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221. Genzo Okusa, Mizue Osada,*1 and Shozo Kamiya*2 : The C-Alkylaminomethylation of 3-Pyridazinol 1-Oxide Derivatives. II.*3 The C-Alkylaminomethylation of 6-Substituted 3-Pyridazinol 1-Oxides.

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The Mannich reaction of 6-chloro- and 6-methyl-3-pyridazinol 1-oxide using morpholine or piperidine gave 6-chloro- and 6-methyl-4-alkylaminomethyl-3-pyridazinol 1-oxide. Treatment of 3-pyridazinol 1-oxide with excess amounts of the reagents gave 4,6-di(morpholinomethyl)-3-pyridazinol 1-oxide in 71% yield. These Mannich bases were catalytically hydrogenated to give the corresponding 4-alkylaminomethyl-3(2*H*)-pyridazinones almost quantitatively.

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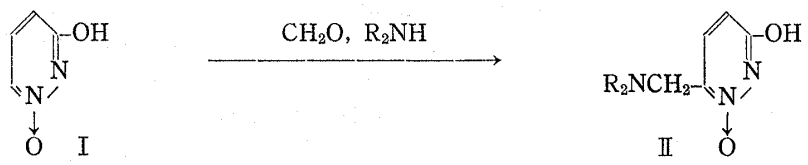
The condensation reaction of a compound containing an active hydrogen atom with formaldehyde and a primary or secondary amine which results replacement of the hydrogen by an alkylaminomethyl group is known as the Mannich reaction. Although much has been reported on mechanism of the Mannich reaction,[1] it is generally said that the initial step is a reaction of formaldehyde with an amine. In the case of phenols, the resulting $R_2NCH_2^+$ or methylenebisamine usually attacks the ortho position of the phenolic hydroxy group.

Since the hydroxy group of 3-pyridazinol 1-oxide (I) is practically phenolic due to the polar effect of the N-oxide group, an electrophyllic substitution such as the Mannich reaction will take place at the 4- or 6-position as in usual phenols.

In the preceding paper, it has been reported that reaction of I with an equimolar mixture of 37% formalin and a secondary amine gave 6-alkylaminomethyl-3-pyridazinol 1-oxide (II) in about 50% yields, but 4-alkylaminomethyl-3-pyridazinol 1-oxide did not be isolated in spite of much effort.



Thus, an attempt was made to investigate a possibility of introducing an alkylaminomethyl group into the 4-position in the cases of 6-substituted 3-pyridazinol 1-oxides (III : R=Cl and R=CH_3).

When 6-chloro-3-pyridazinol 1-oxide (IIIa), suspended in ethanol, was allowed to react with an equimolar mixture of 37% formalin and a secondary amine such as morpholine or piperidine at room temperature, the corresponding Mannich bases were obtained in 54 and 32% yields, respectively. Analogously, the Mannich reaction of 6-methyl-3-pyridazinol 1-oxide (IIIb) using morpholine or piperidine gave the corresponding Mannich bases in 40 and 43% yields.

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*3 Part I : This Bulletin, **15**, 1172 (1967).
1) E. R. Alexander, E. J. Underhill : J. Am. Chem. Soc., **71**, 4014 (1949); S. V. Lieberman, E. C. Wagner : J. Org. Chem., **14**, 1001 (1949); J. H. Burckhalter, J. N. Well, W. J. Meyer : Tetrahedron Letters, **1964**, 1353.

Some of these Mannich bases were produced as a salt of IIIa or IIIb, from which the hydrochlorides were prepared by treatment with hydrochloric acid, along with a quantitative recovery of IIIa or IIIb.

