UDC 547.852.2

7. Masaru Ogata and Hideo Kano: Pyridazines. I.*1 3-Methylpyridazine N-Oxides.

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Although N-oxidation of an unsymmetrical substituted pyridazine, such as 3-methylpyridazine (I), might yield two isomeric mono-N-oxides, i.e. 1-oxide II and 2-oxide III, the survey of the literature did not reveal any such examples.

In the present paper, the authors describe the separation of 3-methylpyridazine 1-oxide (II) and 2-oxide (III) from N-oxidation products of 3-methylpyridazine I. In addition, in order to compare the reactivity of these N-oxides, nitration and some other reactions of 3-methylpyridazine 1-oxide (II), 2-oxide (III) and some related derivatives were studied, and very interesting results were obtained.

In 1960, Kumagai[1] first described the N-oxidation of 3-methylpyridazine (I) with hydrogen peroxide in glacial acetic acid, yielding a mono-N-oxide as hygroscopic crystals. More recently, Nakagome[2] obtained the same N-oxide as crystals, m.p. 85~86° by Kumagai's procedure, and this N-oxide was proved to be identical with that obtained from 3-methyl-6-chloropyridazine N-oxide by catalytic reduction, proposing 2-oxide structure to the N-oxide on the basis of chemical and spectral evidences.

The present authors prepared the 3-methylpyridazine N-oxides according to the procedure of Kumagai.[1] By gas chromatographic procedure, the products gave two distinct peaks, whose relative area was about 3:1 as indicated in Fig. 1. This mixture was chromatographed on alumina, and the column was eluted with benzene and chloroform. The fraction eluted with benzene gave, after recrystallization from benzene, colorless prisms III, $C_5H_6ON_2$, m.p. 83~84°, UV: λ_{max}^{EtOH} mμ (log ε): 257 (4.00), 314 (3.68), IR: ν_{N-O} 1362 cm^{-1} (CS_2). The fraction eluted with chloroform gave, after recrystallization from benzene, very hygroscopic crystals II, $C_5H_6ON_2$, m.p. 68.5~69.5°, UV λ_{max}^{EtOH} mμ (log ε): 262 (4.03), 312 (3.72), IR: ν_{N-O} 1352 cm^{-1} (CS_2).

From the above-mentioned physical properties, it has become evident that these two compounds are two isomeric 3-methylpyridazine mono-N-oxides.

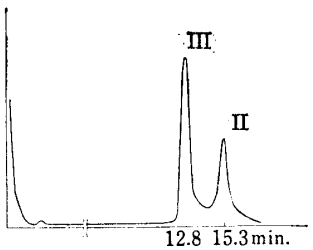

Fig. 1. Gas Chromatography of 3-Methylpyridazine N-Oxides

Conditions: Thermol-2(Shimadzu). 3 m. × 6 mm., column, at 180°, H_2 flow rate 200 cc./min.

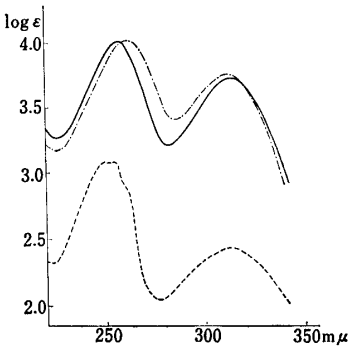

Fig. 2. Ultraviolet Absorption Spectra (in EtOH)

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*1 A brief report of this work was published as a Communication to the Editor in this Bulletin, **9**, 1017 (1961).

