

Studies on Pyridazines.<sup>1)</sup> X.<sup>2)</sup> Reactivity of 3-Hydroxypyridazine  
1-Oxides. (2).<sup>3)</sup> Halogenation and Nitration  
of 3-Hydroxypyridazine 1-Oxides

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3-Hydroxypyridazine 1-oxide (I) and its methyl homologs (II), (III), and (IV) were submitted to electrophilic substitutions such as nitration and halogenation. Due to the additional polar effect of both N-oxide and hydroxyl groups, introduction of nitro group and halogen in 4- and/or 6-positions was successfully concluded.

By heating with potassium hydrosulfide, nucleophilic substitution of the brominated compounds (XXXI and XXXVI) was also carried out, affording mercapto compounds (XXXII and XXXVII).

Similar to pyridine- and quinoline N-oxides, pyridazines are known to become reactive towards electrophilic substitution by N-oxidation, and many works have been reported on nitration of their N-oxides.<sup>5)</sup>

Furthermore, hydroxypyridine- and hydroxyquinoline N-oxides, which have functional groups of both N-oxide and hydroxyl group on the ring, are well known to exhibit phenol-like reactivity and undergo electrophilic substitution reactions such as nitration and halogenation.<sup>6)</sup>

In a previous paper,<sup>3)</sup> we examined bromination and acid- and base-catalysed deuteration of 3-hydroxypyridazine 1-oxide (I) and found that 4- and 6-positions, which are each other *para* and *ortho* positions to the N-oxide and hydroxyl groups, are sensitive to both electro- and nucleo-philic substitution reactions.

This report deals with nitration and halogenation of I and its methyl homologs, and introduction of nitro group and halogen in 4- and/or 6-positions was successfully concluded.

We have already reported<sup>3)</sup> that while non-oxygenated 3-hydroxypyridazine resisted to halogenation, N-oxygenated 3-hydroxypyridazine 1-oxide (I) was, owing to the additional polar effect of N-oxide and hydroxyl groups, easily brominated, affording 4,6-dibromo-3-hydroxypyridazine 1-oxide (V) and reaction of V with potassium hydrosulfide gave a corresponding dimercapto compound (VI).

Bubbling chlorine gas into an aqueous solution of I gave almost quantitatively 4,6-dichloro-3-hydroxypyridazine 1-oxide (VII),<sup>7)</sup> mp 219°, the structure of which is verified by the fact that this was identical with an alkaline hydrolysis product of 3-methoxy-4,6-

1) The title "Syntheses of Pyridazine Derivatives" is converted to this title hereafter.

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3) Part VII. (1): *Chem. Pharm. Bull.* (Tokyo), **15**, 1411 (1967).

4) Location: *Hatanodai, Shinagawa-ku, Tokyo*.

5) a) T. Itai and H. Igeta, *Yakugaku Zasshi*, **74**, 1195 (1954); b) H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **8**, 550 (1960); c) H. Kano, M. Ogata, H. Watanabe, and I. Ishizuka, *ibid.*, **9**, 1017 (1961); d) T. Itai and S. Natsume, *ibid.*, **10**, 603 (1962); e) *Idem*, *ibid.*, **11**, 83 (1963); f) T. Horie, *ibid.*, **11**, 1157 (1963); g) T. Nakagome, *Yakugaku Zasshi*, **82**, 1005 (1962).

6) E. Ochiai, "Aromatic Amine Oxides," Elsevier, Amsterdam, 1967.

7) Melting points were uncorrected.

dichloropyridazine 1-oxide (IX), mp 148—149°, obtained by heating 3-methoxy-4,6-dinitro-pyridazine 1-oxide (VIII)<sup>5a)</sup> with hydrochloric acid.

