C, 68.11; H, 4.84; N, 6.11. Found: C, 68.06; H, 5.21; N, 5.73. IR ν_{max}^{KBr} cm^{-1}: 3400, 2960—2880, 2680—2560, 1660, 1595. NMR (CF_3COOH) ppm: 2.50 (3H, s), 6.80 (1H, s), 7.40—8.10 (5H, m).

Acknowledgement A part of expenses for this work was defrayed by the Grant-in-Aid for Scientific Research from the Ministry of Education, which is gratefully acknowledged.

[Chem. Pharm. Bull. 23(8)1879—1881(1975)]

UDC 547.861.057 : 615.277.3.011.5

Syntheses of 1-Alkoxy-3,6-dimethyl-5-nitro-4(1H)-pyridazinones and Related Compounds[1]

Shozo Kamiya and Masayuki Tanno

National Institute of Hygienic Sciences[2]

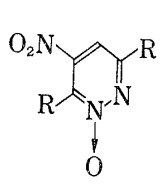
(Received December 4, 1974)

1-Alkoxy-3,6-dimethyl-5-nitro-4(1H)-pyridazinones (VIIa, b) were synthesized by the nitration of 3,6-dimethyl-4-hydroxypyridazine 1-oxide (IV), followed by alkylation with alkyl halides. The catalytic hydrogenation of the nitro compound VIIa gave 1-methoxy-3,6-dimethyl-5-amino-4(1H)-pyridazinone (IX).

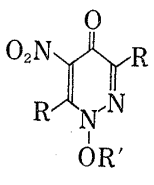
1-Methoxy-3,6-dimethyl-5-bromo-4(1H)-pyridazinone (XI) was similarly synthesized by the bromination of IV, followed by alkylation.

5-Nitropyridazine 1-oxides (A) have mutagenic and prophage-inducing activities for bacteria.[3]

This paper describes the syntheses of 1-alkoxy-5-nitro-4(1H)-pyridazinones (B), in which the aromaticity is considerably reduced as compared with that of A, and related compounds.



A



B

The starting material, 3,6-dimethyl-4-hydroxypyridazine 1-oxide (IV) was first synthesized by Sako[4] from 3,6-dimethyl-4-chloropyridazine. In this experiment we synthesized compound IV from 3,6-dimethyl-4-nitropyridazine 1-oxide (I) according to the synthetic route shown in Chart 1.

The predominance of the hydroxy form in the prototropic tautomers of compound IV is supported by its ultraviolet (UV) spectrum (Fig. 1). Namely, the absorption curve of IV

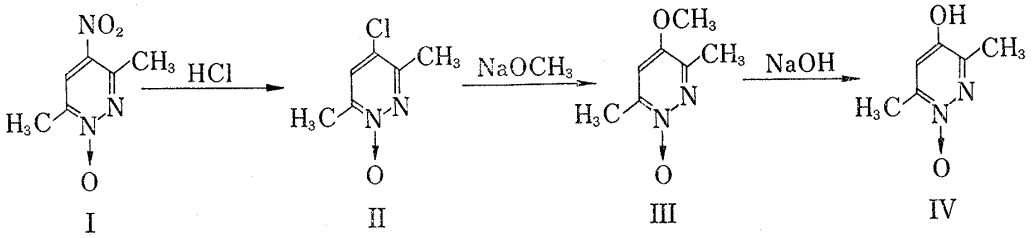


Chart 1

1) S. Kamiya and M. Tanno, *Chem. Pharm. Bull.* (Tokyo), **23**, 923 (1975).
2) Location: *Kamiyoga, 1-18-1, Setagaya, Tokyo.*
3) S. Kamiya, T. Nakashima, S. Sueyoshi, M. Tanno, I. Suzuki, K. Yanagimachi, K. Yoshikawa, and H. Kurata, the 94th Annual Meeting of the Pharmaceutical Society of Japan, Abstracts No. III, p. 104.
4) S. Sako, *Chem. Pharm. Bull.* (Tokyo), **11**, 337 (1963).

is not close to that of 1-methoxy-3,6-dimethyl-4 (1H)-pyridazinone (V), but to that of 3,6-dimethyl -4-methoxypyridazine 1-oxide (III). In addition, IV showed a purple color on the color reaction with a ferric chloride solution.

The nitration of IV with a mixture of conc. nitric acid and conc. sulfuric acid gave 3,6-dimethyl -4-hydroxy-5-nitropyridazine 1-oxide (VI) in 67% yield. The treatment of VI with methyl iodide in the presence of silver oxide, produced 1-methoxy-3,6-dimethyl-5-nitro-4(1H)-pyridazinone (VIIa) in 89% yield, and the corresponding 1-benzyloxy derivative VIIb was similarly synthesized. Their infrared (IR) spectra in nujol showed the presence of a carbonyl group both at 1620 cm^{-1}.

The catalytic hydrogenation of VI with palladium charcoal gave 3,6-dimethyl-4-hydroxy-5-aminopyridazine 1-oxide (VIII) in 94% yield, and the same hydrogenation of VIIa did 1-methoxy-3,6-dimethyl-5-amino-4(1H)-pyridazinone (IX) (Chart 3).

