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The Mannich Reaction of 3,6-Dimethyl-5-hydroxypyridazine 1-Oxide[1]

Shozo Kamiya and Masayuki Tanno[2]

National Institute of Hygienic Sciences[2]

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3,6-Dimethyl-5-hydroxypyridazine 1-oxide (IV) reacted with formalin and a secondary amine such as pyrrolidine, piperidine, morpholine or 2,2′-dihydroxydiethylamine to give the corresponding 3,6-dimethyl-4-alkylaminomethyl-5-hydroxypyridazine 1-oxides (VIa—d).

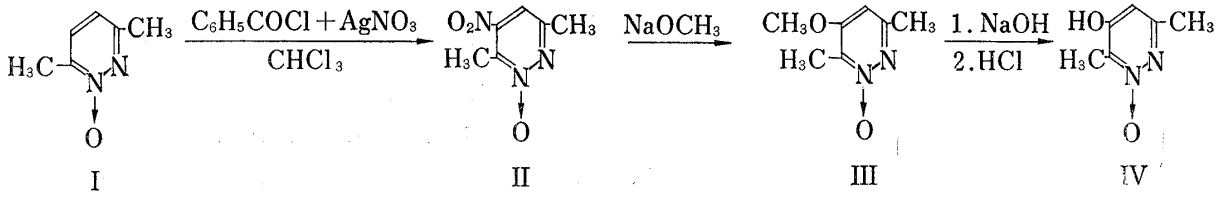
Bromination of this compound with bromine gave 3,6-dimethyl-4-bromo-5-hydroxypyridazine 1-oxide.

In the previous paper[3] it was reported that the Mannich reaction of 5-hydroxypyridazine 1-oxide gave 6-alkylaminomethyl-5-hydroxypyridazine 1-oxide, and that, when treated with excess reagents, it gave a 4,6-bis-Mannich base.

This paper describes the Mannich reaction of 3,6-dimethyl-5-hydroxypyridazine 1-oxide (IV), which must be a potential phenol though the hydroxyl group presents at the *para* position of the 2-nitrogen.

Sako[4] first synthesized compound IV after the three steps including separation of the 1- and 2-oxide produced by the N-oxidation of 3,6-dimethyl-4-chloropyridazine. In this experiment we prepared IV after the three steps from 3,6-dimethylpyridazine 1-oxide (I), as shown in Chart 1.

The nitration of I with benzoyl nitrate gave 3,6-dimethyl-5-nitropyridazine 1-oxide (II)[5] in 30% yield, and the reaction of II with sodium methoxide produced the corresponding 5-methoxy derivative (III). Then, the treatment of III with a 5% sodium hydroxide solution followed by acidification with hydrochloric acid, gave IV in 63% yield.



I II III IV

Chart 1

As shown in Fig. 1, the predominance of the enol form in the prototropic tautomers of compound IV is supported by its ultraviolet (UV) spectrum, of which absorption curve resembles closely those of 3,6-dimethyl-5-methoxypyridazine 1-oxide (III) and a phenol, 3-pyridinol 1-oxide (V).

When IV was treated with an equimolar mixture of 37% formalin and such a secondary amine as pyrrolidine, piperidine, morpholine or 2,2′-dihydroxydiethylamine, 3,6-dimethyl-4-alkylaminomethyl-5-hydroxypyridazine 1-oxides were produced as a salt with IV in 50—70% yields. These salts were immediately converted to the hydrochlorides VIa—d by treatment

1) S. Kamiya and G. Okusa, *Chem. Pharm. Bull.* (Tokyo), **21**, 1510 (1973).
2) Location: *Kamiyoga, 1-18-1, Setagaya, Tokyo.*
3) G. Okusa and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **16**, 142 (1968).
4) S. Sako, *Chem. Pharm. Bull.* (Tokyo), **11**, 337 (1973); *idem, Yakugaku Zasshi*, **82**, 1208 (1962).
5) T. Itai and S. Natsume, *Chem. Pharm. Bull.* (Tokyo), **12**, 228 (1964).