Nitration of I in a mixture of fuming nitric acid and sulfuric acid, afforded 3-hydroxy-4-nitropyridazine 1-oxide (X), mp 125°, in 30% yield. Treatment of 3-methoxy-4-nitropyridazine 1-oxide (XII)<sup>5a)</sup> with hydrochloric acid afforded 3-methoxy-4-chloropyridazine 1-oxide

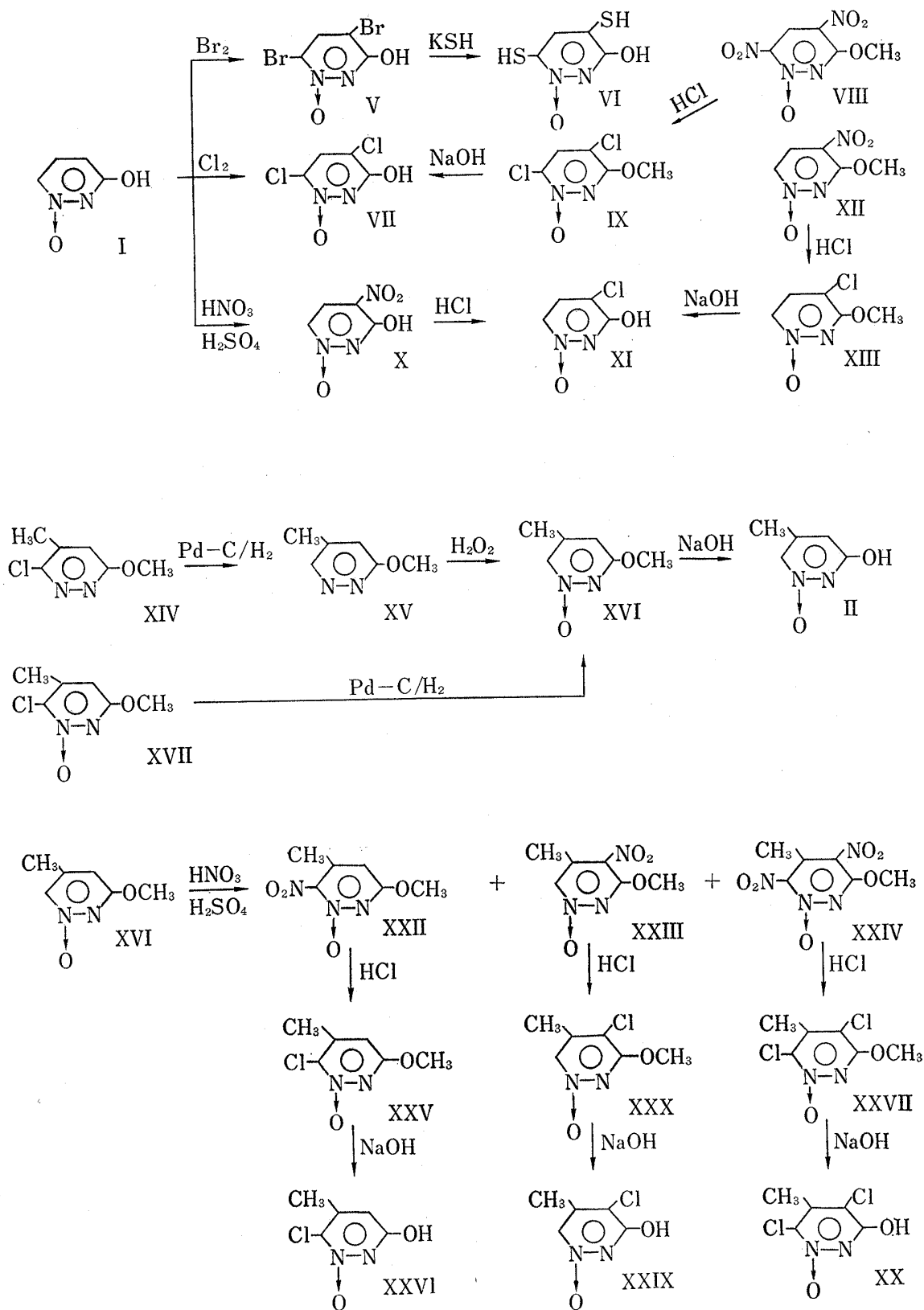


Chart 1

(XIII), mp 120°, which was then hydrolysed with aqueous sodium hydroxide to 3-hydroxy-4-chloropyridazine 1-oxide (XI), mp 212—213°, identical with the compound obtained by heating X with hydrochloric acid. In the case of nitration, 6-nitro and 4,6-dinitro compounds were not isolated.

