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59. **Sigeru Sako**: Syntheses of Pyridazine Derivatives. III.[1] 4- or 5-Chloro-3,6-dimethylpyridazine 1-Oxide.

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In the previous papers of this series,[1,2] it was described that 3-chlorine of 3,6-dichloropyridazine 1-oxide was more reactive than 6-chlorine in nucleophilic substitution, but the chlorine atom at either 3- or 6-position of monochloropyridazine 1-oxide did not show any apparent differece in their reactivity, and they were more reactive than 3-chloropyridazine.

In this paper, the syntheses of 4- and 5-chloro-3,6-dimethylpyridazine 1-oxides and the comparison of the reactivity of the chlorines will be reported.

Heating 3,6-dimethylpyridazine 1-oxide (I) with phosphoryl chloride gave 4-chloro-3,6-dimethylpyridazine (II). When II was N-oxidized with monoperphthalic acid, two kinds of chloro-3,6-dimethylpyridazine 1-oxide, m.p. 133° III and m.p. 127° IV, were obtained. III and IV were obtained in the ratio of two to one, and, the gas chromatographic separation seemed to afford a little more of (IV).[*2]

Previously, the author reported the syntheses of several 3,6-disubstituted 4-nitropyridazine 1-oxides,[3] and, at that time, the position of the nitro group was presumed only from the facts in the nitration of pyridine and quinoline 1-oxides. Igeta[4] proved the position of the nitro group of the nitration products of 3-methoxy- and 3,6-dimethoxypyridazine 1-oxides to be at 4-position. Afterward, the author showed that the nitration of 3-methoxy-6-chloropyridazine 1-oxide gave 4-nitro-derivative.[5] Recently, Itai and Natsume[6] described that the nitration of pyridazine 1-oxide with nitric acid also occurred at 4-position, and they elucidated its structure by synthetic approaches. Considering from these results, the above-mentioned presumption became more likely, and the nitration product must be 4-nitro derivative. When acetyl chloride was reacted with 4-nitro-3,6-dimethylpyridazine 1-oxide[3] (V), 4-chloro-3,6-dimethylpyridazine 1-oxide (III) was produced. This was also obtainable from 4-amino-3,6-dimethylpyridazine 1-oxide (VI) by Gattermann reaction, after reduction of V in about same over all yield.

One of chloro-3,6-dimethylpyridazine 1-oxide (III), m.p. 133°, was identical with above-mentioned 4-chloro-3,6-dimethylpyridazine 1-oxide by admixture and by infrared spectra. Therefore it was presumed that IV might be 5-chloro compound.

In order to prove these structures, III and IV were further treated with sodium methoxide on a steam bath, and methoxy-3,6-dimethylpyidazine 1-oxides, VII m.p. 149° and VIII m.p. 137°, were obtained in good yields respectively. Either VII or VIII was deoxygenated with phosphorus trichloride to 4-methoxy-3,6-dimethylpyridazine (IX), which was found to be as same as 4-methoxy-3,6-dimethylpyridazine prepared from II by admixture and infrared absorption spectra. Hydrolysis of VII and VIII with 5% sodium hydroxide gave two kinds of 3,6-dimethylpyridazinol 1-oxides; X, m.p. 255° (decomp.),

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[*2] Gas chromatographic analysis was kindly performed by Dr. I. Ishizuka of Research Laboratory, Shionogi & Co., Ltd.

1) S. Sako: This Bulletin, **10**, 956 (1962).

2) *Idem*: *Ibid.*, **11**, 261 (1963).

3) T. Itai, S. Sako: *Ibid* **9**, 149 (1961).

4) H. Igeta: *Ibid.*, 8, 550 (1960).

5) T. Itai, S. Sako: *Ibid.*, **10**, 933 (1962).

6) T. Itai, S. Natsume: *Ibid.*, **11**, 83 (1963).

