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234. Masaru Ogata : Pyridazines. V.*1 The Reaction of Methyl Substituted 4-Nitropyridazine 1-Oxides with Acetyl Chloride.

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In the previous paper of this series,[1] it was reported that the reaction of 4-nitro-6-methylpyridazine 1-oxide (Ia or Ib) with acetyl chloride gave the corresponding 4-chloro-6-methylpyridazine (IIa or IIb) along with a high melting point product (IIIa, $C_5H_4O_2N_3Cl$ or IIIb, $C_6H_6O_3N_3Cl$). The present paper deals with studies on the structure of these high melting point products and related investigation.

By the same reaction with 3-chloro-4-nitro-6-methylpyridazine (Ic), a high melting point product (IIIc, $C_5H_3O_2N_3Cl_2$) was obtained besides 6-methyl-3,4-dichloropyridazine 1-oxide (IIc). IIIa, b, c showed similar ultraviolet absorption spectra as shown in Fig. 1. In infrared spectrum, each of these compounds showed a strong absorption band (1000~1020 cm^{-1}) probably due to N-O stretching and O-H stretching band at 2750~3250 cm^{-1} in crystalline state. Nuclear magnetic resonance spectra of these compounds lacked methyl proton signals, which indicates the formation of IIIa, b, c from Ia, b, c involves some transformation of methyl group. From the spectral evidences and the elementary analysis, the structure of IIIa, b, c were deduced as 4-chloro-6-formylpyridazine 1-oxide oximes.

The reaction of IIIa, b, c with acetic anhydride gave monoacetate (IVa, b, c), and with phosphoryl chloride gave the corresponding nitriles (Va, b, c). Va was also obtained from IVa by warming in pyridine, while warming of IVb in pyridine gave 3-hydroxy-4-chloro-6-cyanopyridazine 1-oxide (VI). Vb was obtained from IVb by refluxing with acetic acid. Catalytic hydrogenation of IIIa in methanol gave 3-aminomethylpyridazine (VII), which was isolated as a picrate.

In order to relate the structure of one of these compounds to that of authentic compounds, following experiments were carried out. Hydrolysis of Vb with dil. sodium hydroxide gave 3-hydroxy-4-chloro-6-carboxypyridazine 1-oxide (VIII). Removal of chlorine atom or decarboxylation of VIII gave 3-hydroxy-6-carboxypyridazine 1-oxide (IX) or

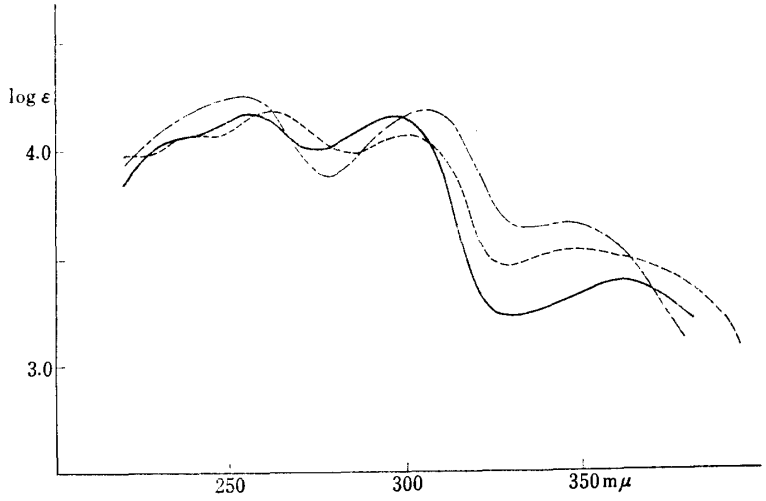

Fig. 1. Ultraviolet Absorption Spectra (in EtOH)

——— IIIa
- - - - - - - IIIb
·-·-·-·-·-· IIIc

*1 Part IV. This Bulletin, **11**, 235 (1963).
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1) M. Ogata, H. Kano : This Bulletin, **11**, 29 (1963).

