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235. **Masaru Ogata**: Pyridazines. VI.*1 Reaction of Methylpyridazine N-Oxides with Amyl Nitrite.

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In the previous paper of this series,*1 it was reported that the reaction of 4-nitro-6-methylpyridazine 1-oxides with acetyl chloride gave 4-chloro-6-formylpyridazine 1-oxide oximes. In order to ascertain the structure of these aldoximes, an unequivocal synthesis of the aldoximes was attempted.

Recently, Kato, *et al.*[1] found a favourable method of nitrosation on methyl group in picolines and its N-oxides. Present author attempted to apply the method to the synthesis of pyridazine aldehyde N-oxide oximes.

3-Methoxy-4-chloro-6-methylpyridazine 1-oxide (I) reacted readily with amylnitrite in liquid ammonia in the presence of sodium amide at −50～−60° to give 3-methoxy-4-chloro-6-formylpyridazine 1-oxide oxime (II) and 3-amyloxy-4-chloro-6-formylpyridazine 1-oxide oxime (III). Surprisingly II was not identical with 3-methoxy-4-chloro-6-formylpyridazine 1-oxide oxime (IV)*1 derived from 3-methoxy-4-nitro-6-methylpyridazine 1-oxide with acetyl chloride, however, II could be isomerized to IV by warming with 6*N* hydrochloric acid. III was also isomerized to a stable oxime (V) with 6*N* hydrochloric acid. The isomerization did not occur when II and III were heated to near melting point. Tentatively, the unstable oximes were named α-aldoxime, and the stable oximes β-aldoxime in present paper.

By the same method, 4-chloro-6-methylpyridazine 1-oxide (VI) reacted with amyl nitrite afforded 4-chloro-6-formylpyridazine 1-oxide oxime (VII),*1 which was identical with that derived from 4-nitro-6-methylpyridazine 1-oxide with acetyl chloride. Since VII was not converted to another isomer, this oxime must exist as the stable β-aldoxime. The similar reaction of 3,4-dichloro (VIII), or 3-chloro-6-methylpyridazine 1-oxide (IX) resulted in decomposition.

In order to compare the reactivity of methyl group, nitrosation of methylpyridazine 1-oxide (X, XIII, XVI, and XIX)[2] are carried out under the same condition. X, XIII, XVI, and XIX reacted to give the corresponding aldoximes (XI, XV, XVII, and XX). Although XI, XVII, and XX are isomerized to XII, XVIII, and XXI respectively with heating alone 180° or warming with 6*N* hydrochloric acid, XV could not isomerize by the same treatment. The infrared spectrum of unpurified XV (namely, XIV) showed a little different absorption bands from those of purified XV as are shown in Fig. 1. When XIV was heated to 180°, the infrared spectrum of the resulting compound was completely identical with that of XV. From these results, it is considered that the XIV is a mixture of α- and β-aldoxime and XV is pure β-aldoxime.

The reaction of 3,6-dimethylpyridazine 1-oxide (XXII) with one mole equivalent amount of amyl nitrite and sodium amide resulted in the recovery of the starting material (34.1%) and formation of dioxime (XXIII) (33.5%), which gave diacetate (XXIV) when treated with acetic anhydride, monoxime could not detect in this reaction. With 2.2 mole equivalent amount of amyl nitrite and sodium amide, this reaction gave XXIII only in low yield. These results showed that there is no difference between the reactivity of 3-methyl group and that of 6-methyl group.

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*1 Part V: This Bulletin, **11**, 1511 (1963).
*2 Fukushima-ku, Osaka (尾形 秀).

1) T. Kato, Y. Goto: This Bulletin, **11**, 461 (1963).
2) M. Ogata, H. Kano: This Bulletin, **11**, 29, 35 (1963).