Next, 3-hydroxy-5-methylpyridazine 1-oxide (II), in which 4- and 6-positions are vacant, was submitted to electrophilic substitution reaction. Synthesis of II was carried out by hydrolysis of 3-methoxy-5-methylpyridazine 1-oxide (XVI) with aqueous sodium hydroxide, which was obtained by dechlorination of 3-methoxy-5-methyl-6-chloropyridazine (XIV)<sup>59)</sup> with Pd-charcoal/H<sub>2</sub> in aqueous methanolic ammonia solution and subsequent N-oxidation or dechlorination of 3-methoxy-5-methyl-6-chloropyridazine 1-oxide (XVII).<sup>59)</sup>

Bromination of II provided 3-hydroxy-4,6-dibromo-5-methylpyridazine 1-oxide (XVIII), mp 240°, which was treated with potassium hydrosulfide to give dimercapto compound (XIX), mp 180—182°. Similar result was obtained by chlorination of II, yielding 4,6-dichloro compound (XX), mp 234°, almost quantitatively.

Nitration of II in a mixture of fuming nitric acid and sulfuric acid gave 4-nitro compound (XXVIII), mp 191—192°, in 20% yield. The structures of these reaction products were elaborated by the following facts.

Nitration of 3-methoxy-5-methylpyridazine 1-oxide (XVI) with fuming nitric acid and sulfuric acid gave three kinds of products, 6-nitro compound (XXII), mp 113—115°, 4-nitro compound (XXIII), mp 148—149°, and 4,6-dinitro compound (XXIV), mp 175—177°, in 13%, 30%, and 2.5% yields respectively. Each of them was treated with hydrochloric acid to give corresponding chloro compounds, (XXV), (XXX), and (XXVII). The compound (XXV) was identical with the N-oxidation product of 3-methoxy-5-methyl-6-chloropyridazine by the method given by Nakagome in the literature,<sup>59)</sup> indicating to be 3-methoxy-5-methyl-6-chloropyridazine 1-oxide. Consequently, another monochloro compound (XXX) was proved inevitably to be 3-methoxy-5-methyl-4-chloropyridazine 1-oxide.

Hydrolysis of dichloro compound (XXVII) with aqueous sodium hydroxide gave a hydroxyl compound (XX), which was identical with the direct chlorination product of II. Treatment of mononitro compound (XXVIII), obtained by nitration of II, with hydrochloric acid gave a chloro compound (XXIX), mp 232°, which was identical with the hydrolysis product of 3-methoxy-5-methyl-4-chloropyridazine 1-oxide (XXX) with aqueous sodium hydroxide, but was not with 6-chloro compound (XXVI).

In the case of 3-hydroxy-4-methylpyridazine 1-oxide (III), in which 4-position is already occupied by methyl group, electrophilic substitution took place at 6-position.

Bromination and chlorination of III afforded 6-bromo-3-hydroxy-4-methylpyridazine 1-oxide (XXXI), mp 158°, and 6-chloro-3-hydroxy-4-methylpyridazine 1-oxide (XXXIII), mp 204°, respectively, in somewhat lower yield compared with the case of I and II.

Nitration of III gave 3-hydroxy-4-methyl-6-nitropyridazine 1-oxide (XXXV), mp 179°, in 30% yield. The nitro compound was treated with hydrochloric acid to give a chloro compound, which is identical with the direct chlorination product (XXXIII) of III. Structure of XXXIII was proved by the identity with the hydrolysis product of 3-methoxy-4-methyl-6-chloropyridazine 1-oxide (XXXIV)<sup>59)</sup> with aqueous sodium hydroxide.

Bromination of IV, in which 6-position is occupied by methyl group, afforded 3-hydroxy-4-bromo-6-methylpyridazine 1-oxide (XXXVI), mp 205—206°, and by chlorination, 3-hydroxy-4-chloro-6-methylpyridazine 1-oxide (XXXVIII), mp 219°, was obtained.

Nitration of IV yielded 4-nitro compound (XL), mp 200°, in 40% yield. This nitro compound was treated with hydrochloric acid to give a chloro compound, which is identical with 3-hydroxy-4-chloro-6-methylpyridazine 1-oxide (XXXVIII), derived from 3-methoxy-4-chloro-6-methylpyridazine 1-oxide (XXXIX)<sup>8)</sup> by hydrolysis with aqueous sodium hydroxide.

8) M. Ogata and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 29 (1963).