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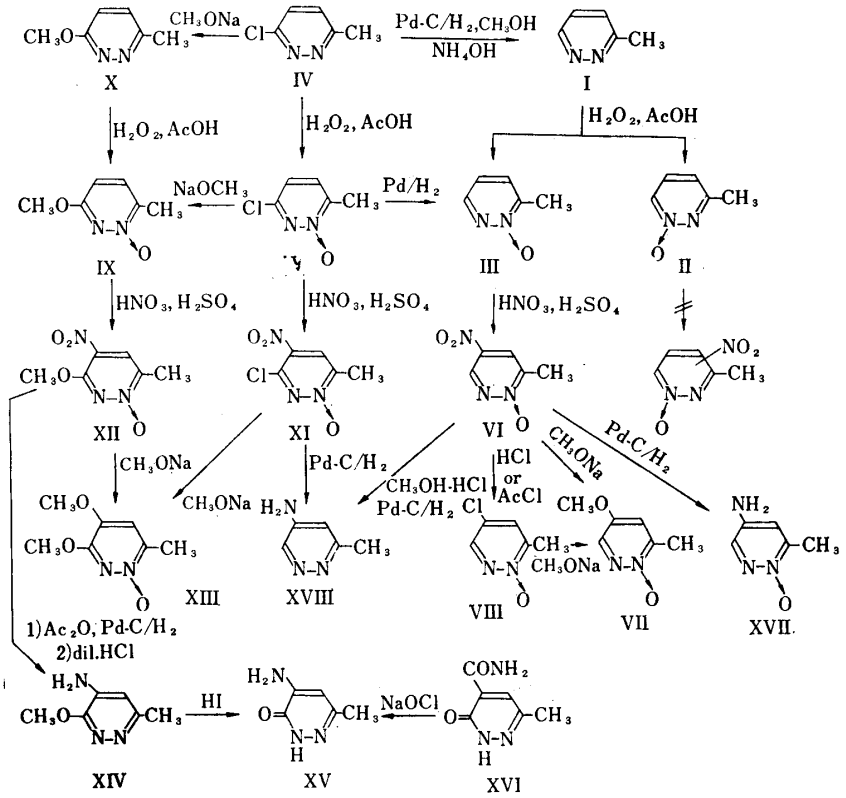
1) M. Kumagai: Nippon Kagaku Zasshi, **81**, 1148 (1960).

2) T. Nakagome: Yakugaku Zasshi, **81**, 1048 (1961).



Chrat 1.

Heating of 3-methyl-6-chloropyridazine (IV) with hydrogen peroxide in glacial acetic acid at 60° for 9 hours, gave 3-methyl-6-chloropyridazine 2-oxide (V).[2] In this case, the 3-methyl-6-chloropyridazine 2-oxide was confirmed to be the sole product by gas chromatography. Catalytic reduction of V with palladiumcarbon in hydrous methanolic ammonia solution gave 3-methylpyridazine 2-oxide, m.p. 83~84°, which was confirmed to be identical with III by mixed melting point determination and comparison of their infrared and ultraviolet absorption spectra. Consequently, the other 3-methylpyridazine N-oxide (II) is 1-oxide evidently. Further evidence for these structures will be provided with dipolemoments studies in Part III of this series.

In order to compare the reactivity of these N-oxide II and III, nitration of 3-methylpyridazine 1-oxide (II) and 2-oxide (III) were carried out, and very interesting result was obtained.

Nitration of 3-methylpyridazine 1-oxide (II) with fuming nitric acid in sulfuric acid could not be accomplished, and the starting material was recovered after being kept at 100° for 6 hours. On the other hand, by the same procedure, 3-methylpyridazine 2-oxide (III) gave mononitro compound VI, in good yield. In order to determine the structure of VI, following experiments were carried out. VI was converted to the corresponding methoxy compound VII with sodium methoxide, and by treating with acetyl chloride or hydrochloric acid to chloro compound VIII. VIII was not identical with 3-methyl-6-chloropyridazine 2-oxide (V),[2] and VII was not identical with 3-methyl-6-methoxypyridazine 2-oxide (IX)[2] derived from 3-methyl-6-chloropyridazine 2-oxide (V) or 3-methyl-6-methoxypyridazine (X) by N-oxidation. Hence the position of nitro group in VI is not 6.

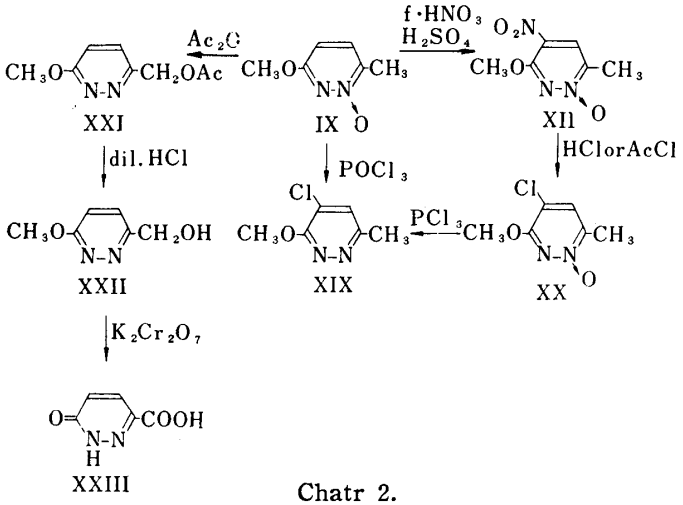
Nitration of 3-methyl-6-methoxypyridazine 2-oxide (IX) and 3-methyl-6-chloropyridazine 2-oxide (V) gave mononitro compounds XII and XI respectively. Treating with sodium methoxide, these nitro compounds XI and XII gave the same dimethoxy compound XIII. Reductive acetylation of XII with palladium-carbon in acetic anhydride gave

