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The C–Alkylaminomethylation of Pyridazinol N–Oxides. III.[1] The Mannich Reaction of 5–Pyridazinol 1–Oxide[2]

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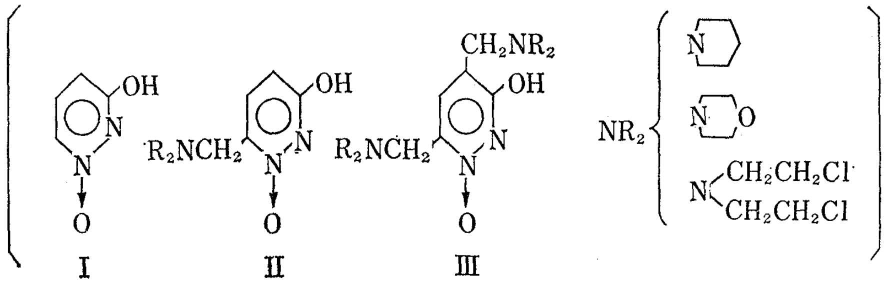
5–Pyridazinol 1–oxide was synthesized from 5–methoxypyridazine 1–oxide which was obtained from 3,4–dichloro–5–methoxypyridazine 1–oxide.

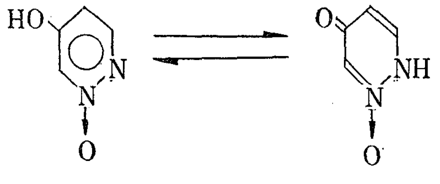
The Mannich reaction of 5–pyridazinol 1–oxide using 37% formalin and piperidine gave 6–piperidinomethyl–5–pyridazinol 1–oxide in 40% yield. Treatment of 5–pyridazinol 1–oxide with excess amounts of the reagents gave 4,6–di(piperidinomethyl)–5–pyridazinol 1–oxide in 56% yield. The alkylaminomethylated positions in these Mannich bases were determined by NMR spectroscopy.

In the preceding paper, it has been reported that the reaction of 3–pyridazinol 1–oxide (I) with an equimolar mixture of 37% formalin and a secondary amine gives 6–alkylaminomethyl–3–pyridazinol 1–oxide (II), and treatment of I with excess amounts of the reagents gives a 4,6–disubstituted derivative (III).


I II III

These results indicate that, in I, the hydroxyl group adjacent to the ring nitrogen of the 2–position is practically phenolic.

5–Pyridazinol 1–oxide (IV), in which a hydroxyl group is present at the *para* position of the 2–nitrogen, can tautomerize to the alternative lactam form as 5(2*H*)–pyridazinone 1–oxide (IV′) by prototropy.


IV IV′

Since the N–oxide function in IV decreases basicity of the 2–nitrogen, contribution of the lactam form (IV′) in such prototropic tautomerizm will be little and the enol form (IV) should be predominant. This consideration suggests that the hydroxyl group attached to a diazine nucleus as an aromatic sextet is phenolic as well as in the case of I. It was, therefore, of interest to study some electrophillic substitution reactions on IV.

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[1] Part II: *Chem. Pharm. Bull.* (Tokyo), **15**, 1733 (1967).

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As an extension of this series, this paper deals with the synthesis of IV and its Mannich reaction which involves the replacement of an active hydrogen with an alkylaminomethyl group.

5–Pyridazinol 1–oxide (IV) may prepare from 5–methoxypyridazine 1–oxide (VIII) by hydrolysis, but somehow it has been not reported yet.

An N–oxidation reaction of 4–methoxypyridazine using a 30% hydrogen peroxide solution in acetic acid, was reported to give VIII in 8% yield, together with 4–methoxypyridazine 1–oxide and 1–methyl–4(1*H*)–pyridazinone.[4] We reexamined this N–oxidation reaction at first by using a 60% or an 80% hydrogen peroxide solution, but the desired compound was obtained in only 10—13% yield.

