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146. Genzo Okusa,*1 Shozo Kamiya, and Takanobu Itai*2 : The C-Alkyl-aminomethylation of 3-Pyridazinol 1-Oxide Derivatives. I.

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The Mannich reaction of 3-pyridazinol 1-oxide using morpholine, piperidine, or dimethylamine gave the corresponding 6-alkylaminomethyl-3-pyridazinol 1-oxides which were also synthesized from 3-methoxy-6-chloromethylpyridazine.

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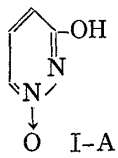
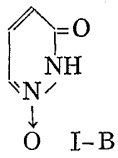
Recently, several carbon-carbon bond formation reactions in quinoline N-oxide derivatives have been reported.[1~5] For instance, Okamoto and Takayama obtained 2-acetonylquinoline by treatment of 1-methoxyquinoline iodide with acetone in alkaline solution. Hamana and Yamazaki[2] synthesized various 2-substituted quinolines by reaction of quinoline 1-oxide with active methylene compounds in the presence of acetic anhydride. Hamana and Noda also obtained 2-(2-quinolyl)cyclohexanone[3] by treatment of quinoline 1-oxide in acylating agent with cyclohexanone enamine. As one of such type nucleophilic substitutions, Richter and Rustad[5] reported the reaction of 4-nitroquinoline 1-oxide with diethyl sodiomalonate to give diethyl 4-nitro-3-quinolylmalonate 1-oxide.

The chemistry of pyridazine N-oxides[6] has been extensively studied in recent few years. However, the introduction of cyano group into 6-position via N-alkoxy or Reissert compounds is only an example concerning carbon-carbon bond formation reaction in this area.[7]

Condensation reaction of a compound containing one or more active hydrogen atoms with formaldehyde and a primary or secondary amine which results in replacement of the hydrogen by an aminomethyl group is known as the Mannich reaction. Although much has been reported on mechanism of the Mannich reaction,[8] it is generally said that the initial step is reaction of formaldehyde with an amine. In the case of phenols, the resulting methylenebisamine or $R_2N\text{-}CH_2^+$ usually attacks ortho position of the hydroxy group.



I-A



I-B

Igeta[9] has investigated on the tautomerism of 3-pyridazinol-1-oxide (I), and concluded that it exists as an enol form (I-A). However, contribution of the amido form (I-B) should be also considered.

Consequently, the hydroxyl group of I-A may be a potential phenol, then an electrophilic substitution (C-alkylaminomethylation) by the Mannich reaction will take

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1) T. Okamoto, H. Takayama : This Bulletin, **11**, 514 (1963).
2) H. Hamana, M. Yamazaki : *Ibid.*, **11**, 415 (1963).
3) H. Hamana, H. Noda : *Ibid.*, **13**, 912 (1965).
4) H. Hamana, O. Hoshino : Yakugaku Zasshi, **84**, 35 (1964).
5) H. J. Richter, N. E. Rustad : J. Org. Chem., **29**, 3381 (1964).
6) T. Itai : Eisei Shikenjo Hokoku, **82**, 1 (1964).
7) M. Ogata : This Bulletin, **11**, 1522 (1963); H. Igeta : *Ibid.*, **11**, 1472 (1963).
8) E. R. Alexander, E. J. Underhill : J. Am. Chem. Soc., **71**, 4014 (1949); J. H. Burckhalter, J. N. Well, W. J. Mayer : Tetrahedron Letters, 1353 (1964).
9) H. Igeta : This Bulletin, **7**, 938 (1959).

place at 4-position adjacent to the hydroxyl group as in usual phenols. On the other hand, in the case that the electron density of 6-position which is also γ-position of the hydroxyl group is higher than that of 4-position by the presence of N-oxide group, the reaction may take place at 6-position.