the corresponding acetamid compound which was hydrolyzed to amino compound XIV. Further hydrolysis of XIV by refluxing with hydriodic acid for 3 hours gave the 3(2*H*)-pyridazinone derivative XV, which was proved to be identical with 4-amino-6-methyl-3(2*H*)-pyridazinone obtained by Hofmann reaction of 3-oxo-6-methyl-2,3-dihydro-4-pyridazinecarboxamide (XVI).[3] From the abovementioned facts, the structure of mononitro compounds XI and XII were confirmed to be 3-methyl-5-nitro-6-chloropyridazine 2-oxide (XI) and 3-methyl-5-nitro-6-methoxypyridazine 2-oxide (XII) respectively.

Catalytic reduction of 3-methyl-5-nitro-6-chloropyridazine 2-oxide (XI) with palladium-carbon in absolute methanol gave 3-methyl-5-aminopyridazine (XVIII). Catalytic reduction of VI with palladium-carbon in methanol gave 3-methyl-monoaminopyridazine 2-oxide (XVII), whereas, with palladium-carbon in hydrous methanolic hydrochloric acid gave 3-methyl-monoaminopyridazine (XVIII), which was identical with XVIII derived from XI. Accordingly, the structure of VI was confirmed to be 3-methyl-5-nitropyridazine 2-oxide.

Treating with phosphoryl chloride of 3-methylpyridazine 1-oxide (II), 2-oxide (III) or 3-methyl-6-chloropyridazine 2-oxide (V), the starting materials were recovered or resinified.

While, 3-methyl-6-methoxypyridazine 2-oxide (IX) was treated with phosphoryl chloride to form monochloropyridazine derivative XIX. On the other hand, 3-methyl-5-nitro-methoxypyridazine 2-oxide (XII) was converted to 3-methyl-5-chloro-6-methoxypyridazine 2-oxide (XX) with acetyl chloride or hydrochloric acid, and XX was deoxygenated with phosphorus trichloride to 3-methyl-5-chloro-6-methoxypyridazine (XIX), which was identical with XIX from IX.



Chatr 2.

Reaction of acetic anhydride with 3-methylpyridazine 1-oxide (II), 2-oxide (III) or 3-methyl-6-chloropyridazine 2-oxide (V) could not be accomplished, and the starting materials were recovered. On the other hand, 3-methyl-6-methoxypyridazine 2-oxide (IX) was treated with acetic anhydride to give a compound (XXI), $C_8H_{10}O_3N_2$, m.p. 60°, whose ultraviolet absorption spectrum was very similar to 3-methyl-6-methoxypyridazine (X). Thus the compound was assumed to be 6-methoxy-3-pyridazine methanol acetate (XXI). XXI was hydrolyzed to the corresponding carbinol XXII, m.p. 53~54°, which was oxidized to known 6-oxo-1,6-dihydro-3-pyridazinecarboxylic acid (XXIII)[4] with potassium dichromate in sulfuric acid. Thus, XXI was confirmed to be 6-methoxy-3-pyridazine methanol acetate. In previous report,[2] Nakagome assigned the same structure

3) I. Satoda, N. Yoshida, K. Mogi : Yakugaku Kenkyū, **28**, 609 (1956).
4) R.F. Homer, Hilda Gregory, W.F. Overend and L.F. Wiggins : J. Chem. Soc., **1948**, 2195.

to XXI by obtaining the semicarbazone of formyl derivative from XXI by selenium dioxide oxidation.

