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176. Hiroshi Igeta: Syntheses of Pyridazine Derivatives. III.[1] 3-Methoxy- and 3-Hydroxy-pyridazine 1-Oxides.

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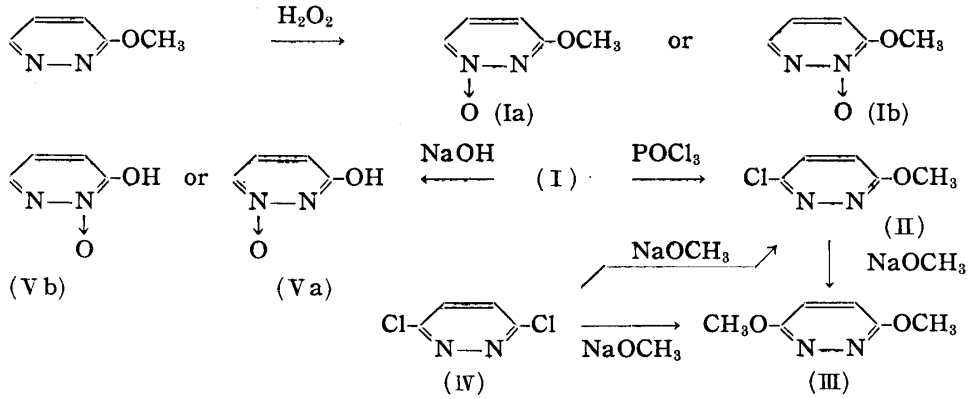
In the preceding work,[1] 3,6-dimethoxypyridazine 1-oxide and its nitro compound were prepared and the reactivity of the nitro group was investigated. The present paper deals with 3-methoxypyridazine 1-oxide and 3-hydroxypyridazine 1-oxide obtained by hydrolysis of the methoxyl compound. On heating 3-methoxypyridazine with hydrogen peroxide in glacial acetic acid at 70° for 6 hours, a mono-N-oxide was obtained in a good yield. The structure of the N-oxide is thought to be (Ia) or (Ib). Some reactions of the N-oxide were investigated to elucidate the structure.

Treatment of this N-oxide compound with phosphoryl chloride at room temperature gave a chloromethoxyl compound (II), m.p. 91°, which was easily converted into a dimethoxyl compound (III), m.p. 106°, by reaction with sodium methoxide. The chloromethoxyl compound (II) and dimethoxyl compound (III) were found to be respectively identical with 3-chloro-6-methoxypyridazine and 3,6-dimethoxypyridazine by admixture and also by comparing the infrared absorption spectra. Samples of 3-chloro-6-methoxypyridazine and 3,6-dimethoxypyridazine were also prepared from dichloropyridazine (IV) by reacting with one or two moles of sodium methoxide.[2] The reaction of an aromatic N-oxide compound and phosphoryl chloride generally gave a compound which has a chlorine atom at a position *ortho* or *para* to the N-oxide group in the original compound.[3] Consequently, from the above-mentioned facts the structure of the N-oxide compound (I) should be considered to be (Ia).



When 3-methoxypyridazine N-oxide (I) was heated with 5% sodium hydroxide on a steam bath, the methoxyl group was easily demethylated to produce 3-hydroxypyridazine N-oxide (Va or Vb). This hydroxyl compound was also proved to be 3-hydroxy 1-oxide (Va) from the following experimental data.

1) When the hydroxyl compound (V) was treated with silver oxide and methyl iodide, the original methoxyl compound (1) was regenerated as a main product. This is in contrast to 2-hydroxypyridine 1-oxide,[4] 2-hydroxyquinoline 1-oxide,[5] and 4-methoxy-

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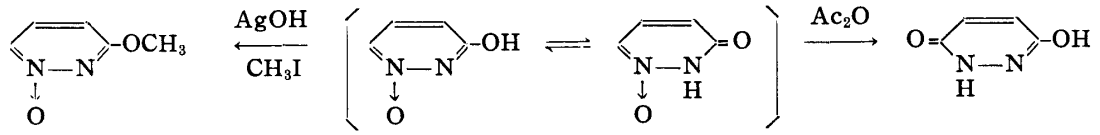
1) Part II. T. Itai, H. Igeta: Yakugaku Zasshi, **75**, 996(1955).
2) Part I. *Idem.*: *Ibid.*, **74**, 1195(1954).
3) E. Ochiai: J. Org. Chem., **18**, 534~551(1953).
4) E. Shaw: J. Am. Chem. Soc., **71**, 67(1949).
5) C. Kaneko: This Bulletin, **7**, 273(1959).