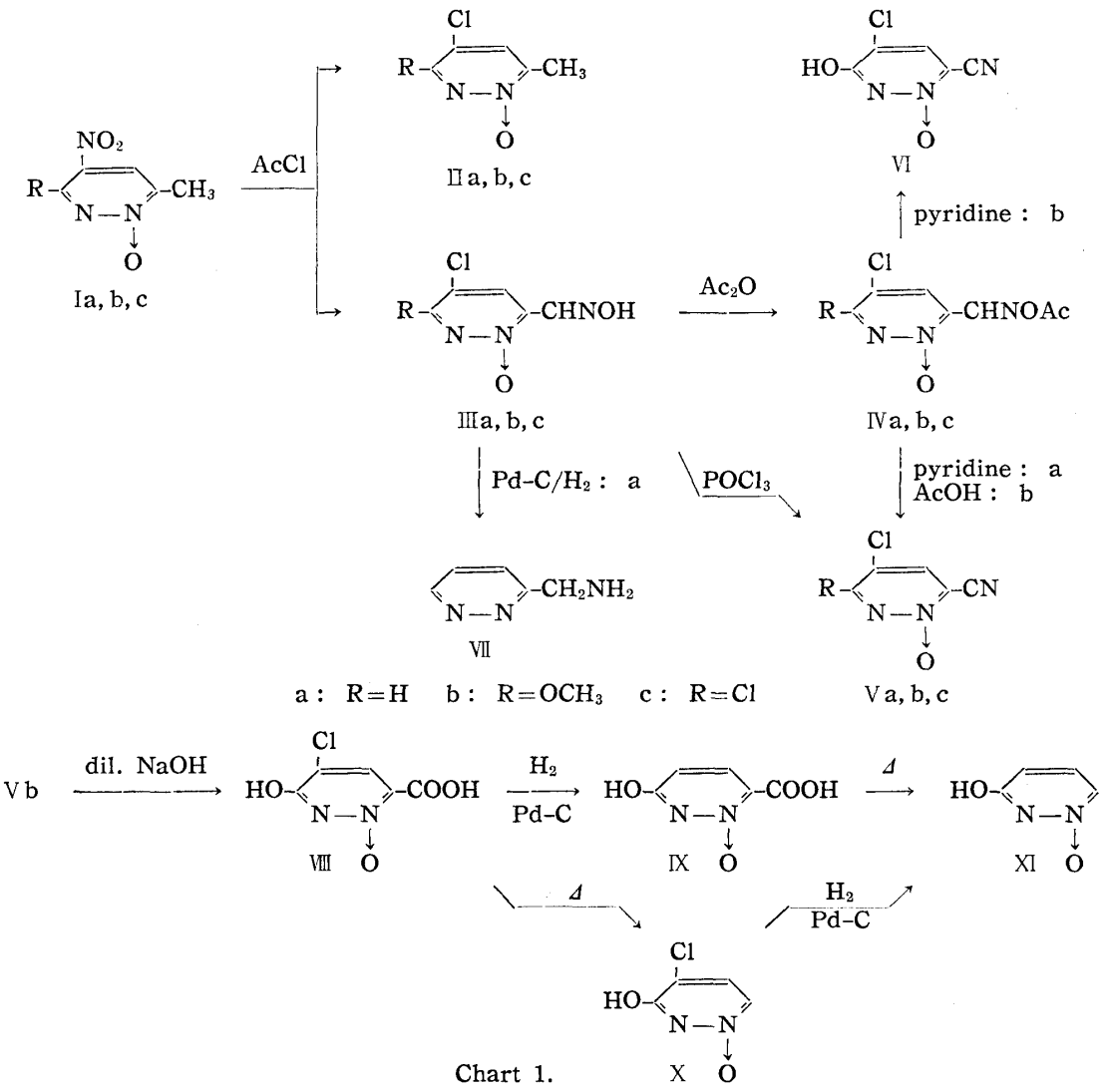

Chart 1.

3-hydroxy-4-chloropyridazine 1-oxide (X) respectively. Decarboxylation of IX or removal of chlorine atom of X gave the same product, which was proved to be identical with the known 3-hydroxypyridazine 1-oxide (XI). These chemical facts can serve as an unambiguous proof for the structures assigned to IIIa, b, c.