Experimental*3

3-Methylpyridazine 1-Oxide (II) and 2-Oxide (III)——A mixture of 2.4 g. of 3-methylpyridazine (I), 15 cc. of glacial AcOH, and 7 cc. of 30% H_2O_2 was heated at 70° for 3 hr., further 7 cc. of 30% H_2O_2 was added, and again heated at the same temperature for 3 hr. To this solution, 15 cc. of water was added, AcOH was evaporated under reduced pressure, and this procedure was repeated twice. After neutralization with Na_2CO_3, the solution was extracted with $CHCl_3$, the $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and evaporated. The residue was dissolved in benzene and chromatographed on alumina (27 g.) and the column was eluted with benzene. The residue from the fraction eluted with benzene was recrystallized from benzene to colorless prisms, III, m.p. 83~84°. Yield, 630 mg. *Anal.* Calcd. for $C_5H_6ON_2$: C, 54.54; H, 5.49; N, 25.44. Found : C, 54.76; H, 5.60; N, 25.29. The residue from the fraction eluted with $CHCl_3$ was recrystallized from benzene to colorless prisms, II, m.p. 68.5~69.5°. Yield, 230 mg. *Anal.* Calcd. for $C_5H_6ON_2$: C, 54.54; H, 5.49; N, 25.44. Found : C, 54.59; H, 5.70; N, 25.78.

3-Methyl-6-chloropyridazine 2-Oxide (V)——A mixture of 1 g. of 3-methyl-6-chloropyridazine (IV), 4 cc. of glacial AcOH, and 2 cc. of 30% H_2O_2 was heated at 60° for 3 hr., further 2 cc. of 30% H_2O_2 was added, and again heated at the same temperature for 3 hr. To this solution, 2 cc. of water was added, AcOH was evaporated under reduced pressure, and this procedure was repeated. After neutralization with Na_2CO_3, the solution was extracted with $CHCl_3$, the $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and evaporated. The residue was recrystallized from benzene to colorless scales, m.p. 157~160°. Yield, 0.7 g. Repeated recrystallization from benzene gave colorless scales, m.p. 163~164°. *Anal.* Calcd. for $C_5H_5ON_2Cl$: C, 41.52; H, 3.46; N, 19.31. Found : C, 41.77; H, 3.67; N, 19.31. Found : C, 41.77; H, 3.67; N, 19.36.

Catalytic Reduction of 3-Methyl-6-chloropyridazine 2-Oxide (V) : Formation of 3-Methylpyridazine 2-Oxide (III)——A mixture of 0.7 g. of V, 10 cc. of MeOH, 1 cc. of 28% NH_4OH and 0.1 g. of 10% Pd-C was subjected to hydrogenation. One mole of H_2 per mole of V was absorbed. The catalyst was filtered, and MeOH was evaporated. The residue was dissolved in H_2O, extracted with $CHCl_3$, and $CHCl_3$ was evaporated. The residue was recrystallized from benzene to colorless prisms, m.p. 70~75°, yield, 450 mg. This product was recrystallized repeatedly from benzene to colorless prisms, m.p. 83~84°. This was identified with III derived from I by comparison of their IR spectra.

3-Methyl-5-nitropyridazine 2-Oxide (VI)——A solution of 500 mg. of III dissolved in 2 cc. of conc. H_2SO_4 was cooled, 0.5 cc. of fuming HNO_3 was added slowly and the mixture was heated on a water bath for 6 hr. The mixture was poured onto ice, extracted with $CHCl_3$ and $CHCl_3$ was evaporated. The residue was recrystallized from benzene to yellow needles, m.p. 118~119°. Yield, 610 mg. *Anal.* Calcd. for $C_5H_5O_3N_3$: C, 38.71; H, 3.25; N, 27.09. Found : C, 38.95; H, 3.42; N, 27.12.

3-Methyl-5-methoxypyridazine 2-Oxide (VII)——i) From VI : To a solution of MeONa, prepared from 100 mg. of Na and 10 cc. of MeOH, 200 mg. of VI was added and the mixture was refluxed for 1 hr. After evaporation of MeOH, the residue was added to sat. NaCl solution and extracted with $CHCl_3$. Evaporation of the solvent gave crystals, which were recrystallized from benzene to colorless needles, m.p. 103~104°. Yield, 70 mg. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found : C, 51.40; H, 5.77; N, 20.05.

ii) From VIII : To a solution of MeONa, prepared from 10 mg. of Na and 5 cc. of MeOH, 60 mg. of VIII was added and the mixture was refluxed for 1 hr. After evaporation of MeOH, the residue was extracted with benzene. Evaporation of the solvent gave crystals, which were recrystallized from benzene to colorless needles, m.p. 103~104°. Yield, 20 mg. This was identified with VII derived from VI by comparison of their IR spectra.

