UDC 547.852.2

On the Characterization of 4-Nitropyridazine 1-Oxide and the N-Oxidation of 4-Methoxypyridazines

When pyridazine 1-oxide (I) was nitrated with the mixed acid at the elevated temperature, a single nitration product corresponding to mononitropyridazine 1-oxide (II), m.p. 151° (*Anal.* Calcd. for $C_4H_3O_3N_3$: C, 34.05; H, 2.14; N, 29.79. Found : C, 34.13; H, 2.07; N, 30.09), was obtained[1,2] in 22% yield. In order to characterize this nitropyridazine 1-oxide and correlate it to the known pyridazine derivative, a series of reactions starting from 4-methoxy-3,6-dichloropyridazine (III) was carried out.[1]

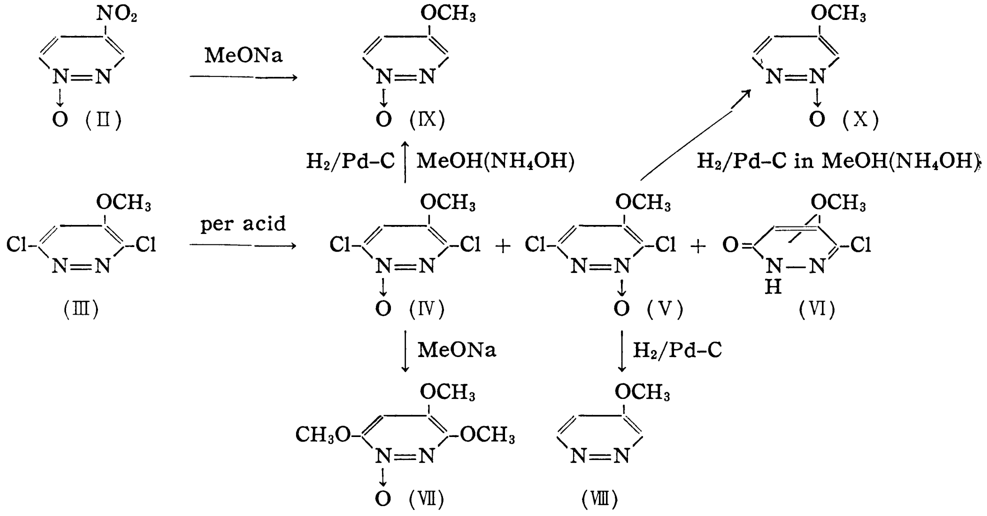

Chart 1.

4-Methoxy-3,6-dichloropyridazine (III) was treated with perphthalic acid in an ethereal solution. Two kinds of its N-oxide, (IV), m.p. 174~175°, and (V), m.p. 162.5~164°, were obtained in 12% and 5% yields respectively, accompanied with a small amount of 4 (or 5)-6-chloro-3(2*H*)-pyridazinone (VI), m.p. 286° (decomp.) (*Anal.* Calcd. for $C_5H_5O_2N_2$-Cl : C, 37.40; H, 3.14; N, 17.45. Found : C, 37.33; H, 3.41; N, 16.89. IR : ν_{max}^{KBr} 1662 cm^{-1}). One of these N-oxides (IV) (*Anal.* Calcd. for $C_5H_4O_2N_2Cl_2$: C, 30.79; H, 2.07; N, 14.37. Found : C, 31.08, H, 2.35; N, 14.24) was converted to 3,4,6-trimethoxypyridazine 1-oxide (VII), whose structure had been established by Igeta,[3] so that the structure of (IV) was confirmed to be 4-methoxy-3,6-dichloropyridazine 1-oxide. This fact has suggested that the other product (V) (*Anal.* Calcd. for $C_5H_4O_2N_2Cl_2$: C, 30.79; H, 2.07; N, 14.37. Found : C, 31.10; H, 2.17; N. 14.68.) was undoubtedly 2-oxide of (III) with consideration of its infrared spectrum (IR : ν_{max}^{KBr} 1330 cm^{-1}; no OH and no CO) and the ready formation of 4-methoxypyridazine (VIII)[4] by catalytic hydrogenation. Catalytic hydrogenation of the former N-oxide (IV), 4-methoxy-3,6-dichloropyridazine 1-oxide, gave 4-methoxypyridazine 1-oxide, which was found to be identical with methoxypyridazine

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1) T. Itai, S. Natsume : in press.
2) Recently, Nakagome reported the same nitro compound, yet the rigorous structural proof has been missing. T. Nakagome : Yakugaku Zasshi, **82**, 253 (1962).
3) H. Igeta : This Bulletin, **8**, 550 (1960).
4) K. Eichenberger, R. Rometsch, J. Druey : Helv. Chim. Acta, **39**, 1755 (1956).