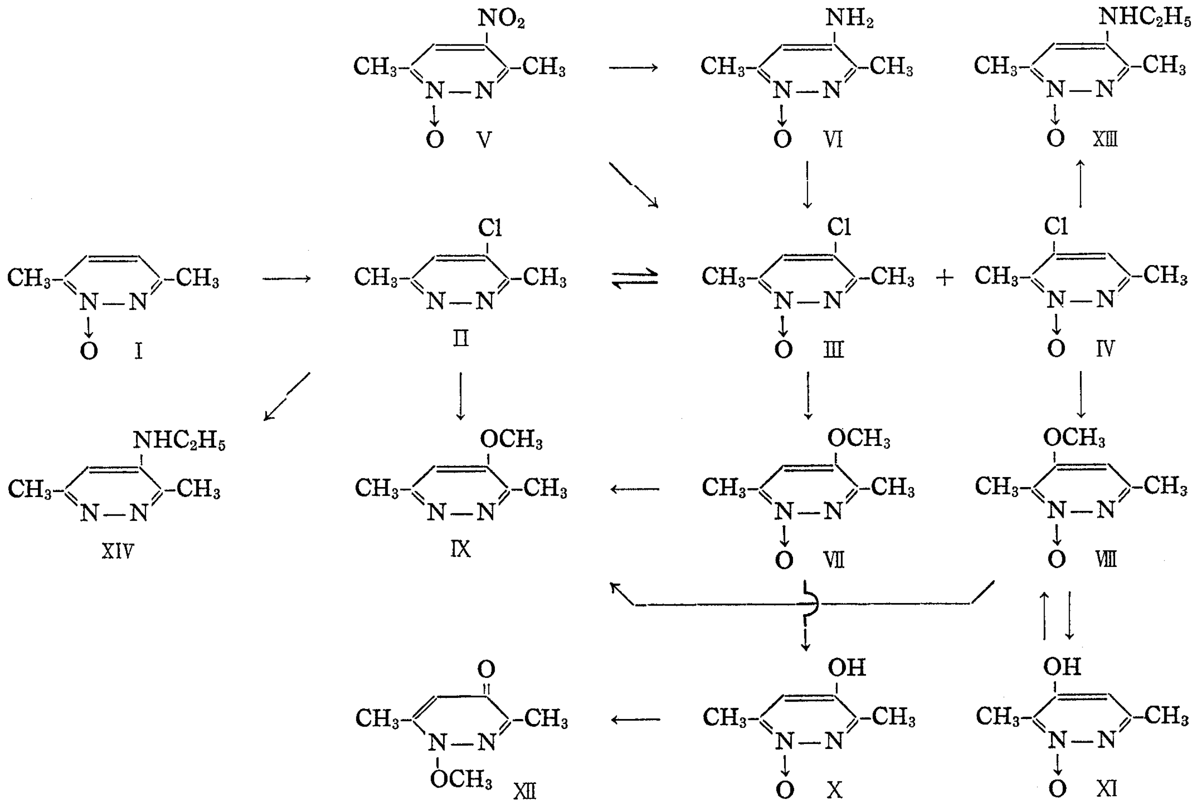

Chart 1.

Table I. Reaction of Chloro-compounds[b] with Sodim Methoxide[c] or Ethylamine[d]

3,6-Dimethylpyridazines		Reaction			Reaction product Yield (%)
		Agent	Temp.	Time (hr.)	
II	4-chloro	CH_3ONa	steam bath	1	80
〃	〃	〃	19°	2	55
III	4-chloro 1-oxide	〃	steam bath	1	82
〃	〃	〃	40°	2	59 (33[a])
〃	〃	〃	19°	4	20 (16[a])
IV	5-chloro 1-oxide	〃	steam bath	1/3	87
〃	〃	〃	19°	2	80 (15[a])
II	4-chloro	$C_2H_5NH_2$	120~130°	6	10.5 (34[a])
III	4-chloro 1-oxide	〃	150°	6	— (82[a])
IV	5-chloro 1-oxide	〃	120~130°	6	85

a) Recovery yield of the starting material. b) ca. 2.5 *M*. c) ca. 0.3 *M*.
d) ca. 7 equivalent.