3-Methyl-5-chloropyridazine 2-Oxide (VIII)——i) Five hundred milligrams of VI was added to 5 cc. of AcCl slowly with cooling, and the mixture was allowed to stand for 2 hr. at room temperature, and AcCl was removed under reduced pressure at room temperature. The residue was treated with MeOH to give yellow crystals, m.p. 212~214°(decomp.). Yield, 150 mg. Repeated recrystallization from MeOH gave colorless prisms, m.p. 220°(decomp.). *Anal.* Calcd. for $C_5H_4O_2N_3Cl$: C, 34.68; H, 2.31; N, 24.33. Found : C, 34.64; H, 2.55; N, 24.07. The structure of this compound has not been determined. The filtrate was chromatographed on alumina, and the column was eluted with $CHCl_3$. Eluted product was recrystallized from benzene to pale green prisms VIII, m.p. 166~167°. Yield, 50 mg. *Anal.* Calcd. for $C_5H_5ON_2Cl$: C, 41.38; H, 3.42; N, 19.31. Found : C, 41.58; H, 3.36; N, 19.98.

ii) 100 mg. of VI was added to 1 cc. of conc. HCl slowly and with cooling, and the mixture was heated

*3 M.p.s were determined on a Kofler-Block "Monoscope IV" and are uncorrected,

on a water bath for 2 hr. The mixture was poured onto ice, extracted with $CHCl_3$ and $CHCl_3$ was evaporated. The residue was recrystallized from benzene to pale green prisms, m.p. 167~168°. Yield, 50 mg. *Anal.* Calcd. for $C_5H_5ON_2Cl$: C, 41.38; H, 3.42; N, 19.31. Found : C, 41.67; H, 3.70; N, 19.61. This sample was proved to be identical with that obtained in i) by comparison of their IR spectra.

3-Methyl-6-methoxypyridazine 2-Oxide (IX)——i) From V : To a solution of MeONa, prepared from 50 mg. of Na and 15 cc. of MeOH, 500 mg. of V was added and the mixture was refluxed for 1 hr. After evaporation of MeOH, the residue was dissolved in H_2O and extracted with $CHCl_3$. Removal of the solvent left crude crystals, which were recrystallized from benzene to colorless plates, m.p. 95~96°. Yield, 360 mg. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found : C, 51.62; H, 5.71; N, 19.37.

ii) From X : A mixture of 3 g. of X, 18 cc. of glacial AcOH, and 6 cc. of 30% H_2O_2 was added at 70° for 3 hr., further 6 cc. of 30% H_2O_2 was added, and again heated at the same temperature for 3 hr. To this solution, 10 cc. of water was added and AcOH was evaporated under reduced pressure. This procedure was repeated. After neutralization with Na_2CO_3, the solution was extracted with $CHCl_3$, and the $CHCl_3$ layer was evaporated. The residue was recrystallized from petr. benzin to 2.5 g. of colorless plates, m.p. 95~96°. This was identified with IX derived from V by comparison of their IR spectra.

3-Methyl-5-nitro-6-chloropyridazine 2-Oxide (XI)——To a solution of 500 mg. of V dissolved in 2 cc. of conc. H_2SO_4, 0.5 cc. of fuming HNO_3 was added slowly with cooling, and the mixture was heated on a boiling water bath for 6 hr. The mixture was poured onto ice, extracted with $CHCl_3$ and $CHCl_3$ was evaporated. The residue was recrystallized from benzene to yellow needles, m.p. 100~103°. Yield, 210 mg. This product was recrystallized form benzene to yellow needles, m.p. 103~103.5°. *Anal.* Calcd. for $C_5H_4O_3N_3Cl$: C, 31.66; H, 2.12; N, 22.17. Found : C, 31.49; H, 2.30; N, 22.05.

3-Methyl-5-nitro-6-methoxypyridazine 2-Oxide (XII)——To a solution of 200 mg. of IX dissolved in 1 cc. of conc. H_2SO_4, 0.2 cc. of fuming HNO_3 was added slowly with cooling, and the mixture was heated at 60° for 1 hr. The mixture was poured onto ice, extracted with $CHCl_3$ and the $CHCl_3$ was evaporated. The residue was recrystallized from MeOH to pale green prisms, m.p. 101~101.5°. Yield, 140 mg. *Anal.* Calcd. for $C_6H_7O_4N_3$: C, 38.92; H, 3.81; N, 22.70. Found : C, 39.33; H, 4.10; N, 22.84.