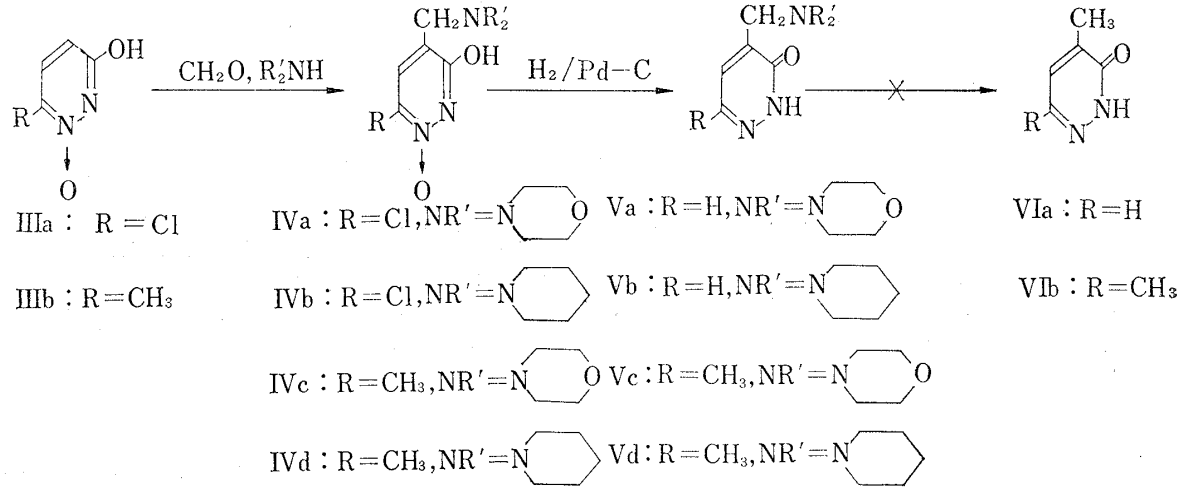


Chart 1.

The analytical data for the products fit the corresponding mono-Mannich bases. In order to elucidate their structures, the Mannich bases derived from IIIa were submitted to hydrogenation over a 10% palladium-on-charcoal catalyst at room temperature, as reported in our previous paper.[2] Consequently, the hydrogenated products were proved to be C-morpholino- or C-piperidino-methyl-3(2*H*)-pyridazinone from their analytical data and infrared spectra showing the presence of a lactam carbonyl at 1650 cm^{-1} and a lactam-NH at 3130 cm^{-1}. These morpholino- and piperidino-methyl-3(2*H*)-pyridazinone were not identical with 6-morpholino- and 6-piperidino-methyl-3(2*H*)-pyridazinone, respectively, of which structures were already established by an independent synthesis.*[3] The Mannich bases derived from IIIb were similarly hydrogenated to give C-morpholino- or C-piperidino-methyl-6-methyl-3(2*H*)-pyridazinone almost quantitatively.

In view of these data, it was considered that this Mannich reaction took place at the 4-position adjacent to the phenolic hydroxy group to give 4-morpholino- or 4-piperidino-methyl-6-chloro-3-pyridazinol 1-oxide (IVa, IVb) and 4-morpholino- or 4-piperidino-methyl-6-methyl-3-pyridazinol 1-oxide (IVc, IVd), as shown in Chart 1.

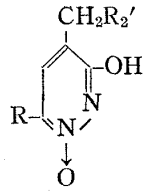
Although no synthetic proof has been made, the assumption was substantiated by comparison of nuclear magnetic resonance (NMR) spectra of these Mannich bases in deuterium oxide with those of various 3-pyridazinol 1-oxides.

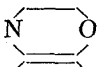
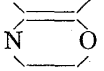
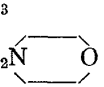
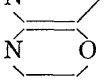
Tori, *et al.*[3] have reported that NMR spectra of various pyridazine 1-oxides show an order, $H_3<H_6<H_5<H_4$ (τ_4 : 2.77~3.34, τ_5 : 2.10~2.48, τ_6 : 1.78~1.90) as the magnitude of shielding of the ring protons, and that except the 6-position, this order is in agreement with a LCAOMO calculation[4] of the local π-electron densities in the pyridazine 1-oxide molecule. Actually, a singlet is observable at 2.18τ in NMR spectrum of IVa and at 1.97τ in that of IVd, and the data are reasonable as the H_5-proton, as shown in Table III.

Further catalytic hydrogenation of Va and Vb to obtain 4-methyl-3(2*H*)-pyridazinones (VIa, VIb) was tried under a variety of reaction conditions, but in both cases, the starting material was always recovered quantitatively.

2) S. Kamiya, A. Nakamura, T. Itai, K. Koshinuma, G. Okusa : Yakugaku Zasshi, **86**, 1099 (1966).
3) K. Tori, M. Ogata, H. Kano : This Bulletin, **11**, 235 (1963).
4) T. Kubota, H. Watanabe : Bull. Chem. Soc. Japan, **36**, 1093 (1963).