and XI, m.p. 260°(decomp.), respectively. By heating them with methyl iodide, XI reproduced VIII in poor yields, while X formed a methoxy derivative XII, m.p. 104°, different from VII. The ultraviolet absorption spectrum of XII in ethanol showed one maximum (λ_{max}^{EtOH} : 278 mμ, log ε 4.15), and this was resembling to that of 1-methoxy-4(1*H*)-pyridazinone (UV : λ_{max}^{EtOH} 272 mμ (log ε 4.15)).[6] Therefore, XII was considered to be 1-methoxy-3,6-dimethyl-4(1*H*)-pyridazinone. This might give another proof that III possessed its chlorine atom at 4-position. From these results, it became clear that III was 4-chloro-3,6-dimethylpyridazine 1-oxide, and that IV was 5-chloro-3,6-dimethylpyridazine 1-oxide. In the ultraviolet absorption spectra, 4-derivatives, III, VII, and X, showed two maxima, and 5-derivatives, IV, VIII, and XI, had three maxima.

II produced from I and phosphoryl chloride was rather unstable, and became dark-red gummy substance when kept in a stoppered flask, but II obtained by deoxygenation of III with phosphorus trichloride was comparatively stable.

VIII has dimorphism, that is, rapid crystallization of VIII, which melted at 137°, from hot benzene-petr. benzin solution gave colorless needles, m.p. 140∼142°. When its chloroform solution was slowly evaporated on a water bath, the latter was transformed to the former. They showed different infrared spectra in the solid state, but the same absorption in chloroform solution. X and XI were also prepared directly from III and IV respectively by hydrolysis.

In order to examine the reactivities of chlorine atoms at 4- and 5-position the reactions with either sodium methoxide or ethylamine were carried out at different temperatures results of which were illustrated in Table I. As shown in the Table, II, III, and IV were allowed to stand with sodium methoxide for 2 hours at room temperature, II and IV gave the corresponding methoxy derivatives in 55 and 80% yields respectively. However, though the reaction was continued for 4 hours for III, the yield of VII was only 20%, and 61% of III was recovered. On the reaction with ethylamine, II and IV gave 10.5% of 5-ethylamino-3,6-dimethylpyridazine (XIV) and 85% of 5-ethylamino-3,6-dimethylpyridazine 1-oxide (XIII) by heating at 120° to 130° for 6 hours. But III did not react even by heating at 150° for 6 hours, and 82% of III was recovered. The chlorines of II and IV are more reactive than that of III in the reactions with sodium methoxide and ethylamine, IV is slightly more reactive than II in the former reaction, but, more distinctly in the latter reaction. From these results, it seems likely that the order of reactivity of these chloro-compounds in nucleophilic substitution are IV > II > III.

Experimental

4-Chloro-3,6-dimethylpyridazine (II)——i) Reaction of 3,6-dimethylpyridazine 1-oxide (I) with $POCl_3$: A mixture of 541.6 mg. of I and 3 cc. of $POCl_3$ was heated at 60° to 70° for 30 min. and $POCl_3$ was distilled off under reduced pressure. The residue was mixed with ice, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. Reddish solid (578.2 mg.) so obtained, was recrystallized from petr. benzin, 38.6 mg. of I was separated at first and 175.2 mg. (28%) of II as colorless plates, m.p. 60∼62°, was obtained from tha mother liquor. This was undepressed in m.p. when mixed with II prepared from III. II became dark-red gummy substance when allowed to stand at room temperature.

ii) Reaction of 4-chloro-3,6-dimethylpyridazine 1-oxide (III) with PCl_3 : A mixture of 108.0 mg. of III, 1 cc. of $CHCl_3$ and 0.3 cc. of PCl_3 was allowed to stand overnight at room temperature. The mixture was shaken well with cracked ice, neutralized with $NaHCO_3$, and extracted with $CHCl_3$, which was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue (m.p. 57∼60°, 95.2 mg.) was recrystallized from petr. benzin, 3.4 mg. of III was separated at first and 57.6 mg. (59%) of II as colorless plates m.p. 60∼62°, was obtained from mother eiquor. *Anal.* Calcd. for $C_6H_7N_2Cl$: C, 50.54; H, 4.95. Found : C, 50.32; H, 4.98. This was comparatively stable.