3-Methyl-5,6-dimethoxypyridazine 2-Oxide (XIII)——i) From XI : To a solution of MeONa, prepared from 50 mg. of Na and 5 cc. of MeOH, 200 mg. of XI was added and the mixture was refluxed for 1 hr. After evaporation of MeOH, the residue was dissolved in H_2O and extracted with $CHCl_3$ and $CHCl_3$ was evaporated. The residue was recrystallized from benzene to colorless needles, m.p. 150~151°. Yield, 50 mg. *Anal.* Calcd. for $C_7H_{10}O_3N_2 \cdot \frac{1}{2}H_2O$: C, 46.92; H, 6.17; N, 15.64; H_2O, 5.03. Found : C, 47.42; H, 6.17; N, 15.68; H_2O, 4.06.

ii) From XII : To a solution of MeONa, prepared from 100 mg. of Na and 10 cc. of MeOH, 500 mg. of XII was added and the mixture was refluxed for 1 hr. After evaporation of MeOH, the residue was dissolved in H_2O and extracted with $CHCl_3$ and $CHCl_3$ was evaporated. The residue was recrystallized from benzene to colorless needles, m.p. 150~151°. Yield, 350 mg. This was identified with XIII derived from XI by comparison of their IR spectra.

3-Methyl-5-amino-6-methoxypyridazine (XIV)——A mixture of 500 mg. of XII, 10 cc. of Ac_2O and 500 mg. of 10% Pd-C was subjected to hydrogenation. Four moles of H_2 per mole of XII were absorbed. The catalyst was filtered, and the solution was evaporated. To the residue was added 5 cc. of 6*N* HCl, and heated on a water bath for 10 min. After neutralization of the solution with NaOH, the solution was saturated with NaCl. This was extracted with $CHCl_3$, and evaporated, the residue recrystallized from AcOEt to colorless prisms, m.p. 156~158°. Yield, 180 mg. This product was recrystallized repeatedly from AcOEt to colorless prisms, m.p. 159~160°. *Anal.* Calcd. for $C_6H_9ON_3$: C, 51.78; H, 6.52; N, 30.20. Found : C, 51.74; H, 6.67; N, 30.53.

4-Amino-5-methyl-3(2*H*)-pyridazinone (XV)——i) From XIV : A solution of 150 mg. of XIV in 2 cc. of conc. HI was refluxed to 3 hr. After cool, the solution was neutralized with $NaHCO_3$ to deposit crystals, which were recrystallized from water to colorless prisms, m.p. 260~261°. Yield, 60 mg. *Anal.* Calcd. for $C_5H_7ON_3$: C, 47.99; H, 5.64; N, 33.58. Found : C, 47.69; H, 5.78; N, 34.07.

ii) From XVI : A suspension of 1.7 g. of XVI in 30 cc. of 5% NaOH was chilled and 10 g. of 13.4% NaOCl was added dropwise under stirring. After a clear solution was obtained, the solution was added dropwise into 10 cc. of boiling water. After 20 min., the solution was cooled, neutralized with HCl, and then basified with NH_4OH. The deposited crystals were collected, washed with water, and recrystallized from water to colorless prisms, m.p. 259~260°. Yield, 1.0 g. *Anal.* Calcd. for $C_5H_7ON_3$: C, 47.99; H, 5.64; N, 33.58. Found : C, 47.74; H, 5.76; N, 33.45. This was identified with XV derived from XIV by comparison of their IR spectra.

3-Methyl-5-aminopyridazine 2-Oxide (XVII)——A mixture of 300 mg. of VI, 20 cc. of MeOH, and 0.2 g. of 10% Pd-C was subjected to hydrogenation. Three moles of H_2 per mole of VI were absorbed.

The catalyst was filtered and MeOH was evaporated. The residue was recrystallized from AcOEt-MeOH affording 150 mg. of colorless needles, m.p. 258°. *Anal.* Calcd. for $C_5H_7ON_3$: C, 47.99; H, 5.64; N, 33.58. Found : C, 47.75; H, 5.81; N, 33.47.