2-hydroxyquinazoline 1-oxide,[6] in which there is a large contribution of the cyclic hydroxamic structure than that of tautomeric hydroxy N-oxide structure, forming N-OR compounds by alkylation. Thus, the hydroxyl group of (V) is not considered to be attached to the carbon atom adjacent to the N-oxide group. Further, this fact also signifies a fairly large contribution of the phenolic structure (Vc) among the possible tautomers (Vc) and (Vd).



2) By refluxing the hydroxyl compound (V) with acetic anhydride, a dihydroxyl compound (VI) of m.p. 300° (decomp.) was obtained. This showed no depression on admixture with maleic acid hydrazide and the infrared absorption spectra of the two samples were the same. The reaction of an aromatic N-oxide compound and acetic anhydride is well known[7] and the above-mentioned fact is only explained by assuming the formula (Vc) for the hydroxyl compound.

3) The ultraviolet absorption spectrum of (V) in ethanol is illustrated in Fig. 1, which shows two absorption maxima at 255 and 305 mμ, and resembles that of 3-hydroxypyridine 1-oxide[4] but differs from that of 1-hydroxy-2-pyridone.[4]

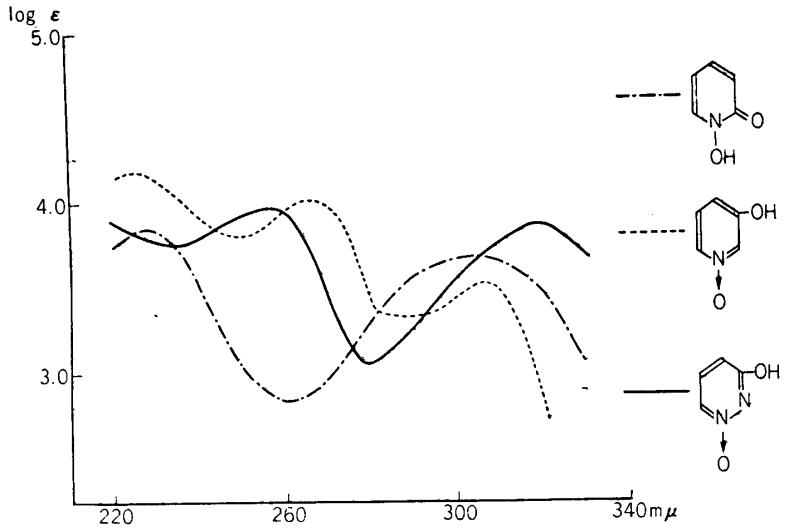


Fig. 1. Ultraviolet Absorption Spectra of 3-Hydroxypyridazine and Its Related Compounds (in EtOH)

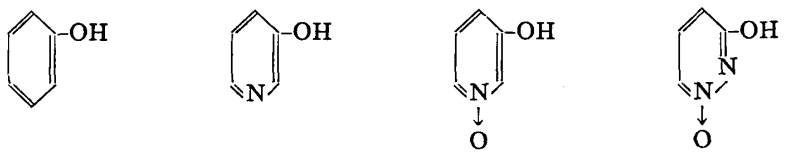
The absorption maxima in water and in *N* NaOH are shown in Table I. The maximum at 315 mμ in water shifted to the bathochromic region by 6 mμ in *N* NaOH, showing that (V) has a phenolic character.

Table I. UV Absorption Maxima of (V)

Solvent	λ_{max} (log ε)	λ_{max} (log ε)
Water	234 (3.96)	315 (3.74)
N NaOH	234 (4.03)	321 (3.77)

6) H. Yamanaka : *Ibid.*, **7**, 152(1959).
7) M. Katada : Yakugaku Zasshi, **67**, 51(1947).

4) pKa′ value of (V) is 4.1 and is fairly strongly acid. pKa′ value of phenol is 10



pKa′	10	8.6	6.4	4.1

and that of 3-hydroxypyridine, in which one of the carbon atoms of phenol is replaced by nitrogen, is 8.6, decreasing by 1.4. Thus, it seems to be natural that pKa value of 3-hydroxypyridazine 1-oxide, in which one more carbon atom of 3-hydroxypyridine 1-oxide is replaced by nitrogen, is smaller than that of the latter by 2.3.