4-Amino-3,6-dimethylpyridazine 1-Oxide (VI)——345.8 mg. of V in 30 cc. of EtOH was hydrogenated by 0.2 g. of 6% Pd-C. After a removal of the catalyst by filtration, EtOH was evaporated to dryness. The residue was recrystallized from EtOH-benzene to colorless fine needles, m.p. 295° (decomp.). Yield, 232.3 mg., 82%. Recently, T. Nakagome[7] reported that VI showed m.p. 291° (decomp.). *Anal.* Calcd. for $C_6H_9ON_3$: C, 51.78; H, 6.52; N, 30.20. Found : C, 51.49; H, 6.56; N, 29.67.

4-Chloro-3,6-dimethylpyridazine 1-Oxide (III)——i) Gattermann reaction of VI : A hot solution of 213.2 mg. of VI, dissolved in 2.5 cc. of 18% HCl, was cooled in ice bath and 130 mg. of $NaNO_2$ was added in small portions, followed by the addition 60 mg. of Cu powder. The mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$, which was dried over anhyd. Na_2SO_4, and evaporated to dryness. The extract (m.p. 120∼128°, 197 mg.) was recrystallized from (*iso*-Pr)$_2$O to colorless needles, m.p. 132∼133°. Yield, 132.8 mg., 55%. *Anal.* Calcd. for $C_6H_7ON_2Cl$: C, 45.44; H, 4.45; N, 17.67. Found : C, 45.19; H, 4.83; N, 17.69. UV λ_{max}^{EtOH} mμ (log ε) : 265 (4.07), 328 (3.78).

ii) Reaction of V with AcCl : 2 cc. of AcCl was added to 201.2 mg. of V under ice cooling, the mixture was allowed to stand for 10 min. at room temperature, and AcCl was distilled off under reduced pressure. The residue was neutralized with $NaHCO_3$, adding simultaneously some water, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was evaporated to dryness. The extract (m.p. 90∼105°) was dissolved in benzene, passed through a column of activated alumina,

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[7] T. Nakagome : Yakugaku Zasshi, 82, 253 (1962).

and eluted with benzene. Benzene was evaporated and the residues of m.p. 125~130° were recrystallized from (iso-Pr)$_2$O to give colorless scales, m.p. 132~133°, yielding 78 mg. (41 %). Admixture with III prepared from VI showed no depression of m.p. and their IR spectra had also the same absorption.

N-Oxidation of 4-Chloro-3,6-dimethylpyridazine (II): Formation of III and 5-Chloro-3,6-dimethylpyridazine 1-Oxide (IV)——A mixture of 2.135 g. of I and 10 cc. of POCl$_3$ was treated as described above, the crude II (m.p. 61~63°) obtained was dissolved in 110 cc. of ethereal solution of monoperphthalic acid (containing 6.6 mg. of activ O per cc.), and the mixture was allowed to stand for 4 days at room temperature. Et$_2$O was evaporated under reduced pressure and the residue was extracted with CHCl$_3$, which was washed with aq. NaHCO$_3$ solution, and an aqueous layer was extracted with CHCl$_3$. It was dried over anhyd. Na$_2$SO$_4$ and was evaporated to dryness. The extract (2.9 g.) was recrystallized from (*iso*-Pr)$_2$O, to colorless scales, m.p. 129~131°, 445.5 mg. Admixture with III prepared from V showed no depression of m.p., and their IR spectra had the same absorption. (*iso*-Pr)$_2$O was distilled-off from the mother liquor, the residue was dissolved in benzene-petr. benzin, passed through a column of activated alumina, and eluted with benzene. The solvent was evaporated from the initial fraction of the eluate, white solid of IV, m.p. 100~115°, was obtained, being recrystallized from petr. benzin, to colorless scales, m.p. 126~127°, yielding 309 mg. of IV, in 11 %. *Anal.* Calcd. for $C_6H_7ON_2Cl$: C, 45.44; H, 4.45. Found: C, 45.60; H, 4.34. UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 221 (4.26), 262 (3.92), 320 (3.70).

The solvent was evaporated from the following fraction of eluate, and the recrystallization of the residue from (*iso*-Pr)$_2$O gave colorless scales of III had m.p. 132~133°, 171.2 mg. Yield of III; 616.7 mg., 23 %.

