-dimercaptopyridazine 1-Oxide——To a solution of 500 mg. of 3-hydroxy-4,6-dibromopyridazine 1-oxide dissolved in 5 ml. of dimethylformamide, 1.18 ml. of an EtOH solution of KSH (36%) was added and the mixture was heated on a boiling water bath for 3 hr. Thirty ml. of H_2O was added and the solution was acidified. The precipitate was collected and recrystallized from EtOH, m.p. 242~247° (decomp.). Yield 200 mg. *Anal.* Calcd. for $C_4H_4O_2N_2S_2$: C, 27.26; H, 2.29; N, 15.90; S, 36.39. Found: C, 27.22; H, 2.31; N, 15.80; S, 36.19.

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

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