In order to compare the reactivity of methyl group at 3-, 4-, and 5-position of pyridazine 1-oxide, the reaction of 3-methyl-4-nitropyridazine 1-oxide (XII),[2] 4-nitro-5-methylpyridazine 1-oxide (XIV)[3] and 4-nitro-3,6-dimethylpyridazine 1-oxide (XVI)[4] with acetyl chloride were carried out.

The reacton of XII and XIV with acetyl chloride gave the corresponding 4-chloro compounds (XIII and XV), while of XVI it gave two products : 4-chloro-3,6-dimethylpyridazine 1-oxide (XVII) and 3-methyl-4-chloro-6-formylpyridazine 1-oxide oxime (XVIII). The structure of XVIII were confirmed by the following transformation reaction. Refluxing of XIII with phosphoryl chloride in chloroform gave the nitrile (XIX), which was hydrolyzed to the carboxylic acid (XX). Decarboxylation of XX yielded XIII, which was identical with XIII derived from XII. Treatment of XIX with methanolic sodium hydroxide gave

2) T. Nakagome : Yakugaku Zasshi, **81**, 1817 (1961).
3) M. Ogata, H. Kano : This Bulletin, **11**, 35 (1963).
4) T. Itai, S. Sako : *Ibid.*, **9**, 149 (1961).