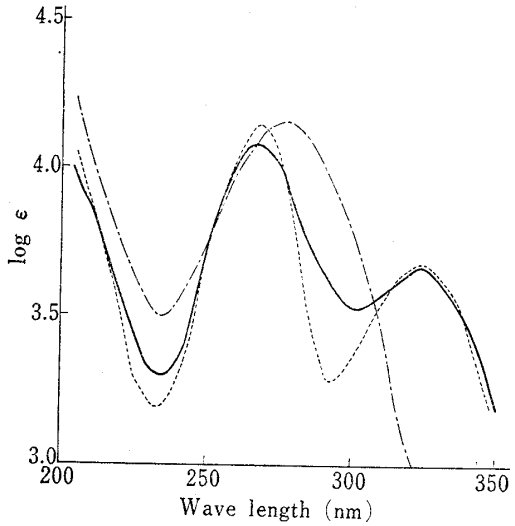
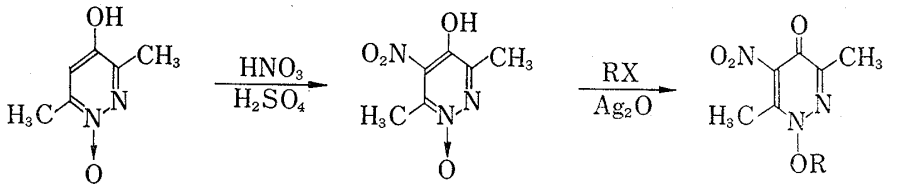


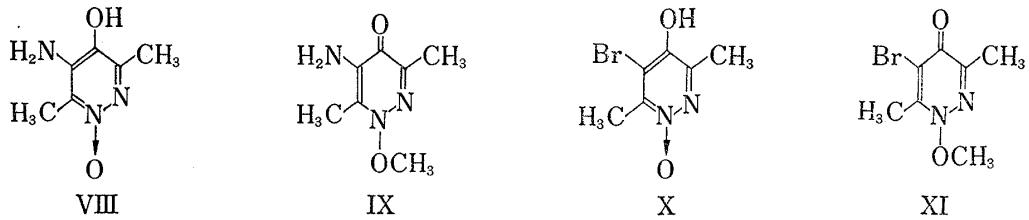
Fig. 1. Ultraviolet Absorption Spectra in Ethanol

——— : 3,6-dimethyl-4-hydroxypyridazine 1-oxide (IV)
····· : 3,6-dimethyl-4-methoxypyridazine 1-oxide (III)
·—·—· : 1-methoxy-3,6-dimethyl-4(1H)-pyridazinone (V)



IV VI VIIa : R=CH_3 VIIb : R=$C_6H_5CH_2$

Chart 2



VIII IX X XI

Chart 3

The bromination of IV with bromine afforded 3,6-dimethyl-4-hydroxy-5-bromopyridazine 1-oxide (X), in 76% yield, which was converted to 1-methoxy-3,6-dimethyl-5-bromo-4(1H)-pyridazinone (XI) by treating with methyl iodide in the presence of silver oxide. This compound also could be synthesized by the bromination of 1-methoxy-3,6-dimethyl-4(1H)-pyridazinone (V) with bromine, in 56% yield.

The mutagenicity of VIIa and VIIb for bacteria and the autitumor activity for experimental tumors are under investigation, and the results will be reported in a separate paper.

Experimental[5]

3,6-Dimethyl-4-hydroxypyridazine 1-Oxide (IV)——This compound was prepared according to the literature.[4,6]

3,6-Dimethyl-4-nitropyridazine 1-oxide (I): Pale yellow needles (from a mixture of benzene and ligroin), mp 117—118° (lit.,[6] 117—118°). Yield, 54%.

3,6-Dimethyl-4-chloropyridazine 1-oxide (II): This compound was synthesized by the treatment of I with conc. hydrochloric acid. Colorless scales (from diisopropyl ether), mp 132—133° (lit.,[4] 132—133°). Yield, 41%.

3,6-Dimethyl-4-methoxypyridazine 1-oxide (III): Colorless leaflets (from diisopropyl ether), mp 149° (lit.,[4] 148—149°). Yield, 85%.

3,6-Dimethyl-4-hydroxypyridazine 1-oxide (IV): Colorless needles (from ethanol), mp 255° (decomp.) (lit.,[4] 255° (decomp.)). Yield, 65%.

3,6-Dimethyl-4-hydroxy-5-nitropyridazine 1-Oxide (VI)——To a cooled solution of 2.24 g (0.016 mole) of IV in 1.6 ml of conc. sulfuric acid, was added dropwise 0.8 ml of fuming nitric acid (d: 1.50), and the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water, the crystals separated were filtered, washed with ice-water, and dried in a desciccator. Recrystallization from acetone gave yellow dices, mp 184—185° (decomp.). Yield, 1.98 g (67%). UV ν_{max}^{EtOH} nm (log ε): 265 (4.12). *Anal.* Calcd. for $C_6H_7O_4N_3$: C, 38.92; H, 3.81; N, 22.70. Found: C, 39.26; H, 3.67; N, 22.29.