A new synthetic route to prepare VIII from easily obtainable 3,4,5–trichloropyridazine (V) was, therefore, attempted.

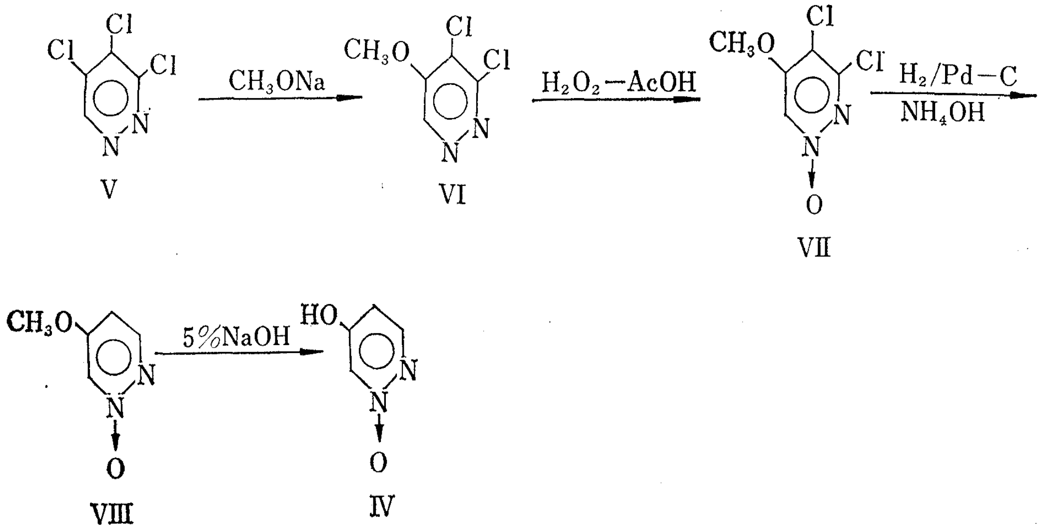

Chart 1

When V reacted with an equimolar amount of sodium methoxide in methanol, 3,4–dichloro–5–methoxypyridazine[5] (VI) was obtained in 65% yield. Treatment of VI with a 60% hydrogen peroxide solution and acetic acid in the presence of acetic anhydride which served to eliminate the water, afforded an N–oxide in 35% yield. Then, its catalytic dehalogenation in the presence of ammonia was tried, and 5–methoxypyridazine 1–oxide (VIII) was obtained in 85% yield. The formation of VIII also proved that the N–oxide arising from VI was 3,4–dichloro–5–methoxypyridazine 1–oxide (VII). Hydrolysis of VIII with a 5% sodium hydroxide solution followed by acidification gave 5–pyridazinol 1–oxide (IV) in 72% yield.

Since the NH and OH regions at 2000—3300 cm^{-1} in the infrared spectrum of IV is complicated, it is difficult to obtain some informations on such prototropic tautomerism. Then, the pK_a value of IV was measured to be 4.0 that was closely similar to 4.1 for 3–pyridazinol 1–oxide and 3.8 for formic acid.[6] Such remarkable acidity of IV could not be expected from the lactam form. Also, it gives a positive ferric chloride test which is charac-

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[4] T. Itai and S. Natsume, *Chem. Pharm. Bull.* (Tokyo), **10**, 643 (1962).

[5] T. Itai and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **11**, 1059 (1963).

[6] A more precise investigation on the prototropic tautomerisms in 3– and 5–pyridazinol 1–oxides by means of deuteration will be reported separately. The pK_a values of various pyridazine oxo–derivatives were measured by Mr. A. Nakamura of this institute, and the detail will be reported separately, along with their color reactions with a ferric chloride solution.

teristic of phenols. As shown in Fig. 1, the predominance of the enol form in the structure of IV is further supported by its ultraviolet spectrum, of which absorption curve resembles those of VIII and 3-pyridinol 1-oxide (IX), but differs from that of 2-methyl-5(2*H*)-pyridazinone 1-oxide (X).