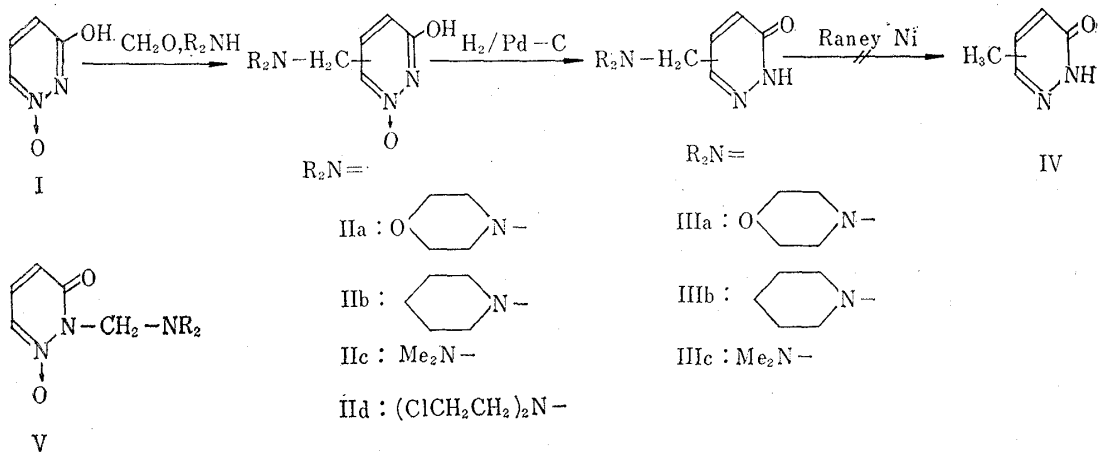


Chart 1.

When 3-pyridazinol 1-oxide (I), suspended in ethanol, was treated with formalin and a secondary amine such as morpholine, piperidine or dimethylamine at room temperature, the corresponding Mannich bases were obtained in about 50% yields. These Mannich bases were salts with I except the one arising from morpholine, and the salts gave hydrochlorides of the Mannich bases on treatment with hydrochloric acid, recovering I quantitatively. Structures of these Mannich bases were considered to be either of C-Mannich bases (IIa, IIb, IIc) or N-Mannich bases (V) depending on the tautomerism of I.

Catalytic hydrogenation of these Mannich bases was carried out to determine alkylaminomethylated position. If they are N-Mannich bases (V), they should back I with tertiary amines on catalytic hydrogenation as reported our preceding paper.[10] However, in the case of C-Mannich bases (II), they yield methyl-3(2*H*)-pyridazinone (IV) or considerably resist to hydrogenation.

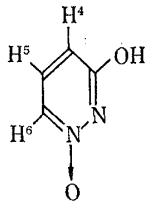
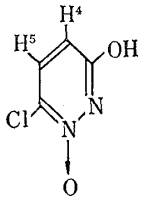
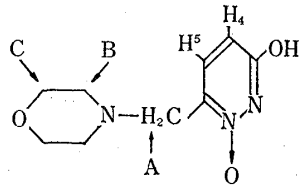
These Mannich bases were hydrogenated over a 10% palladium-on-charcoal catalyst at room temperature, and the products were proved to be alkylaminomethyl-3(2*H*)-pyridazinones (IIIa, IIIb, IIIc,) from their analytical data and infrared spectra showing the presence of amido-type carbonyl at 1660~1665$^{cm^{-1}}$. Further catalytic hydrogenation of IIIa, IIIb and IIIc over Raney Ni catalyst to obtain IV was fruitless recovering the starting material. From these results, they should be neither the N- nor O-, but the C-Mannich bases.

Then, C-alkylaminomethylated position was confirmed to be 6-position from their nuclear magnetic resonance (NMR) spectra as shown in Table I.

NMR studies[11] of various 3-substituted pyridazine 1-oxide derivatives have shown that the signals of these ring protons generally appear in the order of $3<6<5<4$ (τ_4 : 2.77~3.33, : τ_5 : 2.10~2.48, τ_6 : 1.78~1.90, τ_3 : 0.70~1.67) in deuterochloroform. NMR spectra of I, IIa and 6-chloro-3-pyridazinol 1-oxide[12] (VI) in deuterium oxide were assigned as shown in Table I. In that of IIa, the doublet at 3.34τ was assigned as H_4-proton, and the doublet at 2.35τ as the H_5-proton. If the reaction took place at

10) S. Kamiya, *et al.*: Yakugaku Zasshi, **86**, 1099 (1966).
11) K. Tori, M. Ogata, H. Kano: This Bulletin, **11**, 235 (1963).
12) T. Itai, S. Sako: *Ibid.*, **10**, 933 (1962).