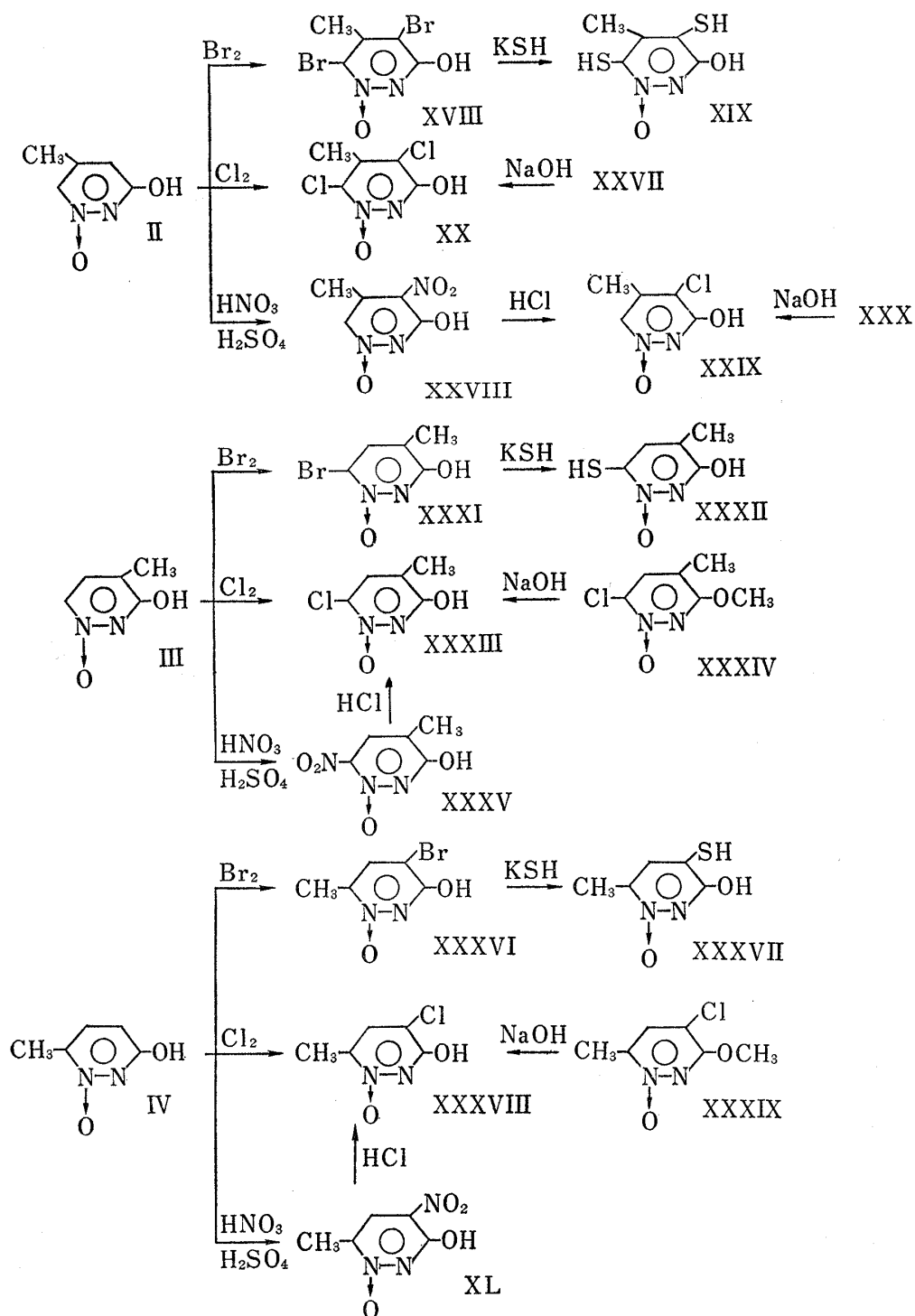


Chart 2

The structures of bromination products (V, XVIII, XXXI and XXXVI) were elucidated by the fact that their patterns of nuclear magnetic resonance (NMR) spectra were almost the same as those of chlorination products (VII, XX, XXXIII, and XXXVIII) respectively.

Though some of the structures of above mentioned products were also determined by analyses of their NMR spectra, the details on the spectra will be published separately in a following paper.