3-Methyl-5-aminopyridazine (XVIII)——From XI : A mixture of 500 mg. of XI, 5 cc. of abs. MeOH and 0.2 g. of 10% Pd-C was subjected to hydrogenation. Five moles of H_2 per mole of XI were absorbed. The catalyst was filtered, and MeOH was evaporated. The residue was neutralized with dil. NH_4OH, and deposited crystals were collected. 50 mg. of colorless prisms, m.p. 117~120°, were obtained. Recrystallization from hot water did not alter the melting point. After thorough drying at 70° for 3 hr. in a vacuum this substance melted at 162~163°. *Anal.* Calcd. for $C_5H_7N_3 \cdot \frac{1}{2}H_2O$: C, 50.83; H, 6.83; N, 35.57. Found : C, 50.80; H, 7.08; N, 35.06. From VI : A mixture of 500 mg. of VI, 10 cc. of MeOH, 4 cc. of methanolic HCl and 0.4 g. of 10% Pd-C was subjected to hydrogenation. Four moles of H_2 per mole of VI were absorbed. The catalyst was filtered, and MeOH was evaporated. The residue was neutralized with dil. NH_4OH, and deposited crystals were collected. Colorless prisms (110 mg.), m.p. 117~120°, were obtained. Recrystallization from hot water did not alter the melting point. After thorough drying at 70° for 3 hr. in a vacuum this substance melted at 162~163°. *Anal.* Calcd. for $C_5H_7N_3 \cdot \frac{1}{2}H_2O$: C, 50.83; H, 6.83; N, 35.57; H_2O, 7.61. Found : C, 50.81; H, 6.90; N, 35.36; H_2O, 7.90. This was identified with XVIII derived from XI by comparison of their IR spectra.

3-Methyl-5-chloro-6-methoxypyridazine (XIX)——From IX : To a cold solution of 1 g. of IX dissolved in 10 cc. of $CHCl_3$, 2 g. of $POCl_3$ was added, the mixture refluxed for 30 min. The solvent was removed *in vacuo*. The residue was neutralized with Na_2CO_3 with cooling, and extracted with $CHCl_3$. $CHCl_3$ was distilled and the residue was dissolved in benzene. The benzene solution was passed through a column of alumina. The colorless residue so obtained was recrystallized from petr. benzin to yield 650 mg. of colorless prisms, m.p. 121~122°. *Anal.* Calcd. for $C_6H_7ON_2Cl$: C, 45.44; H, 4.44; N, 17.66. Found : C, 45.17; H, 4.60; N, 17.92. From XX : To a cold solution of 400 mg. of XX dissolved in 10 cc. of $CHCl_3$, 900 mg. of PCl_3 was added. After being allowed to stand for 24 hr., the reaction mixture was poured onto ice, neutralized with Na_2CO_3, and extracted with $CHCl_3$. The solvent was distilled off and the residue was dissolved in benzene and chromatographed on alumina. The colorless crystals eluted with benzene were recrystallized from petr. benzin affording 150 mg. of colorless prisms, m.p. 121~122°. This was identical with XIX derived from IX by comparison of their IR spectra. The colorless crystals eluted with $CHCl_3$ were recrystallized from petr. benzin giving 20 mg. of starting materials.

3-Methyl-5-chloro-6-methoxypyridazine (XX)——i) Five hundred milligrams of XII was added to 5 cc. of AcCl slowly and with cooling, and the mixture was allowed to stand for 1 hr. at room temperature. AcCl was removed under a reduced pressure at room temperature. MeOH was added to the residue, causing yellow crystals to separate, m.p. 206~207°(decomp.). Yield, 160 mg. This product was recrystallized repeatedly from MeOH to yellow needles, m.p. 220°(decomp.). *Anal.* Calcd. for $C_6H_6O_3N_3Cl$: C, 35.29; H, 2.94; N, 20.59. Found : C, 35.54; H, 3.07; N, 20.68. The structure of this compound has not been determined. The filtrate was chromatographed on alumina, and the column was eluted with $CHCl_3$. Eluted product was recrystallized from benzene to colorless needles XX, m.p. 138~139°. Yield, 70 mg. *Anal.* Calcd. for $C_6H_7O_2N_2Cl$: C, 41.14; H, 4.00; N, 16.00. Found: C, 41.10; H, 4.13; N, 16.16.

ii) Two hundred milligrams of XII was added to 2 cc. of conc. HCl slowly and with cooling, and the mixture was heated on a boiling water bath for 2 hr. The mixture was poured onto ice, extracted with $CHCl_3$, was distilled off. The residue was recrystallised from benzene to colorless needles, m. p. 139~140°. Yield, 90 mg. This was identical with XX derived from i) by comparison of their IR spectra.

6-Methoxy-3-pyridazinemethanol Acetate (XXI)——A mixture of 2 g. of IX and 10 cc. of Ac_2O was refluxed for 2 hr. and evaporated to dryness under reduced pressure and the residue was extracted with cyclohexane to colorless needles, m.p. 59~60°. Yield, 1.1 g. *Anal.* Calcd. for $C_8H_{10}O_3N_2$: C, 52.74; H, 5.53; N, 15.38. Found : C, 53.02; H, 5.59; N, 15.55.