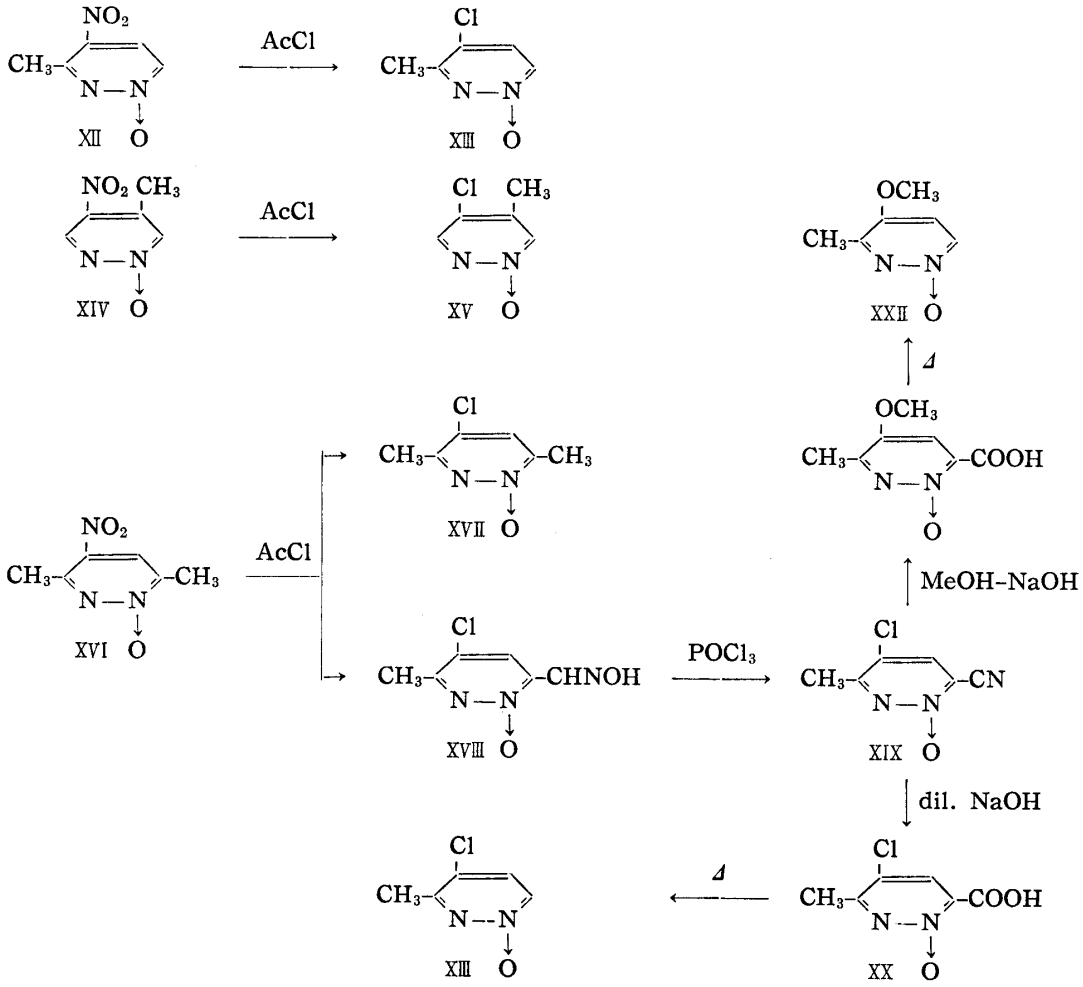

Chart 2.

the methoxy compounds (XXI), which was decarboxylated to 3-methyl-4-methoxypyridazine 1-oxide (XXII). From the results of the reaction of acetyl chloride on Ia, b, c, XII, XIV, and XVI, it was clarified that nitrosation of methyl group proceeds only in α-position to the N-O group.

During the course of this work, analogous nitrosation reactions with 4-nitroquinaldine 1-oxide and 4-nitro-2-picoline 1-oxide were reported by Hamana, *et al.*[5] and Kato, *et al.*[6] independently, in which they obtained 4-chloroquinaldaldehyde 1-oxide oxime and 4-chloropicolinaldehyde 1-oxide oxime respectively.

As for the reaction mechanism, they stated that the reaction would involves formation of acetyl nitrite and following nitrosation on the active methyl group. It seems to be the most probable mechanism for these reactions. The following experiment in pyridazine series was carried out to study, if the liberated acetyl nitrite reacts on the methyl group. When Ic or IIc was refluxed with acetyl chloride and excess 4-nitro-3,6-dimethoxypyridazine 1-oxide which would produce sufficient amount of acetyl nitrite by reacting with acetyl chloride, IIIc was obtained from Ic in the nearly same yield as the case without 3,6-dimethoxy 4-nitro-pyridazine 1-oxide and a trace of IIIc from IIc. Accordingly any definite information for the mechanism could not be obtained from these results.

5) M. Hamana, S. Saeki, Y. Hatano, M. Nagakura : Yakugaku Zasshi, **83**, 348 (1963).
6) T. Kato, H. Hayashi : *Ibid.*, **83**, 352 (1963).

Experimental*3

4-Chloro-6-formylpyridazine 1-Oxide Oxime (IIIa) and 4-Chloro-6-methylpyridazine 1-Oxide (IIa)——These compounds were prepared by the method of the previous work.[1] The reaction of 2.75 g. of Ia with 55 ml. of AcCl gave 0.28 g. (10.1%) of IIa and 0.825 g. (26.8%) of IIIa.

4-Chloro-6-formylpyridazine 1-Oxide Oximeacetate (IVa)——A mixture of 200 mg. of IIIa and 2 ml. of Ac_2O was warmed on a water bath for 1 hr. and Ac_2O was evaporated under reduced pressure. The residue was recrystallized from EtOH to colorless needles, m.p. 100°. Yield, 180 mg. *Anal.* Calcd. for $C_7H_6O_3N_3Cl$: C, 38.99; H, 2.81; N, 19.49. Found: C, 39.25; H, 3.04; N, 19.24.

4-Chloro-6-cyanopyridazine 1-Oxide (Va)——i) From IIIa: To a mixture of 230 mg. of IIIa and 10 ml. of $CHCl_3$, 2 g. of $POCl_3$ was added, and the mixture was refluxed for 2 hr. After evaporation of the solvent, the residue was neutralized with dil. NaOH with cooling, and extracted with $CHCl_3$. $CHCl_3$ was evaparated and the residue was recrystallized from EtOH to colorless plates, m.p. 202~204.5°. Yield, 150 mg. Repeated recrystallization from EtOH gave colorless plates, m.p. 205~206.5°. *Anal.* Calcd. for $C_5H_2ON_3Cl$: C, 38.71; H, 1.28; N, 27.09. Found: C, 38.86; H, 1.47; N, 27.08.

ii) From IVa: A mixture of 100 mg. of IVa and 1 ml. of pyridine was warmed on a water bath for 1 hr. Pyridine was evaporated, and H_2O was added to the residue, which was extracted with $CHCl_3$. $CHCl_3$ was evaporated and the residue was recrystallized from EtOH to colorless plates, m.p. 205~206°. Yield, 30 mg. This was identified with Va derived from IIIa by comparison of their IR spectra.