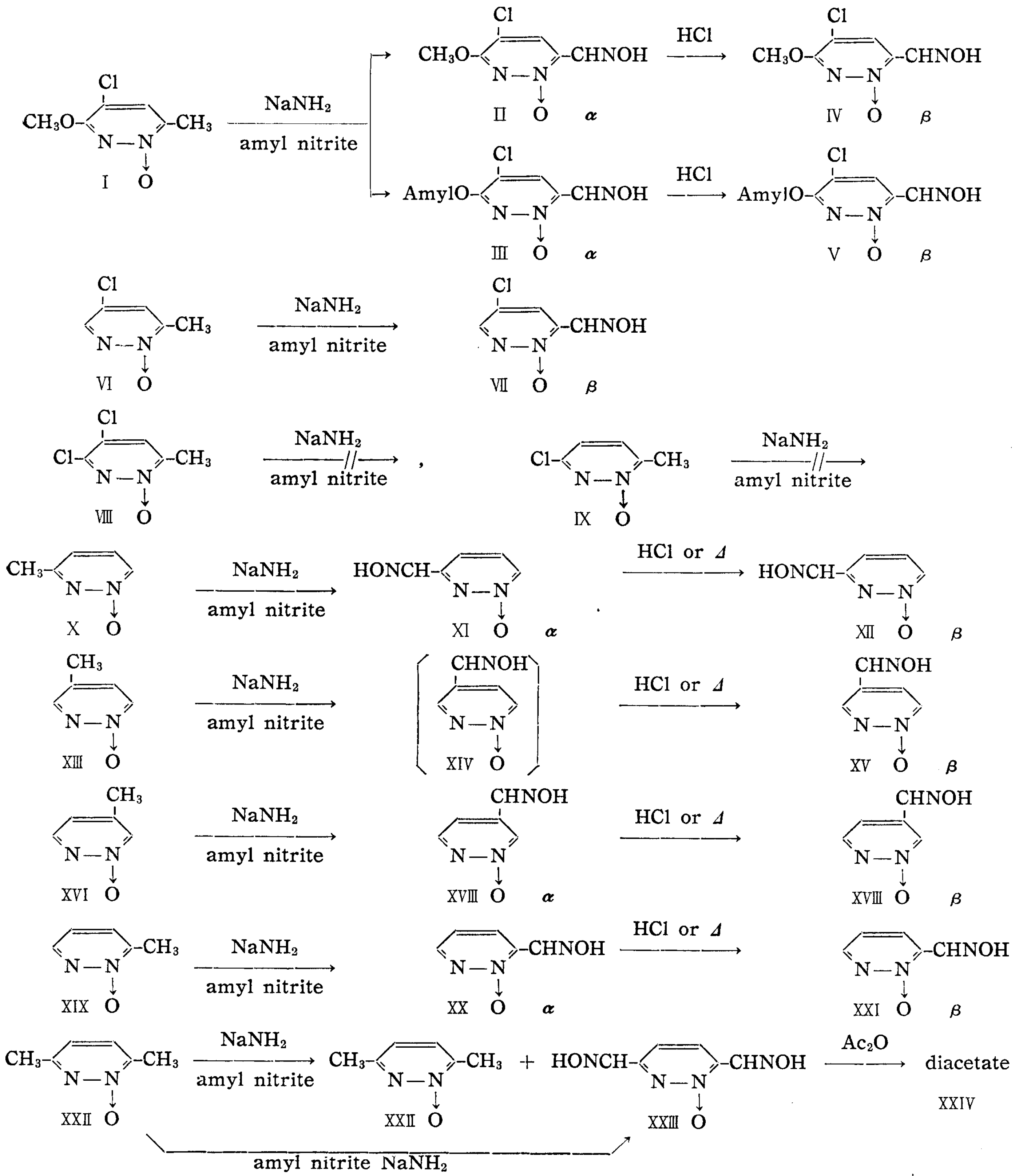


Chart 1.

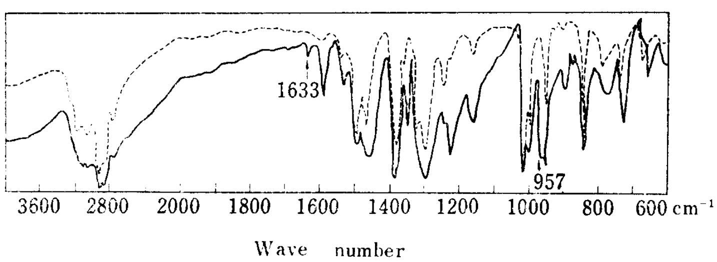


Fig. 1. Infrared Absorption Spectra of 4-Formylpyridazine 1-Oxide Oximes (in Nujol)

——— XIV

------- XV

The α-aldoxime and the corresponding β-aldoxime of 3,4,5,- and 6-formylpyridazine 1-oxide oxime showed almost near melting point, and characterization of both aldoxime was obtained by comparison of their infrared spectra. As an example, infrared spectra of XI and XII are shown in Fig. 2.