N-oxide derived from the nitration product (II) of pyridazine 1-oxide. Consequently, (II) was established to be 4-nitropyridazine 1-oxide.

In a continuation of our study concerning to this subject, the N-oxidation reaction of 4-methoxypyridazine (VIII) itself was next examined. (VIII) was heated with hydrogen peroxide in acetic acid at 70°, followed by the usual treatment of the reaction mixture. Two kinds of its N-oxide, (IX), m.p. 124~124.5°, and (X), m.p. 111°, were obtained by the chromatographical separation of the chloroform extract, and from the alkaline aqueous solution, 4(1*H*)-pyridazinone (XI),[4] m.p. 252°, was isolated as a by-product, which was merely the hydrolyzed product of (VIII) with this reaction medium. This type of hydrolysis has been already observed[5,6] in the case of the N-oxidation reaction of 3-alkoxy-6-chloropyridazine with hydrogen peroxide-acetic acid. The former N-oxide (IX), was identical with the above-mentioned 4-methoxypyridazine 1-oxide by mixed melting points and comparison of the infrared spectra, and the latter (X), m.p. 111°, possessed analytical values corresponding to 4-methoxypyridazine oxide (*Anal.* Calcd. for $C_5H_6O_2N_2$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.88; H, 4.51; N, 22.32.) and its infrared spectrum supported an N-oxide structure (IR: ν_{max}^{KBr} 1241 cm^{-1}; no OH and no CO), so that, (X) is no doubt 4-methoxypyridazine 2-oxide. In order to make sure of this conclusion, 4-methoxy-3,6-dichloropyridazine 2-oxide (V) was hydrogenated over palladized charcoal in an alkaline medium and the reduction product was proved to be identical with the N-oxide (X). When the N-oxidation of (VIII) was carried out at 100°, the formation of 1-methyl-4(1*H*)-pyridazinone (XII)[4] was observed, though in a small yield, in addition to these three products.

Furthermore, N-oxidation of 6-chloro-3,4-dimethoxypyridazine (XIII) was carried out. (XIII) (m.p. 126°. *Anal.* Calcd. for $C_6H_7O_2N_2Cl$: C, 41.27; H, 4.04. Found: C, 41.37; H, 4.01.) was synthesized by the reaction of (III) with an equimolar amount of sodium methoxide and the structure of (XIII) was determined by the formation of 3,4-dimethoxypyridazine (XIV) (hygroscopic needles, m.p. 55~57°. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75. Found: C, 50.99; H, 5.82. Picrate, m.p. 151°. *Anal.* Calcd. for $C_6H_8O_2N_2 \cdot C_6H_3O_7N_3$: C, 39.03; H, 3.00. Found: C, 39.25; H, 3.18), which was identical with the hydrogenated product of known 3,4-dimethoxypyridazine 1-oxide (XV).[3] When (XIII) was treated with perphthalic acid in ethereal solution, an N-oxide (XVI) (m.p. 190°. *Anal.* Calcd. for $C_6H_7O_3N_2Cl$: C, 37.81; H, 3.70. Found: C, 37.80; H, 3.80.) was isolated in 50% yield as a sole product. Since (XVI) gave known 3,4-dimethoxypyridazine 1-oxide[3] by