## Experimental

**3-Hydroxy-4,6-dichloropyridazine 1-Oxide (VII)**—a) Chlorination of 3-Hydroxypyridazine 1-Oxide (I): To a water solution of 500 mg of I, chlorine gas was bubbled until no more precipitate was produced. Collect the precipitate, and recrystallized from MeOH to colorless needles, mp 223° (decomp.). Yield 450 mg. *Anal.* Calcd. for  $C_4H_2O_2N_2Cl_2$ : C, 26.54; H, 1.11; N, 15.48. Found: C, 26.63; H, 1.15; N, 15.69.

b) Hydrolysis of 3-Methoxy-4,6-dichloropyridazine 1-Oxide (IX): A mixture of 100 mg of IX, 3 ml of MeOH, and 5 ml of 5% aq. NaOH was heated on a water bath at 80° for 0.5 hr. After cool, the reaction mixture was made acidic with 10% HCl and evaporated to dryness *in vacuo*. The residue was extracted with AcOEt while hot. After removal of AcOEt, the solid was recrystallized from MeOH to crystals, mp 223° (decomp.). Yield 60 mg, identical with the direct chlorination product by mixed fusion.

**3-Methoxy-4,6-dichloropyridazine 1-Oxide (IX)**: To 200 mg of VIII, 5 ml of conc. HCl was added and the mixture was heated at 80–90° for 2 hr. The mixture was concentrated to a small volume *in vacuo*, made alkaline with  $NaHCO_3$  solution and extracted with  $CHCl_3$ . After removal of solvent, the residue was recrystallized from MeOH to colorless needles, mp 148–149°. Yield 110 mg. *Anal.* Calcd. for  $C_5H_4O_2N_2Cl_2$ : C, 30.79; H, 2.07; N, 14.37. Found: C, 30.58; H, 2.15; N, 14.51.

**Nitration of 3-Hydroxypyridazine 1-Oxide (I): Formation of 3-Hydroxy-4-nitropyridazine 1-Oxide (X)**: To a solution of 1.5 g of I dissolved in 2 ml of  $H_2SO_4$ , 1 ml of fum.  $HNO_3$  was added and the mixture was heated at 70° for 8 hr. After cool, the reaction mixture was poured onto ice, and saturated  $Ba(NO_3)_2$  solution was added until no more precipitate was produced. The precipitate was removed by centrifugation, and water layer was evaporated to dryness *in vacuo*, and extracted with iso-PrOH. After removal of iso-PrOH, the residue was recrystallized from iso-PrOH to crystals, mp 124–126°. Yield 580 mg. *Anal.* Calcd. for  $C_4H_3O_4N_3$ : C, 30.58; H, 1.93; N, 26.75. Found: C, 30.81; H, 2.08; N, 26.45.

**3-Methoxy-4-chloropyridazine 1-Oxide (XIII)**: To 100 mg of XII, was added 2 ml of conc. HCl and the mixture was heated at 80–90° on a water bath. The reaction mixture was then treated similarly as described in the formation of IX from VIII. The residue was recrystallized from MeOH to crystals, mp 120–121°. Yield 60 mg. *Anal.* Calcd. for  $C_5H_5O_2N_2Cl$ : C, 37.40; H, 3.14; N, 17.46. Found: C, 37.32; H, 3.10; N, 17.35.

**3-Hydroxy-4-chloropyridazine 1-Oxide (XI)**—a) Formation from 3-Hydroxy-4-nitropyridazine 1-Oxide (X): To 80 mg of X was added 2 ml of conc. HCl and the mixture was heated at 80–90° for 2.5 hr. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was extracted with AcOEt while hot. After removal of AcOEt, the solid was recrystallized from MeOH–AcOEt to crystals, mp 212–213°. Yield 35 mg. *Anal.* Calcd. for  $C_4H_3O_2N_2Cl$ : C, 32.80; H, 2.07; N, 19.13. Found: C, 32.98; H, 1.89; N, 19.10.

b) Formation from 3-Methoxy-4-chloropyridazine 1-Oxide (XIII): A mixture of 50 mg of XIII, 1 ml of MeOH, and 3 ml of 5% aq. NaOH was heated at 80° on a water bath for 0.5 hr. After cool, the mixture was made acidic with 10% aq. HCl and evaporated to dryness *in vacuo*. The residue was extracted with AcOEt while hot. After removal of solvent, the solid was recrystallized from MeOH–AcOEt to crystals, mp 212–213°. Yield 20 mg, identical with the compound obtained from (X) by mixed fusion.