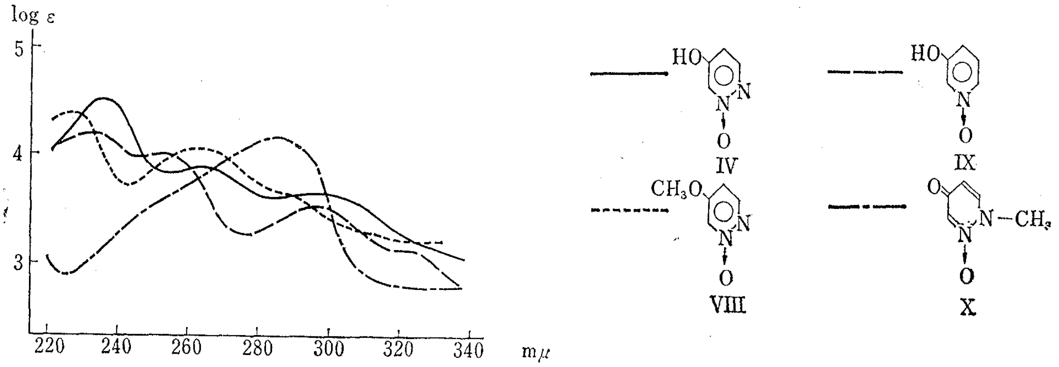

Fig. 1. The Ultraviolet Spectra of 5-Pyridazinol 1-Oxide and Related Compounds in Water

When IV, suspended in ethanol, was allowed to react with an equimolar mixture of 37% formalin and piperidine at room temperature, a mono-Mannich base, mp 176—177° decomp., was isolated as very hygroscopic crystals and its yield was 56%. Further treatment of this mono-Mannich base with an equimolar mixture of these reagents gave a di-Mannich base, mp 191—192° decomp., in 42% yield. In the former reaction, poor formation of the di-Mannich base was also identified by thin-layer chromatography. Similarly, the Mannich reaction of IV using dimethylamine gave the corresponding mono-Mannich base as a salt with IV in 36% yield, but the di-Mannich base could not be isolated purely because of its poor yield.

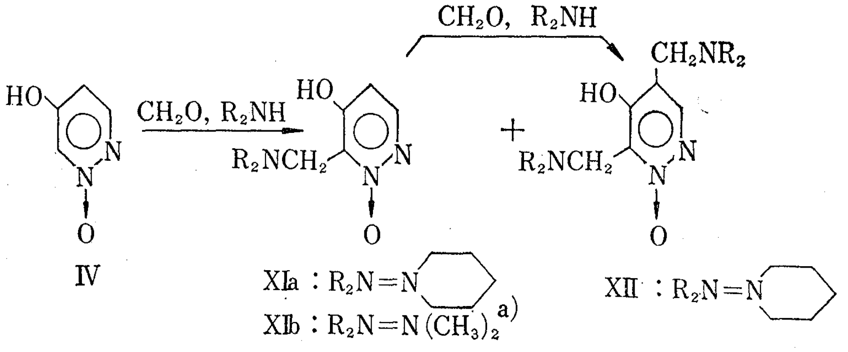

Chart 2

a) Produced as a salt with IV

Our previous results on the Mannich reaction of I mentioned at the first part of this paper, suggest that an alkylaminomethyl group was introduced into the 6-position which is the *ortho* position from the N-oxide function and also from the phenolic hydroxyl group, and that the second alkylaminomethyl group was introduced into the 4-position adjacent to the hydroxyl group.

Finally, the C-alkylaminomethylated positions were correctly confirmed by means of NMR spectroscopy as Fig. 2.

The NMR studies[1,7] of various pyridazine 1-oxides have shown that the signals of these ring protons generally appear in the order of $4>5>6>3$ (τ_4: 2.8—3.3, τ_5: 1.9—2.3, τ_6: 1.7—2.1,

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[7] K. Tori, M. Ogata, and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 235 (1963).