Table I. Nuclear Magnetic Resonance Spectral Parameters for 3-Pyridazinol 1-Oxide Derivatives in Deuterium Oxide

		τ_4	τ_5	τ_6	τ_A	τ_B	τ_C
I		2.92 doub.	2.16 qual.	1.77 doub.	——	——	——
VI		3.12 doub.	1.90 doub.	——	——	——	——
IIa		3.34 doub.	2.35 doub.	——	5.66 sing.	6.53 trip.	5.96 trip.

5-position, the protons of 4- and 6-position should result in the formation of two singlets, respectively. In addition the value of spin-spin coupling constant in IIa ($J_{4,5}$: 9.0) was reasonable for ortho coupling of the ring protons comparing with those of various 3-substituted pyridazine 1-oxides ($J_{4,5}$: 8.2~8.8).

These results indicates that an alkylaminomethyl group was unusually introduced into 6-position of I by the Mannich reaction.

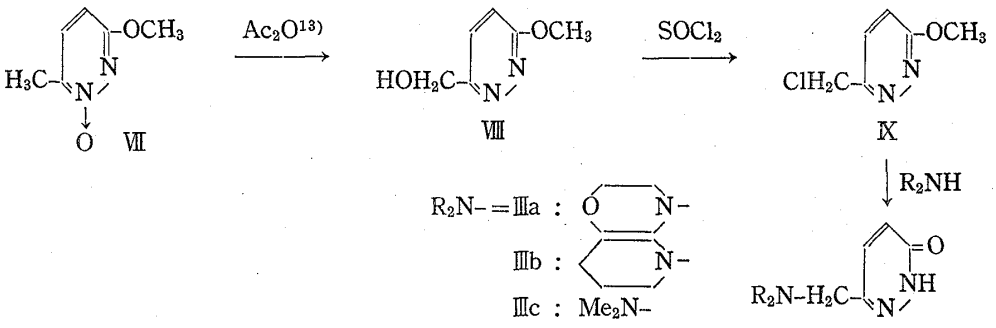


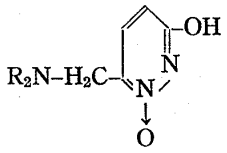
Chart 2.

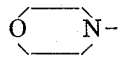
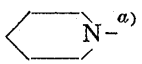
In order to definitely establish the structure as 6-morpholinometyl-3-pyridazinol 1-oxide (IIa), 6-morpholinomethyl-3(2*H*)pyridazinone (IIIa) was independently synthesized from 3-methoxy-6-methylpyridazine 1-oxide (VII) as shown in Chart 2.

3-Methoxy-6-hydroxymethylpyridazine[13] (VIII) derived from VII was treated with thionyl chloride to give 3-methoxy-6-chloromethylpyridazine (IX). Then, without further purification IX was heated with an excess amount of morpholine, and the produced 6-morpholinomethyl-3(2*H*)-pyridazinone (IIIa), m.p. 178~180° (decomp.), was

13) T. Nakagome : Yakugaku Zasshi, **82**, 249 (1962).

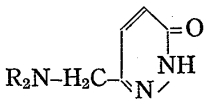
Table Ⅱ. 6-Alkylaminomethyl-3-pyridazinol 1-Oxide Derivatives

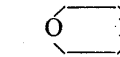
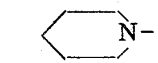


No.	R_2N-	m.p. (℃)	Recryst. solv.	Appearance	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Ⅱa		185～186	EtOH–H_2O	granules	49	$C_9H_{13}O_3N_3$	51.17	6.20	19.90	51.03	6.38	19.49
Ⅱb	 [a]	222～223 (decomp.)	EtOH	leaflets	50	$C_{10}H_{15}O_2N_3 \cdot HCl$	48.83	6.56	17.10	49.18	6.80	17.03
Ⅱc	Me_2N- [a]	229～230	EtOH	leaflets	53	$C_7H_{11}O_2N_3 \cdot HCl$	40.88	5.88	20.43	40.82	5.84	21.41
Ⅱd	$(ClCH_2CH_2)_2N$- [a]	179～181 (decomp.)	EtOH	powder	29	$C_9H_{13}O_2N_3Cl_2 \cdot HCl$	35.72	4.65	13.89	35.94	4.55	14.35

a) as a hydrochloride.