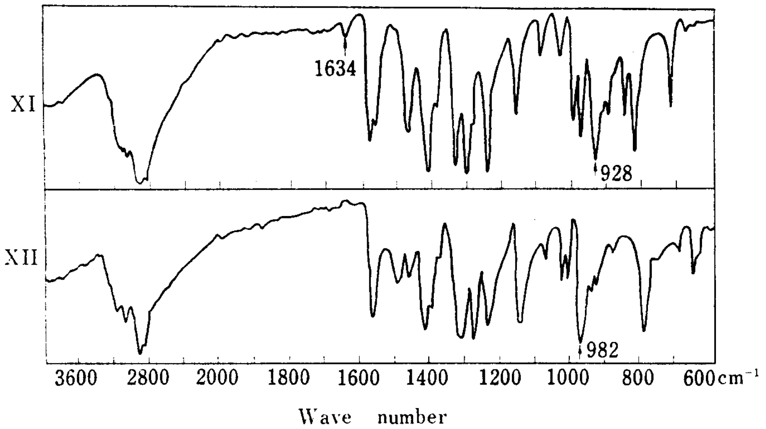


Fig. 2. Infrared Absorption Spectra of 3-Formylpyridazine 1-Oxide Oximes (XI, XII) in Nujol.

The most characteristic difference between the spectra of α-aldoxime and β-aldoxime can be found in the ν_{N-O} band of oxime group, the former showing this band in lower frequency than the latter. Moreover, most of α-aldoxime series showed an absorption band appeared at *ca.* 1630 cm^{-1} probably due to $\nu_{C=N}$, while β-aldoxime series did not. If there is an analogy between benzaldoxime series*[3] and pyridazine N-oxide

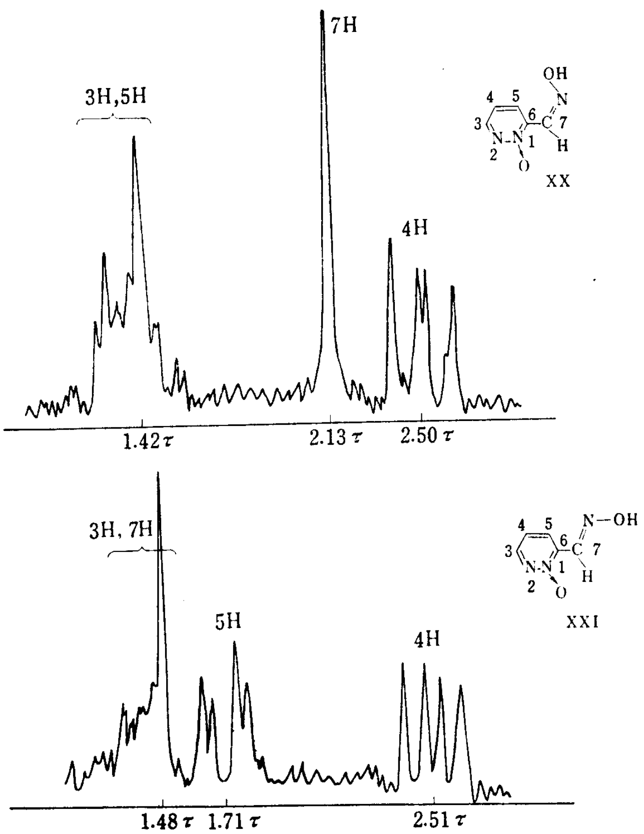


Fig. 3. Nuclear Magnetic Resonance Spectra of 6-Formylpyridazine 1-Oxide Oximes (XX, XXI) at 60 Mc. p. s., in Saturated Solution in Deuterium Oxide

*[3] On infrared spectra of *syn*- and *anti-p*-chlorobenzaldoxime, it was reported that ν_{N-O} of *syn* isomer appears at high frequency than that of *anti* isomer, and the $\nu_{C=N}$ of *syn* isomer did not appears, while that of the *anti* isomer appeared in the solid state. Cf. Y. Matsui: Nippon Kagaku Zasshi, **83**, 990 (1962).

aldoxime series, these spectral evidence supports that α-aldoxime is *anti*-isomer and β-aldoxime is *syn* isomer.