Catalytic Reduction of 4-Chloro-6-formylpyridazine 1-Oxide Oxime (IIIa). Formation of 3-Aminomethylpyridazine Dipicrate (VII)——A mixture of 230 mg. of IIIa, 10 ml. of MeOH, and 200 mg. of 10% Pd-C was subjected to hydrogenation. Four moles of H_2 were absorbed. The catalyst was filtered, and MeOH was evaporated. The residue remained as an oil gave a picrate of m.p. 167~170°. Yield, 290 mg. Recrystallization from EtOH gave yellow scales, m.p. 179~180°. *Anal.* Calcd. for $C_{17}H_{13}O_{14}N_9$: C, 35.10; H, 2.29; H, 22.22. Found: C, 35.73; H, 2.37; N, 21.89.

3-Methoxy-4-chloro-6-formylpyridazine 1-Oxide Oxime (IIIb) and 3-Methoxy-4-chloro-6-methylpyridazine 1-Oxide (IIb)——These compounds were prepared by the method of the previous work.[1] The reaction of 10 g. of Ib and 75 ml. of AcCl gave 2.03 g. (21.4%) of IIb and 2.85 g. (26.4%) of IIIb.

3-Methoxy-4-chloro-6-formylpyridazine Oximeacetate(IVb)——A mixture of 300 mg. of IIIb and 3 ml. of Ac_2O was warmed on a water bath for 1 hr. and evaporated to dryness under reduced pressure, and the residue was recrystallized from EtOH to colorless needles, m.p. 142~143°. Yield, 300 mg. *Anal.* Calcd. for $C_8H_8O_4NCl$: C, 39.10; H, 3.20; N, 17.11. Found: C, 39.45; H, 3.42; N, 16.98.

3-Methoxy-4-chloro-6-cyanopyridazine 1-Oxide (Vb)——i) From IIIb: To a solution of 1.0 g. of $CHCl_3$, 2.5 g. of $POCl_3$ was added and the mixture was refluxed for 40 min. After evaporation of the solvent, the residue was neutralized with dil. NaOH with cooling, and extracted with $CHCl_3$. $CHCl_3$ was evaporated and the residue was recrystallized from EtOH to colorless needles, m.p. 170~171°. Yield, 600 mg. Repeated recrystallization from EtOH gave colorless needles, m.p. 174~175°. *Anal.* Calcd. for $C_6H_4O_2N_3Cl$: C, 38.81; H, 2.15; N, 22.64. Found: C, 38.87; H, 2.25; N, 22.29.

ii) From IVb: A mixture of 400 mg. of IVb and 10 ml. of AcOH was refluxed for 3 hr. AcOH was evaporated, and the residue was recrystallized from EtOH to colorless scales, m.p. 173~174°. Yield, 110 mg. This was identified with Vb derived from IIIb by comparison of their IR spectra.

3-Hydroxy-4-chloro-6-cyanopyridazine 1-Oxide (VI)——A mixture of 150 mg. of IVb and 1 ml. of pyridine was refluxed for 2.5 hr. Pyridine was evaporated, and the residue was acidified with 6*N* HCl, and deposited crystals were collected. 85 mg. of colorless needles, m.p. 258° (decomp.) were obtained. *Anal.* Calcd. for $C_5H_2N_2N_3Cl \cdot H_2O$: C, 31.66; H, 2.11; N, 22.16. Found: C, 31.92; H, 2.17; N, 21.88.