4-Methoxy-3,6-dimethylpyridazine 1-Oxide (VII)——A mixture of 280 mg. of III, 5.6 cc. of MeOH and MeONa in MeOH (2.6 cc. containing 52 mg. of Na) was heated on a steam bath for 1 hr. MeOH was distilled off under reduced pressure and a small amount of water was added to the residue. The mixture was extracted with CHCl$_3$, which was dried over anhyd. Na$_2$SO$_4$ and evaporated to dryness. The extract (265.2 mg.) was recrystallized from benzene to colorless needles, m.p. 148~149°, yielding 224 mg. in 82 %. *Anal.* Calcd. for $C_7H_{10}O_2N_2$: C, 54.53; H, 6.54. Found: C, 54.32; H, 6.56. UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 267 (4.13), 324 (3.69).

5-Methoxy-3,6-dimethylpyridazine 1-Oxide (VIII)——A mixture of 213.6 mg. of IV, 4 cc. of MeOH and MeONa in MeOH (2 cc. containing 40 mg. of Na) was heated on a steam bath for 20 min., and treated as described above. The extract (222 mg.) was recrystallized from benzene-petr. benzin, to colorless needles, m.p. 136~137°, yielding, 180 mg. in 87 %. *Anal.* Calcd. for $C_7H_{10}O_2N_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.76; H, 6.34; N, 18.69. UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 225.5 (4.42), 261.5 (3.96), 298 (3.61).

4-Methoxy-3,6-dimethylpyridazine (IX)——i) A mixture of 307.4 mg. of II, 6 cc. of MeOH and MeONa in MeOH (3 cc. containing 60 mg. of Na) was heated on a steam bath for 1 hr., and treated as described above. The extract (278.6 mg.) was recrystallized from petr. benzin to colorlss needles, m.p. 78~80°, yielding, 253.8 mg. in 80%. Admixture with IX prepared from VII showed no depression of m.p., and their IR spectra had also the same absorption.

ii) Reaction of VII with PCl$_3$: A mixture of 89.0 mg. of VII, 3 cc. of CHCl$_3$ and 0.4 cc. of PCl$_3$ was allowed to stand overnight at room temperature. The mixture was shaken with cracked ice, basified with NaHCO$_3$, and extracted with CHCl$_3$, which was dried over anhyd. Na$_2$SO$_4$, and evaporated to dryness. The extract (white solid, 72.4 mg.) was recrystallized from petr. benzin to colorless needles, m.p. 78~80°, yielding 54.2 mg. in 64 %. *Anal.* Calcd. for $C_7H_{10}ON_2 \cdot \frac{1}{2}H_2O$: C, 57.12; H, 7.53; N, 19.04. Found: C, 57.25; H, 7.51; N, 19.56.

iii) Reaction of VIII with PCl$_3$: A mixture of 68.8 mg. of VIII, 2 cc. of CHCl$_3$ and 0.2 cc. of PCl$_3$ was treated as described above. The extract (white crystals, m.p. 71~75°, 56.4 mg.) was recrystallized from petr. benzin to colorless needles, m.p. 78~80°, yielding, 45.4 mg. in 69 %. Admixture with the sample prepared from VII showed no depression of m.p. and their IR spectra had also the same absorption.

5-Ethylamino-3,6-dimethylpyridazine 1-Oxide (XIII)——A mixture of 220.6 mg. of IV, 4.4 cc. of EtOH and 0.6 g. of 70% aq. EtNH$_2$ was heated in a sealed tube at 120~130° for 6 hr. The solvent was distilled off under reduced pressure, the residue was mixed with a small amount of H$_2$O and NaHCO$_3$, and extracted with CHCl$_3$, which was dried over anhyd. Na$_2$SO$_4$, and evaporated to dryness. The extract (m.p. 170~174°, 229.6 mg.) was recrystallized from benzene-EtOH to colorless needles, m.p. 177~178°, yielding, 197.2 mg. in 85 %. *Anal.* Calcd. for $C_8H_{13}ON_3$: C, 57.46; H, 7.84. Found: C, 57.55; H, 7.58.