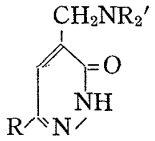
TABLE I. 6-Substituted 4-Alkylaminomethyl-3-pyridazinol 1-Oxides



No.	R	NR_2'	m.p. (decomp.) (°C)	Recryst. solv.	Appearance	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Ⅳa	Cl		204～206	EtOH–H_2O	granules	54	$C_9H_{12}O_3N_3Cl$	44.00	4.92	17.11	43.98	5.21	17.29
Ⅳb[a]	Cl		240～241	EtOH	leaflets	32	$C_{10}H_{14}O_2N_3Cl \cdot HCl$	42.87	5.37	25.31	42.76	5.34	25.53
Ⅳc[b]	CH_3		183～186	EtOH–H_2O	needles	40	$C_{10}H_{15}O_3N_3 \cdot C_5H_6O_2N_2$	51.27	6.02	19.93	51.12	6.09	20.35
Ⅳd[b]	CH_3		162～164	EtOH–Et_2O	granules	43	$C_{11}H_{17}O_2N_3 \cdot C_5H_6O_2N_2$	55.00	6.64	20.05	54.61	6.64	19.71
Ⅷ			187～189	EtOH–iso-Pr_2O	leaflets	60	$C_{14}H_{22}O_4N_4$	54.18	7.15	18.05	53.65	7.38	18.34

a) Hydrochloride. *b*) A salt of the starting material.

TABLE Ⅱ. 6-Substituted 4-Alkylaminomethyl-3(2*H*)-pyridazinones



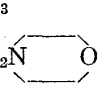
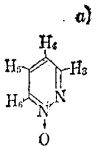
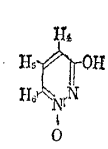
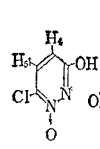
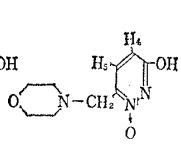
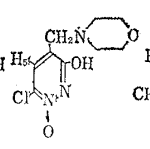
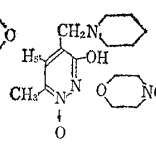
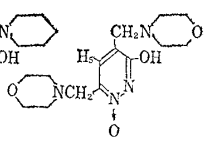
No.	R	NR_2'	m.p. (°C)	Recryst. solv.	Appearance	Yield (%)	IR KBr (cm^{-1}) NH	CO	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Ⅴa	H		167～168	AcOEt	leaflets	97	3130	1650	$C_9H_{13}O_2N_3$	55.37	6.71	21.53	55.58	6.48	21.56
Ⅴb	H		134～136	AcOEt	leaflets	95	3150	1650	$C_{10}H_{15}ON_3$	62.15	7.82	21.79	62.38	7.89	21.30
Ⅴc	CH_3		176～178	AcOEt	plates	80	3150	1650	$C_{10}H_{15}O_2N_3$	57.40	7.23	20.08	57.50	7.43	20.36
Ⅴd	CH_3		161～162	AcOEt	plates	84	3150	1650	$C_{11}H_{17}ON_3$	63.74	8.27	20.27	63.82	8.14	20.58
Ⅸ			165～167	AcOEt	leaflets	95	3130	1685	$C_{14}H_{22}O_3N_4$	57.12	7.53	19.04	57.96	7.84	19.25

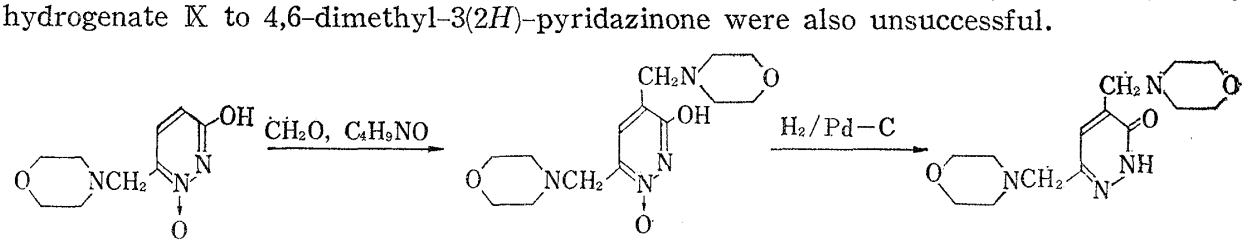
Table III. The NMR Parameters (τ) for Various 3-Pyridazinol 1-Oxides in Deuterium Oxide