**3-Methoxy-5-methylpyridazine 1-Oxide (XVI)**—a) Formation from 3-Methoxy-6-chloro-5-methylpyridazine (XIV): A mixture of 10 g of XIV, 1 g of 10% Pd-charcoal, and 100 ml of 10% aq.  $NH_4OH$  was hydrogenated. After removal of catalyst by filtration, the filtrate was salted out by addition of NaCl, followed by extraction with  $CHCl_3$ . After removal of solvent, 6.5 g of residue was without further purification, dissolved in 50 ml of glacial AcOH, and 10 ml of 30%  $H_2O_2$  was added. The mixture was heated at 65–70° for 10 hr and evaporated to a small volume *in vacuo*. Water was added and evaporation was repeated. The mixture was then made alkaline with  $Na_2CO_3$ , extracted with  $CHCl_3$ . After removal of solvent, residue was washed with ether and recrystallized from *n*-hexane to colorless plates, mp 61–62°. Yield 5.5 g. *Anal.* Calcd. for  $C_6H_8O_2N_2$ : C, 51.42; H, 5.75; N, 19.99. Found: C, 51.51; H, 5.53; N, 19.73.

b) Formation from 3-Methoxy-6-chloro-5-methylpyridazine 1-Oxide (XII): Similar hydrogenation described in a) was carried out on 2 g of XVII, and the product was recrystallized from *n*-hexane to colorless plates, mp 61–62°, identical with the compound obtained from XIV by mixed fusion.

**3-Hydroxy-5-methylpyridazine 1-Oxide (II)**: To 300 mg of XVI, 1 ml of 5% aq. NaOH was added and heated on a boiling water bath for 1 hr. After cool, the reaction mixture was made acidic with 10% aq. HCl and evaporated to dryness *in vacuo*. The residue was extracted with iso-PrOH while hot. After removal of solvent, the solid was recrystallized from iso-PrOH to crystals, mp 206° (decomp.). Yield 200 mg. *Anal.* Calcd. for  $C_5H_6O_2N_2$ : C, 47.62; H, 4.80; N, 22.22. Found: C, 47.22; H, 4.62; N, 22.21.

**3-Hydroxy-4,6-dibromo-5-methylpyridazine 1-Oxide (XVIII)**: To a water solution of II, aq. bromine was added until no more precipitate was produced. Collect the precipitate and recrystallized from MeOH to colorless crystalline powder, mp 240° (decomp.). Yield 210 mg. *Anal.* Calcd. for  $C_5H_4O_2N_2Br_2$ : C, 21.18; H, 1.42; N, 9.89. Found: C, 21.37; H, 1.46; N, 10.11.

**3-Hydroxy-4,6-dimercapto-5-methylpyridazine 1-Oxide (XIX)**: To 200 mg of XVIII dissolved in 3 ml of dimethylformamide, 0.5 g of 0.5 ml of 36.24% KSH alcoholic solution was added and refluxed for 2 hr.

After cool, water was added to the reaction mixture, made acidic with 10% aq. HCl and deposited solid was collected. Recrystallization from iso-PrOH afforded 100 mg of pale yellow crystals, mp 182°. *Anal.* Calcd. for  $C_5H_6O_2N_2S_2$ : C, 31.57; H, 3.18; N, 14.73. Found: C, 31.12; H, 3.41; N, 14.89.

**3-Hydroxy-4,6-dichloro-5-methylpyridazine 1-Oxide (XX):** To a water solution of 3 g of II, chlorine gas was bubbled until no more precipitate was produced. Collect the precipitate and recrystallized from MeOH to colorless needles, mp 234° (decomp.). Yield 2.8 g. *Anal.* Calcd. for  $C_5H_4O_2N_2Cl_2$ : C, 30.79; H, 2.07; N, 14.47. Found: C, 30.96; H, 2.02; N, 14.44.