Table Ⅲ. 6-Alkylaminomethyl-3(2*H*)-pyridazinone Derivatives



No.	R_2N-	m.p. (℃)	Recryst. solv.	Appearance	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Ⅲa		181～182	benzene	leaflets	95	$C_9H_{13}O_2N_3$	55.37	6.71	21.53	56.02	6.89	21.42
Ⅲb		147～148	(iso-Pr)$_2$O	leaflets	96	$C_{10}H_{15}ON_3$	62.15	7.82	21.79	62.70	7.99	22.18
Ⅲc	Me_2N-	104～105	(iso-Pr)$_2$O	leaflets	94	$C_7H_{11}ON_3$	54.88	7.24	27.43	54.56	7.24	27.58

entirely identical with the product obtained from the Mannich base (IIa) by mixed melting point determination and also by infrared spectrum. 6-Piperidinomethyl-3(2*H*)-pyridazinone (IIIb) and 6-dimethylaminomethyl-3(2*H*)-pyridazinone (IIIc) were analogously synthesized from IX.

An alkylating agent, 6-[bis(2-chloroethyl)amino]methyl-3-pyridazinol 1-oxide (IId) was similarly prepared in 29% yield by reaction of I with formalin and bis(2-chloroethyl)amine.

Reaction of I with formalin only did not give the expected C-hydroxymethyl compound recovering the starting material.

Then, the Mannich reaction of 3-methoxypyridazine 1-oxide was carried out in order to know whether 4- or 6-position was sufficiently activated by the N-oxide and methoxy group, which was thought a milder electron-donation group than hydroxyl group. However, the starting material was recovered almost quantitatively.

An attempt to isolate the 4-alkylaminomethyl compounds from the reaction mixtures was failed. However, di(morpholinomethyl)-3-pyridazinol 1-oxide was obtained on treatment of I with excess of formalin and morpholine. The detail will be reported in the forthcoming paper.

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

Experimental*3

6-Morpholinomethyl-3-pyridazinol 1-Oxide (IIa)——To a suspended solution of 0.56 g. (0.005 mole) of 3-pyridazinol 1-oxide (I) in 5.0 ml. of ethanol was added dropwise a solution of 0.5 ml. of 37% formalin and 0.44 g. (0.005 mole) of morpholine in 5.0 ml. of ethanol with stirring, and the reaction mixture was allowed to stand over night at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, the residue was dissolved in ethanol, and ether was added. The separated crystals were collected, and recrystallized from a mixture of ethanol and ether to give 0.55 g. of IIa.

6-Piperidinomethyl-3-pyridazinol 1-Oxide (IIb)——To a suspended solution of 0.56 g. (0.005 mole) of I in 5.0 ml. of ethanol was added dropwise a solution of 0.5 ml. of 37% formalin and 0.43 g. (0.005 mole) of piperidine in 5.0 ml. of ethanol with stirring. The reaction mixture was allowed to stand for 5 hr., evaporated under reduced pressure, and the residue was recrystallized from ethanol. The salt of IIb with 3-pyridazinol 1-oxide: Colorless leaflets, m.p. 184~185°(decomp.). Yield, 0.66 g. *Anal.* Calcd. for $C_{10}H_{15}O_2N_3 \cdot \frac{1}{2}C_4H_4O_2N_2$: C, 54.34; H, 6.46; N, 21.12. Found: C, 54.39; H, 6.43; N, 21.09.

This salt was dissolved in a small amount of water, the solution was acidified with 10% hydrochloric acid, and the precipitated 3-pyridazinol 1-oxide was filtered. The filtrate was concentrated under reduced pressure, and the resulting solution was kept in a refrigerator. The separated crystals were filtered, and recrystallized from ethanol to give the hydrochloride of IIb.

6-Dimethylaminomethyl-3-pyridazinol 1-Oxide (IIc)——The salt of IIc with 3-pyridazinol 1-oxide was similary obtained in 53% yield. Pale yellow granules, m.p. 178°(decomp.). *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, 46.78; H, 5.56; N, 25.45.