1-Alkoxy-3,6-dimethyl-5-nitro-4(1H)-pyridazinone (VIIa, b)——1-Methoxy-3,6-dimethyl-5-nitro-4(1H)-pyridazinone (VIIa): A mixture of 3.00 g (0.016 mole) of VI, 50 ml of methanol, 4.2 g (0.024 mole) of methyl iodide and the silver oxide prepared from 4.2 g of silver nitrate, was heated in a sealed tube at 90°, with occasional shaking for 4 hr. The silver iodide produced was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from diisopropyl ether to give yellow needles, mp 78—79°. UV ν_{max}^{EtOH} nm (log ε): 272 (4.11). Yield, 2.90 g (89%). *Anal.* Calcd. for $C_7H_9O_4N_3$: C, 42.21; H, 4.55; N, 21.10. Found: C, 42.14; H, 4.40; N, 20.73.

1-Benzyloxy-3,6-dimethyl-5-nitro-4(1H)-pyridazinone (VIIb): Yellow plates (from diisopropyl ether), mp 125—126°. UV ν_{max}^{EtOH} nm (log ε): 275 (4.18). Yield, 45%. *Anal.* Calcd. for $C_{13}H_{13}O_4N_3$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.63; H, 4.67; N, 14.84.

3,6-Dimethyl-4-hydroxy-5-aminopyridazine 1-Oxide (VIII)——A mixture of 0.93 g (0.005 mole) of VI, 50 ml of methanol and the palladium charcoal prepared from 8.4 ml of a 1% palladium chloride solution and 0.2 g of charcoal, was shaken in a hydrogen stream. After rapid absorption of the theoretical amount of hydrogen, the catalyst was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol to give colorless granules, mp 203—204°. Yield, 0.76 g (97%). *Anal.* Calcd. for $C_6H_9O_2N_3$: C, 46.44; H, 5.85; N, 27.08. Found: C, 46.52; H, 5.87; N, 27.51.

1-Methoxy-3,6-dimethyl-5-amino-4(1H)-pyridazinone Hydrochloride (IX)——A mixture of 0.96 g (0.005 mole) of VIIa, 50 ml of methanol and the palladium charcoal prepared from 8.4 ml of a 1% palladium chloride solution and 0.2 g of charcoal, was shaken in a hydrogen stream. After absorption of the theoretical amount of hydrogen, the catalyst was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 10 ml of a mixture of ethanol and conc. hydrochloric acid (1: 1), and the solution was evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol to give colorless plates, mp 149—150°. Yield, 0.93 g (94%). *Anal.* Calcd. for $C_7H_{11}O_2N_3 \cdot HCl$: C, 40.87; H, 5.83; N, 20.43. Found: C, 40.86; H, 5.81; N, 20.48.

3,6-Dimethyl-4-hydroxy-5-bromopyridazine 1-Oxide (X)——To an aqueous solution of 0.42 g (0.003 mole) of IV, was added 0.60 g of bromine with vigorous stirring, and the stirring was continued for 3 hr at 40°. The precipitates separated were collected, and recrystallized from methanol to give colorless needles, mp 192—194° (decomp.). Yield, 0.50 g (76%). UV ν_{max}^{EtOH} nm (log ε): 275 (4.45), 325 (sh, 3.40). *Anal.* Calcd. for $C_6H_7O_2N_2Br$: C, 32.87; H, 3.19; N, 12.78. Found: C, 33.11; H, 3.28; N, 12.94.

1-Methoxy-3,6-dimethyl-5-bromo-4(1H)-pyridazinone (XI)——1) From 3,6-dimethyl-4-hydroxy-5-bromopyridazine 1-oxide (X): A mixture of 0.31 g (0.0014 mole) of X, 50 ml of methanol, 0.34 g (0.0020 mole) of methyl iodide, and the silver oxide prepared from 0.34 g of silver nitrate, was heated in a sealed tube in a boiling water bath for 4 hr with occasional shaking. The silver iodide produced was filtered off, the filtrate was evaporated to dryness under reduced pressure, and the residue was extracted with chloroform. The chloroform was evaporated, and the residue was recrystallized from ethanol to give colorless needles, mp 125—126°. Yield, 0.19 g (56%). *Anal.* Calcd. for $C_7H_9O_2N_2Br \cdot 1/2H_2O$: C, 34.72; H, 4.13; N, 11.57. Found: C, 35.02; H, 3.99; N, 11.50.

2) From 1-methoxy-3,6-dimethyl-4(1H)-pyridazinone (V): To an aqueous solution of 0.49 g (0.0032 mole) of V,[6] 0.6 g of bromine was added with stirring, and the stirring was continued for 1 hr at 40°. The crystals separated were collected, and recrystallized from ethanol to give 70 mg (9%) of XI.

5) All melting points are uncorrected. IR and UV spectra were measured on a JASCO IR-S infrared spectrophotometer and on a Hitachi EPS-2 ultraviolet spectrophotometer.

6) T. Itai and S. Sako, *Chem. Pharm. Bull.* (Tokyo), **9**, 149 (1961).