**Nitration of 3-Methoxy-5-methylpyridazine 1-Oxide (XVI): Formation of 3-Methoxy-6-nitro-5-methylpyridazine 1-Oxide (XXII), 3-Methoxy-4-nitro-5-methylpyridazine 1-Oxide (XXIII), and 3-Methoxy-4,6-dinitro-5-methylpyridazine 1-Oxide (XXIV):** To a solution of 3 g of XVI dissolved in 9 ml of conc.  $H_2SO_4$ , 3 ml of  $HNO_3$  ( $d=1.5$ ) was added and the mixture was heated at 70–80° for 2.5 hr. The reaction mixture was poured onto ice and deposited crystals were collected and recrystallized from iso-PrOH to yellow scales (XXIV), mp 175–177°. Yield 100 mg. *Anal.* Calcd. for  $C_6H_6O_6N_4$ : C, 31.31; H, 2.63; N, 24.35. Found: C, 31.36; H, 2.62; N, 24.03.

The filtrate was extracted with  $CHCl_3$  and  $CHCl_3$  was evaporated. The residue was dissolved in a small volume of benzene and passed through a column of alumina and eluted with benzene. After removal of the solvent, the residue was recrystallized from iso-PrOH to yellow crystals (XXII), mp 113–115°. Yield 500 mg. *Anal.* Calcd. for  $C_6H_7O_4N_3$ : C, 38.92; H, 3.81; N, 22.70. Found: C, 39.05; H, 3.68; N, 22.85.

The column was then eluted with  $C_6H_6-CHCl_3$  and the elute was evaporated to dryness. The residue was recrystallized from iso-PrOH to yellow crystals (XXIII), mp 148–149°. Yield 1.2 g. *Anal.* Calcd. for  $C_6H_7O_4N_3$ : C, 38.92; H, 3.81; N, 22.70. Found: C, 39.13; H, 3.90; N, 22.55.

**3-Hydroxy-6-chloro-5-methylpyridazine 1-Oxide (XXVI):** To 200 mg of XXII, 3 ml of conc. HCl was added and heated at 80–90° for 2 hr. After cool, the reaction mixture was made alkaline with  $NaHCO_3$  and extracted with  $CHCl_3$ . The solvent was removed and the residue was recrystallized from benzene to crystals (XXV), mp 151–152°. Yield 130 mg.

A mixture of 100 mg of XXV, 2 ml of MeOH, and 6 ml of 5% aq. NaOH was heated at 80° on a water bath for 0.5 hr. After cool, the reaction mixture was made acidic with 10% aq. HCl and evaporated to dryness *in vacuo*. The residue was extracted with AcOEt while hot and AcOEt was removed. The solid obtained was recrystallized from AcOEt–MeOH to crystals (XXVI), mp 230°. Yield 60 mg. *Anal.* Calcd. for  $C_5H_5O_2N_2Cl$ : C, 37.42; H, 3.14; N, 17.45. Found: C, 37.27; H, 3.25; N, 17.55.

**3-Methoxy-4,6-dichloro-5-methylpyridazine 1-Oxide (XXVII):** To 200 mg of XXIV, 5 ml of conc. HCl was added and heated at 80–90° on a water bath for 2.5 hr. After cool, the mixture was made alkaline with  $NaHCO_3$  and extracted with  $CHCl_3$ . After removal of  $CHCl_3$ , the residue was recrystallized from benzene to crystals, mp 138–139°. Yield 100 mg. *Anal.* Calcd. for  $C_6H_6O_2N_2Cl_2$ : C, 34.48; H, 2.89; N, 13.40. Found: C, 34.42; H, 2.70; N, 13.49.

**3-Methoxy-4-chloro-5-methylpyridazine 1-Oxide (XXX):** To 200 mg of XXIII, 2 ml of conc. HCl was added and heated at 80–90° on a water bath for 2 hr. After cool, the mixture was made alkaline with  $NaHCO_3$  and extracted with  $CHCl_3$ . The solvent was removed and residue was recrystallized from benzene to crystals, mp 156–157°. Yield 110 mg. *Anal.* Calcd. for  $C_6H_7O_2N_2Cl$ : C, 41.32; H, 4.05; N, 16.05. Found: C, 41.70; H, 4.05; N, 16.06.

**Nitration of 3-Hydroxy-5-methylpyridazine 1-Oxide (II): Formation of 3-Hydroxy-4-nitro-5-methylpyridazine 1-Oxide (XXVIII):** To a solution of 2 g of II dissolved in 2 ml of  $H_2SL_4$ , 1 ml of fum.  $HNO_3$  was added and heated at 70° for 2 hr, then additional 0.5 ml of  $HNO_3$  was added and heated at the same temperature for further 5 hr. After cool, the mixture was poured onto ice, and saturated  $Ba(NO_3)_2$  solution was added until no more precipitate was produced. The precipitate was separated by centrifugation, and water layer was evaporated to dryness *in vacuo*. The residue was extracted with AcOEt while hot, and after removal of solvent, the residue was recrystallized from AcOEt to yellow needles, mp 191–192°. Yield 430 mg. *Anal.* Calcd. for  $C_5H_5O_4N_3$ : C, 35.09; H, 2.95; N, 24.56. Found: C, 35.42; H, 3.07; N, 24.77.