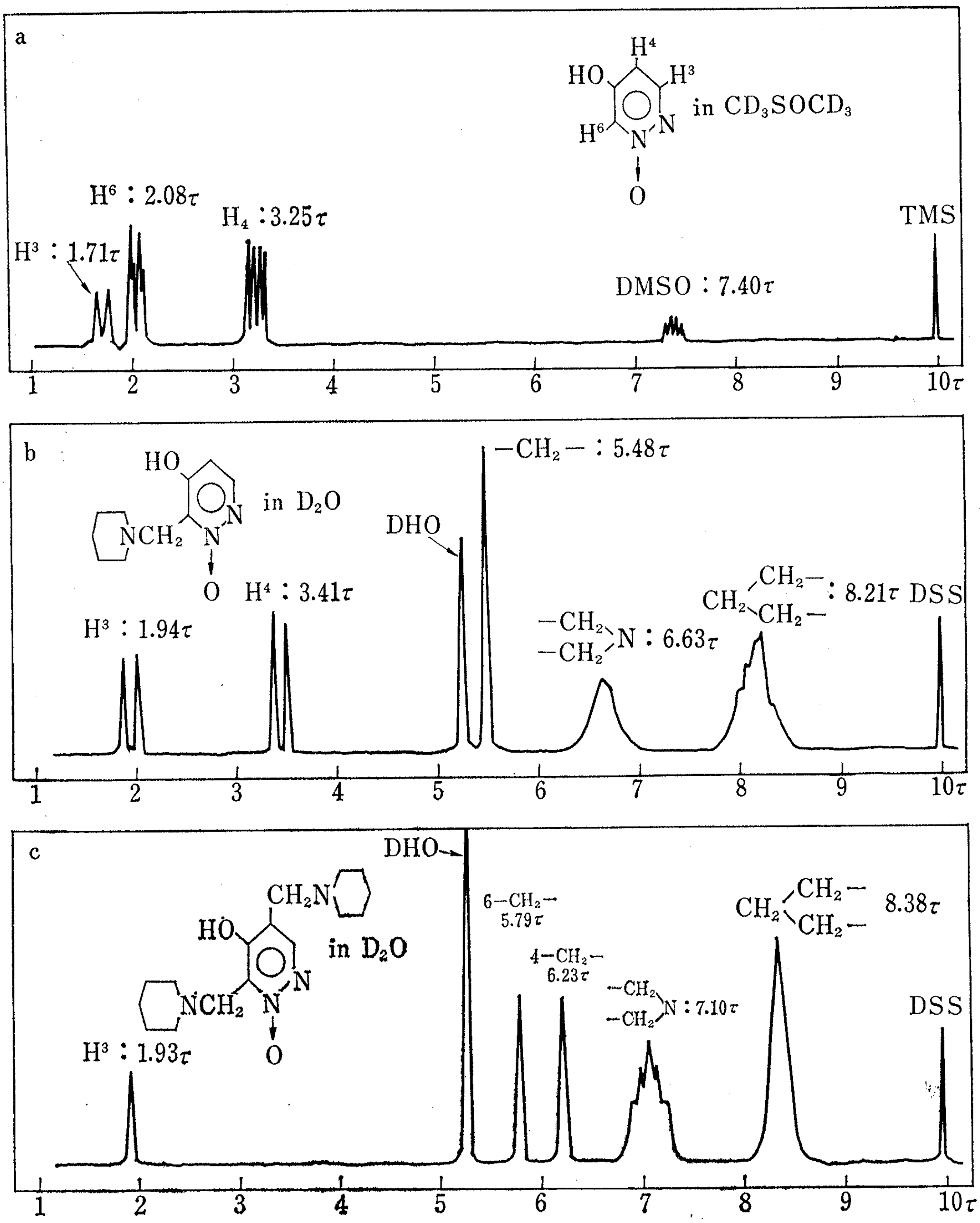

Fig. 2. The NMR Spectra of 5-Pyridazinol 1-Oxide and Its Mannich Bases

τ_3: 0.7—1.9) in deuterium oxide. In the NMR spectrum of IV as shown in Fig. 2a, the doublet (each broad signal) at 1.71τ ($J_{3,4}$=7 cps) was assigned as H³-proton, the quartet at 2.08τ ($J_{6,4}$=2 cps, $J_{6,3}$=0.1 cps) as H⁶-proton and the quartet at 3.25τ ($J_{4,3}$=7 cps, $J_{4,6}$=2 cps) as H⁴-proton. In that of the mono-Mannich base (Fig. 2b), the signal corresponding to H⁶-proton is not observable and, in Fig. 1c for the di-Mannich base, only an aromatic proton due to H³-proton appears at 1.93τ as a singlet.

Consequently, it is concluded that the mono-Mannich bases are 6-piperidinomethyl-5-pyridazinol 1-oxide (XIa) and 6-dimethylaminomethyl-5-pyridazinol 1-oxide (XIb), and the di-Mannich base is 4,6-di(piperidinomethyl)-5-pyridazinol 1-oxide (XII).

The Mannich reaction of 5-methoxypyridazine 1-oxide (VIII) was tried under the same reaction condition in order to know whether the hydroxy group or the N-oxide function was more responsible for achieving the present reaction, but the starting material was recovered unchanged. This fact indicates that strong electron–donating character of the phenolic hydroxy group in the 5–position together with influence of the N–oxide function, makes the 6–position most and secondarily the 4–position negative. Therefore, the Mannich reaction that is known as a mild electrophillic attack, takes place firstly at the 6–position and, with excess amounts of the reagents, at the 6– and 4–positions to give a 4,6–disubstituted derivative.

The compounds prepared in the present work have been submitted to biological tests, the results of which willl be reported separately.

Experimental[8]