3-Hydroxy-4-chloro-6-carboxypyridazine 1-Oxide (VIII)——A mixture of 500 mg. of Vb, 2 ml. of MeOH and 10 ml. of 10% NaOH was warmed on a water bath for 15 min., and acidified with 6*N* HCl, and deposited crystals were collected. 450 mg. of colorless needles m.p. 213° (effervesced at 180°) were obtained. Repeated recrystallization from H_2O gave colorless needles, m.p. 214° (effervesced at 180°). *Anal.* Calcd. for $C_5H_3O_4N_2Cl$: C, 31.50; H, 1.57; N, 14.70. Found: C, 31.50; H, 1.87; N, 14.38.

3-Hydroxy-4-chloropyridazine 1-Oxide (X)——Five hundred milligrams of VIII was heated on an oil bath at 190~200° for several min. After cool, the resulting product was recrystallized from EtOH to colorless needles, m.p. 217°. Yield, 240 mg. *Anal.* Calcd. for $C_4H_3O_2N_2Cl$: C, 32.70; H, 2.06; N, 19.11. Found: C, 33.00; H, 2.37; N, 19.33.

3-Hydroxy-6-carboxypyridazine 1-Oxide (IX)——A mixture of 300 mg. of VIII, 10 ml. of 5% NaOH and 200 mg. of 10% Pd-C was subjected to hydrogenation. One mole of H_2 was absorbed. The catalyst was filtered, the filtrate neutralized with dil. HCl, and deposited crystals were collected. One hundred

*3 Melting points were determined on a Kofler-Block "Monoscope IV" and uncorrected.

and twenty milligrams of colorless prisms, m.p. 197~198° (decomp.) were obtained. Recrystallization from MeOH did not alter the melting point. *Anal.* Calcd. for $C_5H_4O_4N_2$: C, 38.47; H, 2.58; N, 17.95. Found : C, 38.48; H, 2.71; N, 17.83.

3-Hydroxypyridazine 1-Oxide (XI)——i) From X : A mixture of 140 mg. of XVI, 10 mlg. of 1% NaOH and 100 mg. of 10% Pd-C was subjected to hydrogenation. One mole of H_2 was absorbed. The catalyst was filtered, the filtrate was neutralized with dil. HCl, and the solvent was evaporated to dryness. The residue was extracted with EtOH. EtOH was evaporated. The residue was recrystallized from EtOH to give 60 mg. of colorless prisms, m.p. 195~197°. Repeated recrystallization from EtOH gave colorless prisms, m.p. 197~198°. This was identified with an authentic sample prepared according to the method of Igeta[7] by comparison of their IR spectra.

ii) From IX : Twenty milligrams of IX was heated on an oil bath at 200~220° for several min. After cool, the resulting product was recrystallized from EtOH, and identified with XI derived from X by comparison of their IR spectra.

6-Formyl-3,4-dichloropyridazine 1-Oxide Oxime (IIIc) and 6-Methyl-3,4-dichloropyridazine 1-Oxide (IIc)——Ten grams of Ic was added to 200 ml. of AcCl, and the mixture was allowed to stand at room temperature. After the initial vigorous reaction had subsided, the mixture was heated under reflux for 0.5 hr. AcCl was removed under reduced pressure, MeOH was added to the residue, and the deposited colorless crystals were collected. This product was digested with hot MeOH and filtered. Yield, 5.05 g. (46.3%), colorless crystals (IIIc), m.p. 234° (decomp.). *Anal.* Calcd. for $C_5H_3O_2N_3Cl_2$: C, 28.84; H, 1.44; N, 20.19. Found : C, 29.37; H, 1.48; N, 19.79. MeOH of the filtrate was evaporated and the residue was recrystallized from MeOH repeatedly, and gave 1.18 g. (15.7%) of IIc as a colorless needles, m.p. 165~166°, and 290 mg. of IIIc (the total yield of IIIc was 5.34 g. (49.0%). IIc was identified with 3,4-dichloro-6-methylpyridazine 1-oxide*[1] by comparison of their IR spectra.

6-Formyl-3,4-dichloropyridazine 1-Oxide Oximeacetate(IVc)——A mixture of 1 g. of IIIc and 10 ml. of Ac_2O was warmed on a water bath for 1 hr. and evaporated to dryness under reduced pressuer, and the residue was recrystallized from EtOH to colorless prisms, m.p. 110~112.5°. Yield, 750 mg. Repeated recrystallization from EtOH gave colorless prisms, m.p. 111~112°. *Anal.* Calcd. for $C_7H_5O_3N_3Cl_2$: C, 33.62; H, 2.02; N, 16.81. Found : C, 33.68; H, 3.42; N, 16.66.