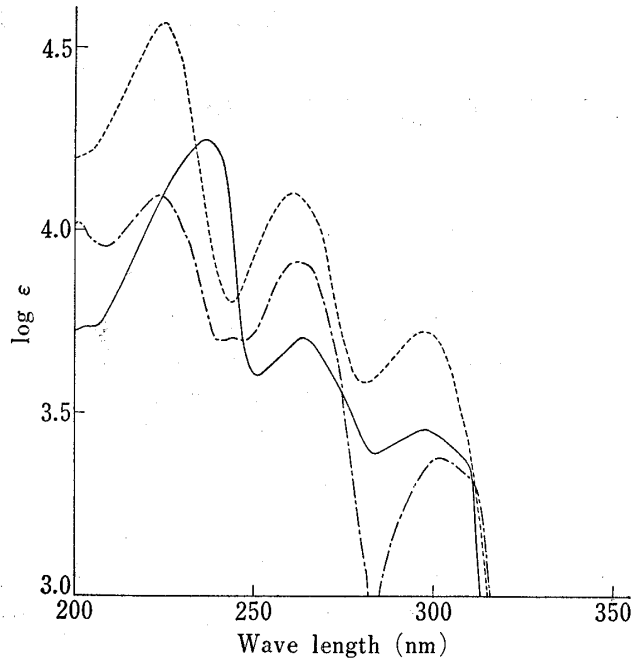


Fig. 1. Ultraviolet Absorption Spectra in Ethanol
———: 3,6-dimethyl-5-hydroxypyridazine 1-oxide (IV)
---------: 3,6-dimethyl-5-methoxypyridazine 1-oxide (III)
—·—·—: 3-pyridinol 1-oxide (V)

with hydrochloric acid. The nuclear magnetic resonance (NMR) spectra of these Mannich base hydrochlorides showed a 2H singlet due to the methylene and did not show any aromatic protons.

The carbon moiety of these Mannich bases suggests a possibility for the synthesis of a pyridazine analogue of pyridoxine.

Compound IV yielded, 3,6-dimethyl-4-bromo-5-hydroxypyridazine 1-oxide (VII) on the reaction with bromine, in 96% yield. On the other hand the nitration of IV with a mixture of nitric acid and sulfuric acid at 100° strangely recovered the starting material, and, when the temperature was raised to 130—140°, it afforded unknown, brownish granules, mp 237—240°, which did not show the presence of a nitro group in its infrared (IR) spectrum.

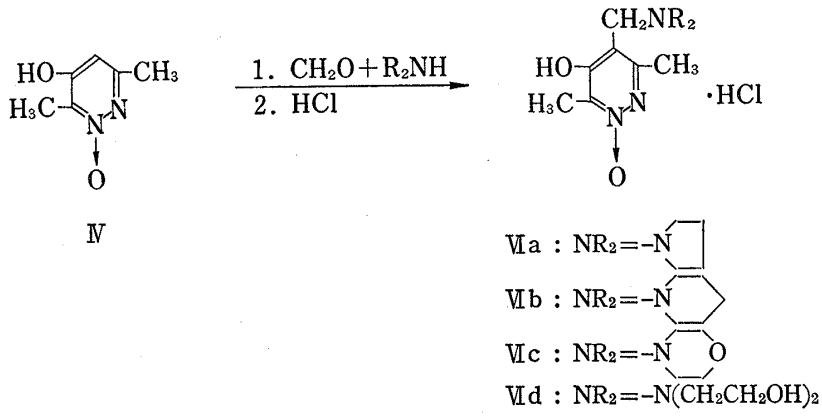


Chart 2

Experimental[6]

3,6-Dimethyl-5-hydroxypyridazine 1-Oxide (IV)——1) 3,6-Dimethyl-5-nitropyridazine 1-Oxide (II): This compound was prepared according to the literature.[5] Yellow needles (from diisopropyl ether), mp 81—83°. Yield, 30%.

2) 3,6-Dimethyl-5-methoxypyridazine 1-Oxide (III): This compound was prepared according to the literature.[5] Yellow, long needles (from a mixture of benzene and diisopropyl ether), mp 136—137°. Yield, 75%.

3) 3,6-Dimethyl-5-hydroxypyridazine 1-Oxide (IV): A mixture of 0.77 g (0.005 mole) of III and 6 ml of a 5% sodium hydroxide solution was heated on a water bath for 50 min, and the reaction mixture was acidified with conc. hydrochloric acid. The crystals separated were collected, washed with cold water,

6) All melting points are uncorrected. IR and UV spectra were measured on a JASCO Model IR-S infrared spectrophotometer and on a Hitachi Model EPS-2 ultraviolet spectrophotometer. NMR spectra were determined on a JEOL JNM-C60H spectrometer, and tetramethylsilane for $CDCl_3$ or sodium 3-(trimethylsilyl)propanesulfonate for D_2O was used as an internal standard.

and recrystallized from ethanol to give pale brownish leaflets, mp 257—258° (decomp.) (lit.[4], mp 260° (decomp.)). Yield, 0.44 g (61%). NMR in DMSO-d_6 (τ): 7.82, 7.72 (s, CH_3), 3.52 (s, H^4).