3,4-Dichloro-5-methoxypyridazine 1-Oxide (VII)——To a solution of 4.30 g (0.025 mole) of 3,4–dichloro–5–methoxypyridazine[5] in a mixture of 160 ml of acetic acid and 7.7 ml of acetic anhydride was added 2.3 ml (*ca.* 0.038 mole) of a 60% hydrogen peroxide solution, the mixture was heated at 55° for 2 hr, and continuously at 70—80° for 9 hr. A mixture of 5.0 ml of acetic acid, 3.8 ml of acetic anhydride and 1.5 ml of a 60% hydrogen peroxide solution was added to the reaction mixture, and the mixture was heated again at 70—80° for 5 hr. After cooling, 5.0 g of manganese dioxide was added in order to decompose the unchanged hydrogen peroxide, the reaction mixture was filtered, and the filtrate was concentrated to about $^1/_4$ volume under reduced pressure. To the solution was added a small amount of water and the mixture was neutralized with sodium carbonate. The alkaline solution was extracted with chloroform several times, the chloroform layer was dried over anhyd. sodium sulfate. The chloroform was evaporated to dryness and the residue was recrystallized from methanol to give colorless plates, mp 155—157°. Yield, 1.64 g (35%). *Anal.* Calcd. for $C_5H_4O_2N_2Cl_2$: C, 30.79; H, 2.07; N, 14.37. Found: C, 30.88; H, 2.38; N, 14.51.

5-Methoxypyridazine 1-Oxide (VIII) from 3,4-Dichloro-5-methoxypyridazine 1-Oxide (VII)——A solution of 5.85 g (0.03 mole) of VII and 6 ml of conc. ammonia in 180 ml of methanol was submitted to a dehalogenation over a catalyst prepared from 17 ml of a 1% palladium chloride solution and 1.0 g of charcoal. After two molar equivalent of hydrogen was absorbed, the catalyst was removed by filtration. The filtrate was concentrated, and the separated crystals were collected. Recrystallization from benzene gave colorless prisms, mp 112—114°. This product was identical with authentic 5–methoxypyridazine 1–oxide[4] by usual criteria. Yield, 3.20 g (85%).