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Experimental

3-Methoxypyridazine 1-Oxide (I)—A mixture of 11 g. of 3-methoxypyridazine, 83 cc. of glacial AcOH, and 22 cc. of 30% H_2O_2 was heated at 70° for 3 hr., further 11 cc. of H_2O_2 was added, and again heated at the same temperature for 3 hr. To this solution, 100 cc. of water was added, AcOH was evaporated under a reduced pressure, and this procedure was repeated 3 times. After neutralization of the residue with Na_2CO_3, this was extracted with $CHCl_3$, the $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and $CHCl_3$ was evaporated. The oily residue was distilled under a reduced pressure to collect the fraction of $b.p_4$ 143°, which solidified into 8.7 g. of hygroscopic crystals (70%). $HgCl_2$-double salt: m.p. 147° (from water).

Reaction of 3-Methoxypyridazine 1-Oxide (I) with $POCl_3$: Formation of 3-Methoxy-6-chloropyridazine (II)—To a cold solution of 1 g. of (I) dissolved in 10 cc. of $CHCl_3$, 2 cc. of $POCl_3$ was added, the mixture was cooled for a short time, and then allowed to stand for 90 min. at room temperature (30°). The reaction mixture was poured into ice, neutralized with Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, passed through a column of activated alumina to remove colored material, and $CHCl_3$ was evaporated from the effluent. The yellowish white residue so obtained was recrystallized from petr. benzine and 0.6 g. of white needles, m.p. 91°, was obtained. This showed no depression on admixture with 3-methoxy-6-chloropyridazine (II), m.p. 91°, prepared from (IV), and gave an entirely the same IR spectrum as that of (II).

3-Hydroxypyridazine 1-Oxide (V)—A solution of 3 g. of (I) dissolved in 75 cc. of 5% NaOH was warmed on a steam bath for 1 hr. After acidification of the solution, water was evaporated under a reduced pressure, the residue was dried at 105° for 2 hr., and extracted with EtOH while hot, removing NaCl by filtration. The filtrate was concentrated to a small volume, the crystals that separated out were collected, and recrystallized from EtOH to white needles, m.p. 200~205° (decomp.). Yield, 2 g. (74%). *Anal.* Calcd. for $C_4H_4O_2N_2$: C, 42.86; H, 3.59; N, 24.99. Found: C, 42.75; H, 3.61; N, 24.82.

Methylation of 3-Hydroxypyridazine 1-Oxide (V): Formation of 3-Methoxypyridazine 1-Oxide (I)—A mixture of 0.5 g. of (V), 1.5 g. of MeI, Ag_2O prepared from 1.5 g. of $AgNO_3$ by the usual method, and MeOH was sealed in a tube and heated at 100° for 2 hr. with occasional shaking. The mixture was filtered with suction and the filtrate was evaporated. The residue was extracted with $CHCl_3$, the $CHCl_3$ layer was dried over anhyd. Na_2SO_4, passed through a column of activated alumina to remove colored material, and $CHCl_3$ was evaporated from the effluent. The oily residue so obtained was submitted to a low-pressure distillation, collecting the fraction of $b.p_{10}$ 150°. The distillate solidified into 0.2 g. of hygroscopic crystals, giving white needles of $HgCl_2$-double salt, m.p. 147°, undepressed on admixture with that of (I).

Reaction of 3-Hydroxypyridazine 1-Oxide (V) with Acetic Anhydride: Formation of Maleic Acid Hydrazide (VI)—A mixture of 0.2 g. of (V) and 2 cc. of Ac_2O was refluxed for 30 min. and pour-

ed into water. The solution was evaporated to dryness under a reduced pressure and the solid so obtained was recrystallized from water to white needles, m.p. 300°(decomp.). This showed no depression of m.p. on admixture with maleic acid hydrazide (VI) and gave an entirely the same IR spectrum as that of (VI).

Summary

Reaction of 3-methoxypyridazine with hydrogen peroxide in glacial acetic acid afforded a mono-N-oxide compound (I). On being treated with phosphoryl chloride, (I) yielded 3-methoxy-6-chloropyridazine (II), whose identification by admixture with an authentic specimen proved (I) to be the 1-oxide (Ia). (I) was hydrolyzed to 3-hydroxypyridazine 1-oxide (V). Methylation of (V) afforded the original base (I) as the main product and the reaction of (V) with acetic anhydride yielded maleic acid hydrazide (VI). From the consideration of ultraviolet spectrum and pKa values, it was concluded that the phenolic structure (Vc) has a larger contribution than the tautomeric pyridazone N-oxide structure (Vd).

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