	a)							
		I	IIIa	VII	IVa	IVd	VIII	
H_3	1.46	—	—	—	—	—	—	
H_4	2.78	2.92 (doub.)	3.12 (doub.)	3.34 (doub.)	—	—	—	
H_5	2.17	2.16 (qual.)	1.90 (doub.)	2.35 (doub.)	2.18 (sing.)	1.97 (sing.)	2.27 (sing.)	
H_6	1.74	1.77 (doub.)	—	—	—	CH_3 : 7.54 (sing.)	—	
$-CH_2-$	—	—	—	5.66 (sing.)	5.69 (sing.)	5.63 (sing.)	5.90, 5.98 (sing.)	
$-CH_2-$ $-CH_2>N-$	—	—	—	6.53 (trip.)	6.55 (trip.)	6.48 (mult.)	6.08, 7.06 (trip.)	
$O<CH_2-$ CH_2-	—	—	—	5.96 (trip.)	5.93 (trip.)	—	6.02, 6.11 (trip.)	

a) Reported by K. Tori, *et al.*[8] (measured in deuterochloroform).

Similarly, the Mannich reaction of 6-morpholinomethyl-3-pyridazinol 1-oxide (VII) using morpholine gave 4,6-di(morpholinomethyl)-3-pyridazinol 1-oxide (VIII) in 60% yield. Its NMR spectrum shows a singlet at 2.27τ which is also attributable to the H_5-proton, as shown in Table III.

Treatment of I with excess amounts of 37% formalin and morpholine also afforded VIII in 71% yield. Subsequently, the VIII dihydrochloride was slowly hydrogenated over a 20% palladium-on-charcoal catalyst, and 4,6-di(morpholinomethyl)-3(2*H*)-pyridazinone (IX) dihydrochloride was obtained almost quantitatively. Several attempts to catalytically hydrogenate IX to 4,6-dimethyl-3(2*H*)-pyridazinone were also unsuccessful.



VII VIII IX

Chart 2.

These results obtained in the Mannich reaction of 3-pyridazinol 1-oxide (I) indicates that the phenolic hydroxy group at the 3-position, together with the influence of the N-oxide group, makes the carbon atom of the 6-position most negative, and that in the cases of 6-substituted 3-pyridazinol 1-oxides, the 4-position adjacent to the phenolic hydroxy group is the most negative center.

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

Experimental*4

4-Morpholinomethyl-6-chloro-3-pyridazinol 1-Oxide (IVa)——To a suspended solution of 0.44 g. (0.003 mole) of 6-chloro-3-pyridazinol 1-oxide[5] in 3 ml. of ethanol was added dropwise a solution of 0.3 ml. of 37%

*4 All melting points are uncorrected. Infrared and ultraviolet spectra were measured on a JASCO Model-IR infrared spectrophotometer. NMR spectra were determined on a Varian A-60 spectrophotometer.

formalin and 0.26 g. (0.003 mole) of morpholine in 3 ml. of ethanol, and the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, the residue was treated with a small amount of ethanol, and the solution was let stand in a refrigerator. The separated crystals were filtered, and recrystallized from a mixture of ethanol and water. Colorless granules, m.p. 204~206° (decomp.).

Hydrochloride: Hygroscopic, colorless needles (from a mixture of ethanol and iso-propylether), m.p. 233° (decomp.). *Anal.* Calcd. for $C_9H_{12}O_3N_3Cl \cdot HCl \cdot H_2O$: C, 36.01; H, 5.03. Found: C, 36.46; H, 5.48.

4-Morpholinomethyl-6-methyl-3-pyridazinol 1-oxide (Ⅳc) was similarly synthesized from 6-methyl-3-pyridazinol 1-oxide.[6]

4-Piperidinomethyl-6-chloro-3-pyridazinol 1-Oxide (IVb)——To a suspended solution of 0.88 g. (0.006 mole) of 6-chloro-3-pyridazinol 1-oxide in 10 ml. of ethanol was added a solution of 1.02 g. (0.012 mole) of piperidine and 2.0 ml. of 37% formalin in 5 ml. of ethanol with shaking, and the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was treated with a mixture of acetone and iso-propylether (1:1). The separated crystals were collected, and recrystallized from acetone to give colorless needles, m.p. 120~121°. *Anal.* Calcd. for $C_{10}H_{14}O_2N_3Cl \cdot C_4H_3O_2N_2Cl \cdot H_2O$: C, 41.19; H, 4.20; N, 17.16. Found: C, 41.06; H, 4.36; N, 17.07. This salt was dissolved in a small amount of water, the solution was acidified with 10% hydrochloric acid, and the precipitated Ⅲa was filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue was recrystallized from ethanol to give the hydrochloride of Ⅳb. Yield, 0.27 g. (32%). A 10% ferric chloride color reaction: Blood red.