6-Cyano-3,4-dichloropyridazine 1-Oxide (Vc)——To a solution of 500 mg. of IIIc and 5 ml. of $CHCl_3$, 5 g. of $POCl_3$ was added and the mixture was refluxed for 1.5 hr. After evaporation of the solvent, the residue was neutralized with dil. NaOH with cooling, and extracted with $CHCl_3$. $CHCl_3$ was evaporated, the residue was recrystallized from EtOH to colorless plates, m.p. 131~133°. Yield, 320 mg. Repeated recrystallization from EtOH gave colorless plates, m.p. 132~133°. *Anal.* Calcd. for $C_5HN_3OCl_2$: C, 31.57; H, 0.53; N, 22.11. Found : C, 32.49; H, 0.73; N, 21.58.

3-Methyl-4-chloropyridazine 1-Oxide (XIII)——i) From XII : One hundred and ninety milligrams of XII was added to 2 g. of AcCl, and the mixture was allowed to stand for 30 min. at room temperature. AcCl was removed under reduced pressure, a small quantities of EtOH was added to the residue, causing crystals to separate. Resulting crystals were collected. 100 mg. of colorless needles, m.p. 130~133°, were obtained. From the filtrate, 35 mg. of colorless needles, m.p. 126~130° were obtained. These were combined, and recrystallized from EtOH to colorless needles, m.p. 132.5~133°. *Anal.* Calcd. for $C_5H_5ON_2Cl$: C, 41.52; H, 3.46; N, 19.31. Found : C, 41.32; H, 3.49; N, 19.35.

ii) From XX: One hundred and fifty milligrams of XX was heated on an oil bath at 120~130° for several min. After cool, the resulting product was recrystallized from EtOH to colorless needles, m.p. 133°. Yield, 40 mg. This was identified with XIII derived from XII by comparison of their IR spectra.

4-Chloro-5-methylpyridazine 1-Oxide (XV)——Three hundred and twenty milligrams of XIV was added to 4 g. of AcCl, and the mixture was allowed to stand for 30 min. at room temperature. AcCl was removed under reduced pressure, the residue was added to H_2O and extracted with $CHCl_3$. $CHCl_3$ was evaporated and the residue was dissolved in benzene, and chromatographed on alumina and the column was eluted with benzene and then $CHCl_3$. The residue from the fraction eluted with $CHCl_3$ was recrystallized from benzene-cyclohexane to colorless needles, m.p. 61~62°. Yield, 85 mg. *Anal.* Calcd. for $C_5H_5ON_2Cl$: C, 41.52; H, 3.46; N, 19.31. Found : C, 41.30; H, 3.43; N, 19.01.

3-Methyl-4-chloro-6-formylpyridazine 1-Oxide Oxime (XVIII) and 4-Chloro-3,6-dimethylpyridazine 1-Oxide (XVII)——Treatment of 2.7 g. of XVI and 25 ml. of AcCl by the same procedure as for Ia, and digestion with MeOH afforded 1.09 g. (38.0%) of colorless prisms (XVIII), m.p. 224° (decomp.). *Anal.* Calcd. for $C_6H_7ON_2Cl$: C, 45.43; H, 4.41; N, 17.66. Found : C, 45.48; H, 4.42; N, 17.80. MeOH of the filtrate was evaporated, and the residue was chromatographed on alumina with $CHCl_3$. The residue eluted with $CHCl_3$ was recrystallized from benzene to give colorless needles (XVII), m.p. 130~131°. Yield, 300 mg. (11.9%). *Anal.* Calcd. for $C_6H_6O_2N_3Cl$: C, 38.80; H, 3.20; N, 22·40. Found : C, 38.53; H, 3.37; N, 22.01.

7) H. Igeta : This Bulletin, **7**, 938 (1959).