4-Ethylamino-3,6-dimethylpyridazine (XIV)——A mixture of 125.2 mg. of II, 3 cc. of EtOH and 0.4 g. of 70% aq. EtNH$_2$ was treated as described above. The extract (77.8 mg.) was washed with warm petr. benzin, and 42.6 mg. (m.p. 62~64°, 34%) of II was recovered from the washings. The petr. benzin insoluble substance (19.6 mg.) formed a picrate in Et$_2$O, and it was recrystallized from benzene-EtOH to yellowish fine needles, m.p. 187~188°. Yield, 35.2 mg., 10.5 %. *Anal.* Calcd. for $C_8H_{13}N_3 \cdot C_6H_3O_7N_3$: C, 44.21; H, 4.24. Found: C, 44.19; H, 4.22.

3,6-Dimethyl-4-hydroxypyridazine 1-Oxide (X)——A mixture of 571.3 mg. of Ⅶ and 12 cc. of 5% NaOH was heated on a steam bath for 2 hr. After acidification of the solution, white crystals deposited were collected, m.p. 249°(decomp.), 414 mg., 80%. Recrystallization from EtOH gave colorless needles, m.p. 255°(decomp.). *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found : C, 51.06; H, 5.50; N, 19.75. UV λ_{max}^{EtOH} mμ (log ε) : 280 (4.11), 326 (3.76).

X was also obtained from Ⅲ using the same method.

3,6-Dimethyl-5-hydroxypyridazine 1-Oxide (XI)——A mixture of 207.6 mg. of Ⅷ and 4 cc. of 5% NaOH was heated on a steam bath for 1 hr. After acidification of the solution, white precipitate deposited was collected, and recrystallized from EtOH to colorless prisms, m.p. 260°(decomp.), yielding 131.4 mg. in 70%. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75. Found : C, 51.50; H, 5.77. UV λ_{max}^{EtOH} mμ (log ε) : 237 (4.58), 267 (3.84), 300 (3.65).

1-Methoxy-3,6-dimethyl-4(1*H*)-pyridazinone (XII)——A mixture of 524.5 mg. of X, 15 cc. of MeOH, 1.5 g. of MeI and Ag_2O prepared from 1.5 g. of $AgNO_3$ was heated in a sealed tube on a steam bath for 4 hr. with occasional shaking. The precipitate was removed by filtration, and the solvent was evaporated from the filtrate. The residue (519 mg.) was extracted with Et_2O, which was evaporated to dryness. The solid (m.p. 96~101°, 180.6 mg.) was recrystallized from (*iso*-Pr)$_2$O to colorless needles, m.p. 102~104°, 66.6 mg. *Anal.* Calcd. for $C_7H_{10}O_2N_2$: C, 54.53; H, 6.54; N, 18.17. Found : C, 54.06; H, 6.34; N, 17.92. UV λ_{max}^{EtOH} : 278 mμ (log ε, 4.15). Picrate; yellow needles, m.p. 132~134°(from EtOH). *Anal.* Calcd. for $C_7H_{10}O_2N_2 \cdot C_6H_3O_7N_3$: N, 18.27. Found : N, 17.84.

Methylation of X : Formation of VIII——A mixture of 100 mg. of Ⅺ, 3 cc. of MeOH, 0.4 g. of MeI and Ag_2O prepared from 0.4 g. of $AgNO_3$ was heated in a sealed tube on a steam bath for 2 hr. with occasional shaking. The precipitate was removed by filtration, and the solvent was evaporated from the filtrate. The residue (brown viscous liquid, 115 mg.) was extracted with $CHCl_3$, passed through column of activated alumina, and eluted with $CHCl_3$. It was evaporated from the initial 80 cc. of eluate and 29.4 mg. of white crystals, m.p. 130~137° were obtained. Recrystallization from benzene-petr. benzin gave colorless prisms, m.p. 135~137°. Admixture with Ⅷ prepared above showed no depression of m.p., and their IR spectra had also the same absorption in $CHCl_3$ solution.

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Summary

N-Oxidation of 4-chloro-3,6-dimethylpyridazine (Ⅱ) with monoperphthalic acid gave 4-chloro-3,6-dimethylpyridazine 1-oxide (Ⅲ) and 5-chloro-3,6-dimethylpyridazine 1-oxide (Ⅳ). The order of reactivity of these chloro-compounds in nucleophilic substitution are Ⅳ > Ⅱ > Ⅲ.

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