The hydrochloride was obtained by the same way as described in IIb.

6-[Bis(2-chloroethyl)amino]methyl-3-pyridazinol 1-Oxide (IId)——To a cold solution of 0.3 g. of sodium hydroxide in 4 ml. of water was added 2.2 g. (0.012 mole) of bis(2-chloroethyl) amine hydrochloride, and the separated bis(2-chloroethyl) amine as an oil was extracted with ether three times. The combined extract was washed with ice-water, dried over anhyd. sodium sulfate, and ether was evaporated under reduced pressure from an ice-bath. The oily residue was dissolved in 10 ml. of ethanol, and 2.0 ml. of 37% formalin was added with stirring. To this mixture was added a suspended solution of 1.34 g. (0.012 mole) of 3-pyridazinol 1-oxide in 10 ml. of ethanol, and the mixture was heated at 40~50° till a clear solution was obtained. The solution was allowed to stand over night, evaporated under reduced pressure, and the produced oil was treated with 10% hydrochloric acid. The separated hydrochloride was collected, and recrystallized from ethanol. Yield, 1.05 g. (29%).

*3 All melting points were uncollected. Infrared and ultraviolet spectra were measured on a JASCO Model-IR infrared spectrophotometer, and on a Hitachi Model EPS-2 ultraviolet spectrophotometer. NMR spectra were determined on a Varian HR-100 spectrophotometer.

Catalytic Hydrogenation of 6-Alkylaminomethyl-3-pyridazinol 1-Oxides (IIa, IIb, IIc)——1) 6-Morpholinomethyl-3(2*H*)-pyridazinone (IIIa) : A solution of 0.63 g. (0.003 mole) of IIa in 50 ml. of methanol was submitted to a hydrogenation over a catalyst, prepared from 3.8 ml. of 1% $PdCl_2$ solution and 0.2 g. of charcoal. After one molecular equivalent of hydrogen was absorbed, the catalyst was removed by filtration. Methanol was evaporated to dryness, and the oily residue was treated with ether. The crystals separated were collected, and recrystallized from benzene to give 0.55 g. (95%) of IIIa. Hydrochloride : Colorless granules, m.p. 246~248°.

2) 6-Piperidinomethyl-3(2*H*)-pyridazinone (IIIb) and 6-Dimethylaminomethyl-3(2*H*)-pyridazinone (IIIc) : The hydrochlorides of IIb and IIc were similarly hydrogenated with a 10% palladium-on-charcoal catalyst. Removal of the catalyst and solvent left the hydrochloride of IIIb, colorless scales, m.p. 291°. Hydrochloride of IIIc : Colorless scales, m.p. 259~261°(decomp).

The free bases were 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. sodium sulfate, chloroform was evaporated under reduced pressure, and the residue was recrystallized. Their physical properties and analytical data are shown in Table III.

6-Alkylaminomethyl-3(2*H*)-pyridazinone (IIIa, IIIb, IIIc) from 3-Methoxy-6-hydroxymethylpyridazine[13] (VIII)——A typical experiment for these 6-alkylaminomethyl-3(2*H*)-pyridazinones is described with 6-morpholinomethyl-3(2*H*)-pyridazinone (IIIa).

To a solution of 0.50 g. of VIII in 5.0 ml. of benzene was added dropwise a solution of 0.6 g. of thionyl chloride in 5.0 ml. of benzene under ice-cooling. The mixture was refluxed in a water bath for 2 hr., and evaporated under reduced pressure. To the residue was added a solution of 1.0 ml. of morpholine in 10 ml. of ethanol, the mixture was refluxed for 2 hr., and evaporated under reduced pressure. The morphline hydrochloride separated during concentration was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in chloroform, then the chloroform solution was passed through an alumina column. After washing with chloroform, a mixture of chloroform and methanol was passed. The solvent was evaporated to dryness, and the residue was recrystallized from benzene to give IIIa, colorless leaflets, m.p. 178~180°. Yield, 0.28 g. (40%, calculated from VIII).

Similarly, 6-piperidinomethyl-3(2*H*)-pyridazinone (IIIb) and 6-dimethylaminomethyl-3(2*H*)-pyridazinone (IIIc) were synthesized from VIII in 36% and 58% yield, respectively.

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