The Mannich Reaction of 3,6-Dimethyl-5-hydroxypyridazine 1-Oxide (IV)——3,6-Dimethyl-4-pyrrolidinomethyl-5-hydroxypyridazine 1-Oxide (VIa): A solution of 0.3 ml of 37% formalin and 0.142 g (0.002 mole) of pyrrolidine in 2 ml of ethanol, was added to a suspended solution of 0.28 g (0.002 mole) of IV in 10 ml of ethanol, the mixture was warmed on a water bath until a clear solution was obtained, and the solution was allowed to stand for two days at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was treated with a mixture of conc. hydrochloric acid and ethanol (1: 1). The acidic solution was evaporated to dryness under reduced pressure, and the residue was recrystallized from a mixture of ethanol and diisopropyl ether to give colorless granules, mp 185—186° (decomp.). Yield, 0.32 g (71%). IR in nujol (cm^{-1}): 2860 (NH^+). NMR in DMSO-d_6 (τ): 7.72, 7.51 (s, CH_3), 5.69 (s, CH_2). *Anal.* Calcd. for $C_{11}H_{17}O_2N_3 \cdot HCl$: C, 50.86; H, 6.98; N, 16.11. Found: C, 51.06; H, 6.92; N, 16.23.

Other Mannich bases VIb—d were similarly prepared as noted for VIa.

3,6-Dimethyl-4-piperidinomethyl-5-hydroxypyridazine 1-Oxide Hydrochloride (VIb): Colorless granules (from a mixture of ethanol and diisopropyl ether), mp 187—188° (decomr.). Yield, 53%. IR in nujol (cm^{-1}): 2860 (NH^+). NMR in DMSO-d_6 (τ): 7.71, 7.50 (s, CH_3), 5.74 (s, CH_2). *Anal.* Calcd. for $C_{12}H_{19}O_2N_3 \cdot HCl$: C, 52.64; H, 7.36; N, 15.34. Found: C, 52.25; H, 7.73; N, 15.28.

3,6-Dimethyl-4-morpholinomethyl-5-hydroxypyridazine 1-Oxide Hydrochloride (VIc): Colorless granules (from a mixture of methanol and ethanol), mp 208—209° (decomp.). Yield, 58%. NMR in DMSO-d_6 (τ): 7.63, 7.45 (s, CH_3), 5.67 (s, CH_2). *Anal.* Calcd. for $C_{11}H_{17}O_3N_3 \cdot HCl$: C, 47.92; H, 6.56; N, 15.24. Found: C, 48.01; H, 6.66; N, 15.20.

3,6-Dimethyl-4-bis(2-hydroxyethyl)aminomethyl-5-hydroxypyridazine 1-Oxide Hydrochloride (VId): Pale brownish dices (from ethanol), mp 172—173° (decomp.). Yield, 67%. NMR in D_2O (τ): 7.50, 7.55 (s, CH_3), 5.59 (s, CH_2). *Anal.* Calcd. for $C_{11}H_{17}O_4N_3 \cdot HCl$: C, 44.97; H, 6.86; N, 14.30. Found: C, 45.14; H, 6.92; N, 14.59.

3,6-Dimethyl-4-bromo-5-hydroxypyridazine 1-Oxide (VII)——Three drops of bromine were added to a suspended solution of 0.14 g (0.001 mole) of IV in 20 ml of ethanol with vigorous shaking. After 30 min, the reaction mixture was evaporated to dryness under reduced pressure, and the residue was recrystallized from ethanol to give straw yellow prisms, mp 200—201° (decomp.). Yield, 0.21 g (96%). *Anal.* Calcd. for $C_6H_7O_2N_2Br$: C, 32.89; H, 3.22; N, 12.79. Found: C, 32.95; H, 3.17; N, 12.91.

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Steroid Saponins of *Heloniopsis orientalis* (Thunb.) C. Tanaka

Toshihiro Nohara, Yoshitake Ogata, Misuzu Aritome, Kazumoto Miyahara, and Toshio Kawasaki

Faculty of Pharmaceutical Sciences, Kyushu University[1]

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The steroid glycosides in the fresh whole plants of *Heloniopsis orientalis* (Thunb.) C. Tanaka were examined and the following four steroid saponins were isolated and identified: pennogenin 3-O-rhamnosyl-chacotrioside (II); methyl proto-dioscin; 26-O-β-D-glucopyranosyl-25D-furost-5-ene-3β,17α,22,26-tetraol 3-O-rhamnosyl-chacotrioside (III) (the proto-type compound of II); 26-O-β-D-glucopyranosyl-17(20)-dehydrokryptogenin 3-O-rhamnosyl-chacotrioside (VI) (an artefact produced from III).

III is the second furostanol 3,26-O-bisglycoside corresponding to a coexisting pennogenin 3-O-glycoside and could be regarded as a "nolonin".

Okanishi and his collaborators[2] have reported isolation of pennogenin (I) and kryptogenin along with diosgenin, gentrogenin and heloniogenin from the whole plants of *Heloniopsis*

1) Location: *3-1-1, Maedashi, Higashi-ku, Fukuoka, 812, Japan.*

2) K. Takeda, T. Okanishi, and A. Shimaoka, *Yakugaku Zasshi*, **73**, 84 (1953); T. Okanishi, A. Akahori, and F. Yasuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 1195 (1962); *idem.*, *Ann. Rept. Shionogi Res. Lab.*, **10**, 137 (1960); **14**, 202 (1964).