3-Methyl-4-chloro-6-cyanopyridazine 1-Oxide (XIX)——To a mixture of 150 mg. of XVIII and 20 ml. of $CHCl_3$, 5 g. of $POCl_3$ was added and the mixture was refluxed for 2 hr. After evaporation of the solvent, the residue was neutralized with dil. NaOH with cooling, and extracted with $CHCl_3$. $CHCl_3$ was evaporated and the residue was recrystallized from EtOH to colorless plates, m.p. 149.5~151°. Yield, 320 mg. Repeated recrystallization from EtOH gave colorless plates, m.p. 150~151°. *Anal.* Calcd. for $C_6H_4ON_3Cl$: C, 42.48; H, 2.36; N, 24.78. Found: C, 42.43; H, 2.57; N, 24.37.

3-Methyl-4-chloro-6-carboxypyridazine 1-Oxide (XX)——A mixture of 150 mg. of XIX and 2 ml. of 5% NaOH was warmed on a water bath for 2 min., and acidified with 6*N* HCl, and deposited crystals were collected. Recrystallization from H_2O gave colorless needles, m.p. 115° (decomp.). Yield, 50 mg. *Anal.* Calcd. for $C_6H_5O_3N_2Cl$: C, 38.19; H, 2.65; N, 14.85. Found: C, 37.86; H, 2.72; N, 14.50.

3-Methyl-4-methoxy-6-carboxypyridazine 1-Oxide (XXI)——A mixture of 280 mg. of XIX, 2 ml. of MeOH and 2 ml. of 10% NaOH was warmed on a water bath for 5 min., and then MeOH was evaporated under reduced pressure and the residue was acidified with 6*N* HCl. The resulting colorless needles were collected by filtration, and recrystallized from H_2O to colorless needles, m.p. 141~142° (decomp.). Yield, 120 mg. *Anal.* Calcd. for $C_7H_8O_4N_2$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.44; H, 4.46; N, 15.28.

3-Methyl-4-methoxypyridazine 1-Oxide (XXII)——Thirty milligrams of XXI was heated on an oil bath at 150~160° for several min. After cool, the resulting product was recrystallized from benzene-petr. benzin to colorless needles, m.p. 118~119°. Yield, 10 mg. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.61; H, 5.75; N, 19.99.

Formation of IIIc from Ic or IIc in the Presence of 4-Nitro-3,6-dimethoxypyridazine 1-Oxide——
i) From Ic: To a mixture of 1.0 g. of Ic and 2.0 g. of 3.6-dimethoxy-4-nitropyridazine 1-oxide, 15 ml. of AcCl was added, and the mixture was allowed to stand at room temperature. After initial vigorous reaction had subsided, the mixture was heated under reflux for 0.5 hr. AcCl was removed under reduced pressure, MeOH was added to the residue, and the resulting colorless crystals were collected. This product was digested with hot MeOH and filtered. Yield, 500 mg. (45.5%), m.p. 234° (decomp.).
ii) From IIc: To a refluxing solution of 0.5 g. of IIc dissolved in AcCl of 10 ml., 1.0 g. of 4-nitro-3,6-dimethoxypyridazine 1-oxide was added in a portionwise. After 5 min., AcCl was evaporated to dryness and a portion of MeOH was added to the residue. The resulting crystals were collected and digested with hot MeOH, and the insoluble residue was collected, m.p. 234° (decomp.). Yield, 10 mg. This was identical with IIIc derived from Ic by comparison of their IR spectra.

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Summary

Reaction of excess acetyl chloride on a 3-substituted 4-nitro-6-methylpyridazine 1-oxide (Ia, b, c and XIII) result in the formation of 3-substituted 4-chloro-6-formylpyridazine 1-oxide oximes (IIa, b, c and XVIII), together with 3-substituted 4-chloro-6-methylpyridazine 1-oxides (IIa, b, c and XVII). Reaction of 3-methyl-4-nitropyridazine 1-oxide (XII) and 4-nitro-5-methylpyridazine 1-oxide (XIV) with acetyl chloride gave only 3-methyl-4-chloropyridazine 1-oxide (XIII) and 4-chloro-5-methylpyridazine 1-oxide (XV) respectively.

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