Further evidence for the configuration of α- and β-aldoxime was provided by nuclear magnetic resonance spectra of *syn*- and *anti*-isonicotin aldehyde oxime, Poziomek, *et al.*[*4] observed that the signal from the hydrogen on the oximino carbon was shifted to down field in the *syn* isomer, and the signals from the *ortho* ring proton to the oximino group are shifted further down field in the spectrum of *anti* isomer. This finding should be applicable to pyridazine 1-oxide aldoxime. Comparing the nuclear magnetic resonance spectra of XX and XXI, it was observed that the signal from H_7 on the oximino carbon was shifted to lower field in the spectrum of β-aldoxime (XXI) and the signal from ring proton H_5 was shifted to lower field in the spectrum of α-aldoxime (XX). From these results, it is considered that XX is *anti* oxime, and XXI is *syn* oxime. The results of nuclear magnetic resonance spectra study are consistent with those of infrared spectral study.

Experimental[*5]

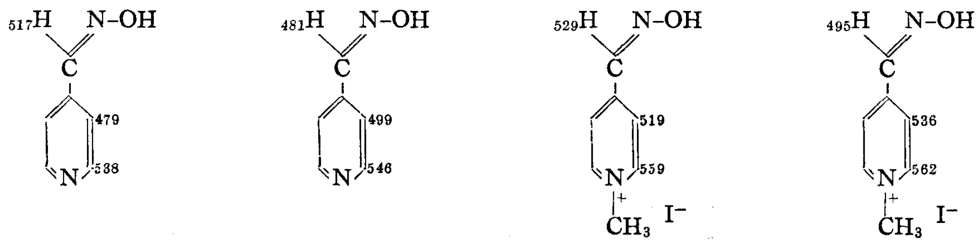
3-Methoxy-4-chloro-6-formylpyridazine 1-Oxide Oximes (II), (IV) and 3-Pentyloxy-4-chloro-6-formylpyridazine 1-Oxide Oximes (III), (V)——In a 100 ml. three necked flask a mixture of 430 mg. (0.011 mole) of $NaNH_2$ and 1.75 g. (0.01 mole) of I in *ca.* 10 ml. of liq. NH_3 was placed, and 1.29 g. (0.011 mole) of amylnitrite were added, and stirred for 2 hr. at $-50\sim-60°$. After evaporation of liq. NH_3, a small amount of H_2O was added. After cool, the solution was acidified with 6*N* HCl. The deposited crystals were collected, washed with hot MeOH to colorless crystals (II), m.p. 206° (decomp.). Yield, 1.0 g. (44.6%). Recrystallization from MeOH did not alter the melting point. *Anal.* Calcd. for $C_6H_6O_3N_3Cl$: C, 35.29; H, 2.94; N, 20.59. Found: C, 35.39; H, 3.14; N, 20.36. The filtrate was evaporated under reduced pressure, and the residue was recrystallized from abs. MeOH to give colorless needles (III), m.p. 110~114°. Yield, 0.28 g. (10.8%). Repeated recrystallization from abs. MeOH gave colorless needles, m.p. 112.5~113.5°. *Anal.* Calcd. for $C_{10}H_{14}O_3N_3Cl$: C, 46.24; H, 5.40; N, 16.18. Found: C, 46.47; H, 5.58; N, 15.84.

A mixture of 20 mg. of II and 0.5 ml. of 6*N* HCl was warmed on a water bath for 5 min., and neutralized with Na_2CO_3, then the deposited crystals (13 mg., m.p. 205° (decomp.)) were collected. Recrystallization from MeOH gave colorless needles, m.p. 211° (decomp.). This was identical with IV[*1] derived from the reaction of 3-methoxy-4-nitro-6-methylpyridazine 1-oxide with AcCl by comparison of their IR spectra.

A mixture of 100 mg. of III and 2 ml. of 6*N* HCl was treated in the same way as described above. Recrystallization from hydr. MeOH gave colorless needles, m.p. 136~137°. Yield, 90 mg. *Anal.* Calcd. for $C_{10}H_{14}O_3N_3Cl$: C, 46.24; H, 5.40; N, 16.18. Found: C, 46.28; H, 5.50; N, 15.85.

4-Chloro-6-formylpyridazine 1-Oxide Oxime (VII)——A mixture of 1.2 g. (0.008 mole) of VI, 360 mg. (0.009 mole) of $NaNH_2$, and 1.07 g. (0.009 mole) of amyl nitrite were treated in the same way as described above. The deposited brown crystals were collected, and recrystallized from EtOH to give colorless prisms, m.p. 218~219° (decomp.). Yield, 270 mg. From the filtrate, 340 mg. of m.p. 218~219° (decomp.) was obtained. The total yield of VII was 610 mg. (37.8%). This was identical with VII[*1] derived from the reaction of 4-nitro-6-methylpyridazine 1-oxide with AcCl by comparison of their IR spectra.