Similarly, 4-piperidinomethyl-6-methyl-3-pyridazinol 1-oxide (Ⅳd) was obtained from 6-methyl-3-pyridazinol 1-oxide as a salt, m.p. 162~164° (decomp.), and the hydrochloride was prepared by the method described above. Hygroscopic, colorless granules (from a mixture of ethanol and iso-propylether), m.p. 214~217° (decomp.). *Anal.* Calcd. for $C_{11}H_{17}O_2N_3 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 49.75; H, 7.13. Found: C, 49.77; H, 7.03.

Catalytic Hydrogenation of 4-Alkylaminomethyl-6-substituted 3-Pyridazinol 1-Oxides (IV)——A typical experiment for catalytic hydrogenation of these Mannich bases is described with 4-morpholinomethyl-6-chloro-3-pyridazinol 1-oxide (Ⅳa).

A solution of 0.28 g. (0.001 mole) of the Ⅳa hydrochloride in 70 ml. of methanol was submitted to hydrogenation over a catalyst, prepared from 1.9 ml. of 1% $PdCl_2$ solution and 0.1 g. of charcoal. After about 45 ml. of hydrogen was absorbed during 40 min., the catalyst was removed by filtration. The solvent was evaporated to dryness and the residue was recrystallized from 95% ethanol to give colorless granules, m.p. 216~220° (decomp.). 4-Morpholinomethyl-3(2*H*)-pyridazinone hydrochloride, 0.2 g. (97%).

The free base was obtained as follows. The hydrochloride was dissolved in a small amount of water, the solution was basified with sodium bicarbonate, and extracted with chloroform. After drying over anhyd. Na_2SO_4, the chloroform was evaporated on a water bath. The residue was recrystallized from ethyl acetate to give colorless leaflets, m.p. 167~168°.

4,6-Di(morpholinomethyl)-3-pyridazinol 1-Oxide (VIII) from 3-Pyridazinol 1-Oxide (I)——To a suspended solution of 0.56 g. (0.005 mole) of I in 5 ml. of ethanol was added a solution of 1.76 g. (0.02 mole) of morpholine and 2.0 ml. (0.02 mole) of 37% formalin in 3 ml. of ethanol. The reaction mixture was let stand overnight at room temperature, and evaporated to dryness under reduced pressure. The oily residue was dissolved in a small amount of ethanol, iso-propylether was added, and the mixture was let stand in a refrigerator. The separated plates were collected, and recrystallized from a mixture of ethanol and iso-propylether. Colorless leaflets, m.p. 187° (decomp.). Yield, 1.05 g. (71%).

Dihydrochloride: Very hygroscopic, colorless granules (from 95% ethanol), m.p. 205° (decomp.).

Catalytic Hydrogenation of 4,6-Di(morpholinomethyl)-3-pyridazinol 1-Oxide (VIII)——A solution of 0.27 g. of Ⅷ dihydrochloride in 40 ml. of methanol was submitted to hydrogenation in the presence of 0.12 g. of 20% palladium-on-charcoal. Absorption of about 30 ml. of hydrogen was completed during 5 hr., and the catatyst was removed by filtration. The solvent was evaporated, and the residue was recrystallized from 95% ethanol. Colorless granules, m.p. 232~235° (decomp.). 4,6-Di(morpholinomethyl)-3(2*H*)-pyridazinone dihydrochloride, 0.25 g. (95%). *Anal.* Calcd. for $C_{14}H_{22}O_3N_4 \cdot 2HCl \cdot H_2O$: C, 43.63; H, 6.80. Found: C, 43.93; H, 6.94.

The dihydrochloride was converted to the free base by the method described above.

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5) T. Itai, S. Sako: This Bulletin, **10**, 933 (1962).
6) T. Nakagome: Yakugaku Zasshi, **82**, 249 (1962).