6-Methoxy-3-pyridazinemethanol (XXII)——A mixture of 500 mg. of XXI and 10 cc. of 3*N* HCl was heated on a water bath for 30 min., and neutralized with Na_2CO_3, then evaporated to dryness. The residue was extracted with EtOH, and EtOH was evaporated. The residue was recrystallized from benzene to colorless prisms, m.p. 48~50°. Yield, 150 mg. This product was recrystallized repeatedly from benzene to colorless prisms, m.p. 53~54°. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found : C, 51.47; H, 6.00; N, 19.79.

6-Oxo-1,6-dihydro-3-pyridazine Carboxylic Acid (XXIII)——A mixture of 1.4 g. of XXI and 20 cc. of 3*N* HCl was heated on a water bath for 30 min., then neutralized with Na_2CO_3. After evaporation of the solvent, the residue was extracted with EtOH. EtOH was distilled off, and to the residue was added 5 cc. of conc. H_2SO_4 containing 2 g. of $K_2Cr_2O_7$ with cooling. After being stirred at 50° for 3 hr., the mixture was poured onto ice and allowed to stand overnight. The deposited crystals

(150 mg., m.p. 260°) were collected. Recrystallization from hot water gave colorless prisms, m.p. 260°. *Anal.* Calcd. for $C_5H_4O_3N_2 \cdot H_2O$: C, 37.98; H, 3.83; N, 17.72. Found : C, 38.48; H, 4.01; N, 17.91. This was identified with an authentic sample prepared according to the method of Homer *et al.*[4] by comparison of their IR spectra.

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Summary

3-Methylpyridazine 1-oxide (II) and 2-oxide (III) were separated from the N-oxidation products of 3-methylpyridazine (I). Nitration of II could not be accomplished, but III gave 3-methyl-mononitropyridazine 2-oxide (VI) in good yield. The nitro group of VI was proved to be in 5-position. Reaction of 3-methyl-6-methoxypyridazine 2-oxide (IX) with phosphoryl chloride gave 3-methyl-5-chloro-6-methoxypyridazine (XIX) and with acetic anhydride gave 6-methoxy-3-pyridazinemethanol acetate (XXI).

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8. Masaru Ogata and Hideo Kano : Pyridazines. II.[*1]
4-Methylpyridazine N-Oxides.

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In the first paper of this series,[*1] it was reported that N-oxidation of 3-methylpyridazine gave two isomeric mono-N-oxides, i. e. 3-methylpyridazine 1-oxide (I) and 2-oxide (II). Some reactions of these N-oxides were also investigated. It seemed of interest to study the preparation of other two possible, but unknown methylpyridazine mono-N-oxides, 4-methylpyridazine 1-oxide (IV) and 2-oxide (V).

The present paper deals with the synthesis and nitration of these two N-oxides.

Heating of 4-methylpyridazine (III) with hydrogen peroxide in glacial acetic acid at 70° for 6 hours, gave a product. By gas chromatographic procedure, the product gave two distinct peaks, one of which was much larger than the other as indicated in Fig. 1. There was no evidence of decomposition of the product on the column, so the product must be a mixture of two compounds. A small amount of crystals was separated from the reaction product, which was recrystallized from the benzene to yield a mono-N-oxide IV, m.p. 83~84°, UV λ_{max}^{EtOH} mμ (log ε) : 266 (4.05), 314 (3.61), IR : ν_{N-O} 1328 cm^{-1} (CS_2). The filtrate was chromatographed on alumina and the column was eluted with benzene and chloroform. The fraction eluted with benzene gave, after distillation under reduced pressure, another mono-N-oxide V, b.p_4 135°, UV λ_{max}^{EtOH} mμ (log ε) : 265 (4.01), 305 (3.52), IR : ν_{N-O} 1322 cm^{-1} (CS_2).

In order to deduce the structure of these isomeric 4-methylpyridazine N-oxides, the following experiments were carried out. 4-Methyl-3(2*H*)-pyridazinone (VIII), m.p. 165~166°, and 5-methyl-3(2*H*)-pyridazinone (IX), m.p. 160~161°, were synthesized according to the procedure of Takabayashi.[1] The melting point of VIII did not agree with

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*1 Part I : This Bulletin, **11**, 29 (1963).
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1) N. Takabayashi : This Bulletin, **5**, 229 (1957).