*4 Nuclear magnetic resonance (c.p.s.) of isonicotin aldehyde oximes and 1-methyl-4-formylpyridinium iodide oximes in deuterium oxide at 60 Mc.p.s. Tetramethylsilane was used as internal reference at 0 with respect to observed resonance.



cf. E.J. Poziomek, D.N. Kramer, W.A. Mosher, H.O. Michel: J. Am. Chem. Soc., 83, 3916 (1961).

*5 All melting points were determined on a Kofler-Block "Monoscope IV" and are uncorrected.

3-Formylpyridazine 1-Oxide Oximes (XI) and (XII)——A mixture of 1.1 g. (0.01 mole) of X, 430 mg. (0.011 mole) of $NaNH_2$ and 1.29 g. (0.011 mole) of amyl nitrite were treated in the same way as described above. The deposited crystals (450 mg., 34.9%, m.p. 212~215°(decomp.)) were recrystallized from H_2O to give colorless needles (XI), m.p. 215°(decomp.). *Anal.* Calcd. for $C_5H_5O_2N_3$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.04; H, 3.79; N, 30.02. From the H_2O soluble fraction, after evaporation of H_2O, 210 mg. (16.3%) of XII was obtained. This was identical with XII derived by the isomerization of XI by comparison of their IR spectra.

When 120 mg. of XI was heated with 6*N* HCl in the same way as described above, the reaction gave 55 mg. of XII as a colorless needles, m.p. 219°(decomp.). And also, when XI was heated at 180° for several min., XI isomerized to XII. *Anal.* Calcd. for $C_5H_5O_2N_3$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.35; H, 3.69; N, 29.61.

4-Formylpyridazine 1-Oxide Oximes (XIV) and (XV)——A mixture of 1.1 g. (0.01 mole) of XIII, 430 mg. (0.011 mole) of $NaNH_2$, and 1.29 g. (0.011 mole) of amyl nitrite were treated in the same way as described above. The deposited crystals (XIV) (400 mg., 31.0%, m.p. 247~248°(decomp.)) were recrystallized from H_2O to give colorless needles (XV), m.p. 258°(decomp.). From the H_2O soluble fraction, after evaporation of H_2O, 470 mg. (36.4%) of XV was obtained. This was identical with XV by comparison of their IR spectra. When XIV was heated at 180° for several min., resulting product was identical with XV by comparison of their IR spectra. *Anal.* calcd. for $C_5H_5O_2N_3$(XV): C, 43.17; H, 3.62; N, 30.21. Found: C, 43.07; H, 3.97; N, 29.81.

5-Formylpyridazine 1-Oxide Oximes (XVII) and (XVIII)——A mixture of 1.1 g. (0.01 mole) of XVI, 430 mg. (0.011 mole) of $NaNH_2$, and 1.29 g. (0.011 mole) of amyl nitrite were treated in the same way as described above. The deposited crystals (XVII) (900 mg., 69.8%, m.p. 221°(decomp.)) were recrystallized from H_2O to give colorless needles (XVII), m.p. 221°(decomp.). *Anal.* Calcd. for $C_5H_5O_2N_3$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.05; H, 3.72; N, 30.03. From the H_2O soluble fraction, after evaporation of H_2O, 10 mg. (7.2%) of XVIII was obtained. This was identical with XVIII by comparison of their IR spectra.

When XVII was heated with 6*N* HCl in the same way as described above, the reaction gave 85 mg. of XVIII as a colorless needles, m.p. 229°(decomp.). And also, when XVII was heated at 180° for several min., XVII isomerized to XVIII. *Anal.* Calcd. for $C_5H_5O_2N_3$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.11; H, 3.70; N, 29.68.

6-Formylpyridazine 1-Oxide Oximes (XX) and (XXI)——A mixture of 1.1 g. (0.01 mole) of XIX, 430 mg. (0.011 mole) of $NaNH_2$, and 1.29 g. (0.11 mole) of amyl nitrite were treated in the same way as described above. The deposited crystals (XX) (680 mg., 48.9%, m.p. 211~213°(decomp.)) were recrystallized from H_2O to give colorless needles (XX), m.p. 212~213°(decomp.). *Anal.* Calcd. for $C_5H_5O_2N_3$(XX): C, 43.17; H, 3.62; N, 30.21. Found: C, 43.38; H, 3.63; N, 29.84. From the H_2O soluble fraction, after evaporation of H_2O, 160 mg. (11.5%) of XXI was obtained. This was identical with XXI by comparison of their IR spectra. When 100 mg. of XX was heated with 6*N* HCl in the same way as described above, the reaction gave 60 mg. of XXI as colorless needles, m.p. 213~214°(decomp.), and also, when XX was heated at 180° for several min., XX isomerized to XXI. *Anal.* Calcd. for $C_5H_5O_2N_3$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.35; H, 3.84; N, 30.14.