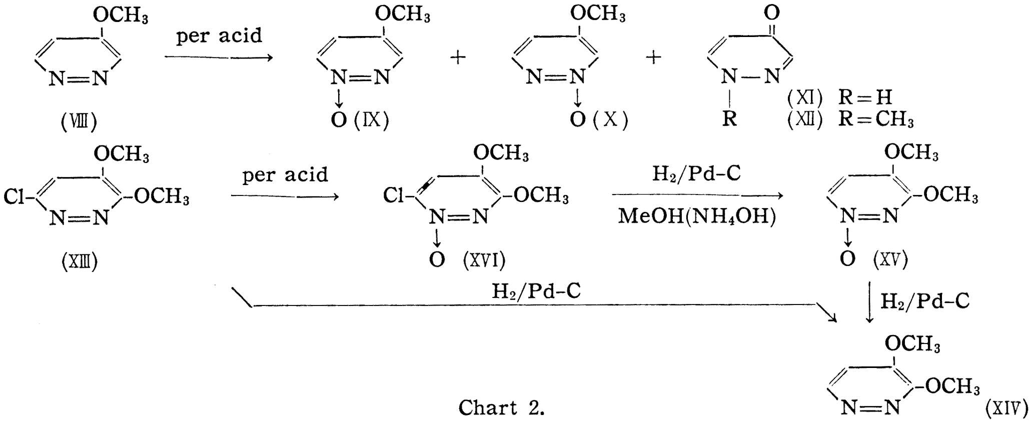

Chart 2.

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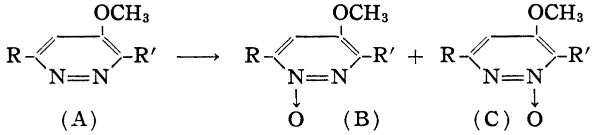
[5] T. Itai, S. Sako: in press.

[6] T. Nakagome: Yakugaku Zasshi, 82, 244 (1962).

Table I.



Compounds (A)	Oxidizing agents	N-Oxides (%) 1-Oxide (B)	N-Oxides (%) 2-Oxide (C)	Other products (%)	Recovery (%)
(III) R=R′=Cl	a)	(IV) 12	(V) 5	MeO-Cl-pyridazine 0.7	45
(VIII) R=R′=H	b)	(IX) 11	(X) 8	4(1*H*)-Pyridazinone 2	54
(XIII) R=Cl, R′=OMe	a)	(XVI) 50	—	—	—

a) Monoperphthalic acid. *b*) H_2O_2-AcOH at 70°

catalytic hydrogenation in an alkaline medium, the structure of (XVI) was shown to be 1-oxide of 6-chloro-3,4-dimethoxypyridazine.

Table I summarized the above-mentioned experimental results. The N-oxidation reactions of (III) and (VIII) do not give so preferentially 1-oxide to 2-oxide in both cases as expected, while in the case of (XIII), the oxidizing agent seems to attack almost selectively to 1-nitrogen as observed in the N-oxidation of 3-methoxy-6-chloropyridazine.[5,6] Thus, it may be concluded that the methoxyl group in 4-position of the pyridazine ring exhibits only a weak polar effect to the ring nitrogen.

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Preparation of 3β-Acetoxy-14β,15β-epoxy-5β-card-20(22)enolide

It has been reported that resibufogenin possessed a stimulating effect of respiratory center.[1] In order to compare the pharmacological action of the corresponding cardenolide derivative with that of resibufogenin, partial synthesis of the 14β,15β-epoxide of cardenolide was made using "β"-anhydrodigitoxigenin acetate as the starting material.

"β"-Anhydrodigitoxigenin acetate (I) was oxidized with monoperphthalic acid to give 3β-acetoxy-14α,15α-epoxy-5β-card-20(22)-enolide (II), m.p. 199~206°, $[\alpha]_D^{21}$ +12.0° ($CHCl_3$), UV: λ_{max}^{EtOH} 216 mμ (log ε 4.20). Hydrolytic cleavage of (II) with perchloric acid afforded a *trans*-glycol, 15α-hydroxydigitoxigenin 3-acetate (IV), m.p. 247~250°, $[\alpha]_D^{26}$ +35.6° ($CHCl_3$). Treatment of (IV) with mesyl chloride in pyridine and purification of the resulting product by chromatography on alumina gave a sulfur-free compound (V), $C_{25}H_{34}O_5$, m.p. 180~181°, $[\alpha]_D^{24}$ +34.4° ($CHCl_3$). Since (V) showed no hydroxyl band in its infrared spectrum and gave a negative reaction with hydroxylamine, this compound (V) was assumed to be 14β,15β-epoxide isomeric with (II).

The structures of the compounds (II), (IV) and (V) were proved by the following experiments: (a) The configuration of the 14,15-epoxy group of (II) was α, since (II) was converted into the known methyl 3β-acetoxy-14α,15α-epoxy-5β-etianate[2] (III) by oxidation

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[1] M. Okada: Nippon Yakurigaku Zasshi, **57**, 160 § (1961).

[2] A. Lardon, H.P. Sigg, T. Reichstein: Helv. Chim. Acta, **42**, 1457 (1959).