5-Pyridazinol 1-Oxide (IV)——A solution of 4.80 g (0.038 mole) of 5–methoxypyridazine 1–oxide in 30 ml of a 5% sodium hydroxide solution was heated on a water bath for 1.5 hr. The reaction mixture was acidified with 10% hydrochloric acid, the separated crystals were collected, and recrystallized from ethanol to give colorless needles, mp 273° decomp. Yield, 3.10 g (72%). *Anal.* Calcd. for $C_4H_4O_2N_2$: C, 42.86; H, 3.60; N, 24.99. Found: C, 43.08; H, 3.71; N, 24.82.

6-Piperidinomethyl-5-pyridazinol 1-Oxide (XIa)——To a suspended solution of 0.56 g (0.005 mole) of 5–pyridazinol 1–oxide (IV) in 10 ml of ethanol was added 0.50 g (0.006 mole) of piperidine and 0.6 ml of 37% formalin (*ca.* 0.006 mole), and the mixture was allowed to stand overnight at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was recrystallized from a mixture of ethanol and iso–propylether twice. Colorless, very hygroscopic, fine crystals, mp 175—176° decomp. Yield, 0.41 g (40%). *Anal.* Calcd. for $C_{10}H_{15}O_2N_3$: C, 57.40; H, 7.23; N, 20.08. Found: C, 56.61; H, 7.60; N, 21.08.

4,6-Di(piperidinomethyl)-5-pyridazinol 1-Oxide (XII)——1) From 5–pyridazinol 1–oxide (IV): To a suspended solution of 0.56 g (0.005 mole) of IV in 10 ml of ethanol was added 2.00 g(0.024 mole) of piperidine and 2.5 ml (*ca.* 0.025 mole) of 37% formalin, and the mixture was allowed to stand at room temperature for two days. The reaction mixture was evaporated to dryness, the residue was washed with ether and recrystallized from a mixture of ethanol and iso–propylether. The separated crystals were collected, and repeated recrystallization gave colorless fine crystals, mp 192—193° decomp. Yield, 0.85 g (56%). *Anal.* Calcd. for $C_{16}H_{26}O_2N_4$: C, 62.72; H, 8.55; N, 18.29. Found: C, 63.19; H, 8.84; N, 18.35.

2) From 6–piperidinomethyl–5–pyridazinol 1–oxide (XIa): To a solution of 0.26g (0.0012 mole) of XIa in 5 ml of ethanol was added 0.22 g (0.0026 mole) of piperidine and 0.4 ml (*ca.* 0.0026 mole) of 37% formalin, and the mixture was allowed to stand overnight. The reaction mixture was treated as described in 1), and 0.16 g (42%) of XII was obtained.

Similarly, the reaction of IV with dimethylamine and 37% formalin gave 6–dimethylaminomethyl–5–pyridazinol 1–oxide (XIb) as a salt with IV in 36% yield. Colorless granules, mp 181—183° decomp. Yield, 0.51 g (36%). *Anal.* Calcd. for $C_7H_{11}O_2N_3 \cdot C_4H_4O_2N_2$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.95; H, 5.41; N, 24.99. This salt was converted to the corresponding hydrochloride. Colorless granules, mp

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[8] All melting points are uncorrected. Infrared and ultraviolet spectra were measured on a JASCO Model–IR and on a Hitachi Model EPS–2 spectrophotometer. NMR spectra were determined on a Varian A–60 spectrophotometer.

203—204° decomp. *Anal.* Calcd. for $C_7H_{11}O_2N_3 \cdot HCl$: C, 40.88; H, 5.88; N, 20.43. Found: C, 40.80; H, 5.85; N, 20.12.

The same reaction of IV using excess amounts of dimethylamine and 37% formalin gave 0.62 g (44%) of XIb, but the di-Mannich base could not be isolated.

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