Reaction of 3,6-Dimethylpyridazine 1-Oxide (XXII)——i) A mixture of 1.24 g. (0.01 mole) of XXII, 860 mg. (0.022 mole) of $NaNH_2$, and 2.57 g. (0.022 mole) of amyl nitrite were treated in the same way as described above. The deposited brown crystals (XXIII) (110 mg., 6.6%, m.p. 224°(decomp.)) were recrystallized from MeOH to give pale yellow needles (XXIII), m.p. 224°(decomp.). *Anal.* Calcd. for $C_6H_6O_3N_4$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.84; H, 3.46; N, 29.96. Acetylation with Ac_2O on a water bath for 1 hr. gave diacetate (XXIV), yellow green needles, m.p. 183°. *Anal.* Calcd. for $C_{10}H_{10}O_5N_4$: C, 45.11; H, 3.79; N, 21.05. Found: C, 45.37; H, 3.84; N, 21.05.

ii) A mixture of 1.24 g. (0.01 mole) of XXII, 400 mg. (0.01 mole) of $NaNH_2$, and 1.15 g. (0.01 mole) of amyl nitrite were treated in the same way as described above. After evaporation of liq. NH_3, a small amount of H_2O was added and the solution was extracted with $CHCl_3$. The solvent was evaporated and the deposited crystals were collected and washed with petr. benzin to nearly colorless crystals (XXII), m.p. 115~116°. Yield, 410 mg., (34.1%). This was identical with the starting material by comparison of their IR spectra.

The H_2O soluble fraction was acidified with 6*N* HCl, and the deposited crystals (XXIII) were collected (210 mg., m.p. 224°(decomp.)), and from the filtrate, after evaporation of H_2O, 300 mg. (m.p. 216~217° (decomp.)) and 80 mg. (m.p. 190~195°(decomp.)) of XXIII were obtained. The total yield of XXIII was 590 mg. (33.5%). The compound (XXIII) did not gave pure sample by recrystallization alone, therefore XXIII was purified by conversion to diacetate, which was identical with XXIV obtained in i) by comparison of their IR spectra.

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Summary

The reaction of methylpyridazine N-oxides with amyl nitrite in the presence of sodium amide in liquid ammonia afforded the corresponding *syn*-aldoximes. These *syn*-aldoximes were isomerized to *anti*-aldoximes with hydrochloric acid or heating alone except the case of some aldoximes. The configuration of the aldoximes was confirmed by the infrared and nuclear magnetic resonance spectra.

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236. **Masaru Ogata**: Pyridazines. VII.*1 Synthesis of Cyanopyridazines.

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There are two reports on the synthesis of cyanopyridazines. Schmidt, *et al.*[1] obtained 4-cyano-3(2*H*)-pyridazinone derivatives, and recently Robba[2] obtained 3-cyano- and 4-cyano-pyridazines from the corresponding amides. Several methods are known for the direct introduction of cyano group into heteroaromatic ring.

In this paper, application of two of these methods, the reaction of benzoylchloride and potassium cyanide on N-oxides (method A)[3] and the reaction of potassium cyanide on quarternary salt of N-oxides (method B)[4] on pyridazine series is described.

With pyridazine 1-oxide (I), these reaction (method A and B) failed to obtain the objective compound, giving oily product. The method A on 3-chloropyridazine 1-oxide (II)[5] resulted in the recovery of the starting material, but the method B afforded the

Table I. 3-Cyanopyridazines

Compd. No.	Solvent of recrystn.	m.p. (°C)	Yield (%)	
			Method A	Method B
III	benzene-petr. benzin	94~95	~0	34.6
VI	〃	90~91	~2	35.0
X	〃	94~95	28.4	72.2
XII	〃	93~94	10.0	68.5
XIV	EtOH	184.5~5.5	41.6	57.1

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*1 Part VI. This Bulletin, **11**, 1517 (1963).
*2 Fukushima-ku, Osaka (尾形 秀).

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2) Max Robba: Ann. Chim. (Paris), **5**, 351 (1960); C. A., **56**, 5961 (1962).
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