**3-Hydroxy-4-chloro-5-methylpyridazine 1-Oxide (XXIX)—a)** Formation from 3-Methoxy-4-chloro-5-methylpyridazine 1-Oxide (XXX): A mixture of 100 mg of XXX, 1 ml of MeOH, 6 ml of 5% aq. NaOH was heated at 80° on a water bath for 30 min. After cool, the reaction mixture was made acidic with 10% aq. HCl and evaporated to dryness *in vacuo*. The residue was extracted with AcOEt while hot. Solvent was removed and solid was recrystallized from AcOEt–MeOH to crystals, mp 232° (decomp.). Yield 55 mg. *Anal.* Calcd. for  $C_5H_5O_2N_2Cl$ : C, 37.42; H, 3.14; N, 17.45. Found: C, 37.43; H, 3.23; N, 17.54.

**b)** Formation from 3-Hydroxy-4-nitro-5-methylpyridazine 1-Oxide (XXVIII): To 150 mg of XXVIII, 4 ml of conc. HCl was added and heated at 80–90° for 2.5 hr. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was extracted with AcOEt while hot. After removal of solvent, solid was recrystallized from AcOEt–MeOH to crystals, mp 232° (decomp.), identical with the compound obtained from XXX by mixed fusion.

**3-Hydroxy-6-bromo-4-methylpyridazine 1-Oxide (XXXI):** To a water solution of 1 g of III, 15 ml of  $Br_2-CHCl_3$  solution was added. The mixture was shaken for a short time and evaporated to dryness. The

residue was recrystallized from AcOEt-MeOH to colorless needles, mp 158° (decomp.). Yield 1.4 g. *Anal.* Calcd. for  $C_5H_5O_2N_2Br$ : C, 29.29; H, 2.46; N, 13.67. Found: C, 29.58; H, 2.58; N, 13.91.

**3-Hydroxy-6-mercapto-4-methylpyridazine 1-Oxide (XXXII):** To a solution of 200 mg of XXXI dissolved in 1 ml of dimethylformamide, 0.3 ml of 36.2% KSH alcoholic solution was added and refluxed for 2 hr. Water and 10% aq. HCl was added to make acidic, and the mixture was extracted with  $CHCl_3$ . After removal of solvent, the residue was recrystallized from benzene to crystals, mp 213° (decomp.). Yield 50 mg. *Anal.* Calcd. for  $C_5H_6O_2N_2S$ : C, 37.98; H, 3.83; N, 17.72. Found: C, 37.72; H, 3.89; N, 17.90.

**3-Hydroxy-6-chloro-4-methylpyridazine 1-Oxide (XXXIII)—a)** Chlorination of 3-Hydroxy-4-methylpyridazine 1-Oxide (III): To a solution of 1 g of III dissolved in  $CHCl_3$ , chlorine gas was bubbled. After removal of solvent, the residue was recrystallized from AcOEt to colorless needles, mp 204° (decomp.). Yield 150 mg. *Anal.* Calcd. for  $C_5H_5O_2N_2Cl$ : C, 37.40; H, 3.13; N, 17.44. Found: C, 37.05; H, 3.13; N, 17.42.

b) Formation from 3-Methoxy-6-chloro-4-methylpyridazine 1-Oxide (XXXIV): A mixture of 200 mg of XXXIV, 1 ml of MeOH, and 10 ml of 5% aq. NaOH was heated on a boiling water bath for 0.5 hr. The mixture was made acidic with 10% aq. HCl and evaporated to dryness. The residue was extracted with AcOEt while hot. Concentration of solvent afforded crystals, mp 204° (decomp.). Yield 100 mg, identical with the chlorination product of III by mixed fusion.

c) Formation from 3-Hydroxy-6-nitro-4-methylpyridazine 1-Oxide (XXXV): To 150 mg of XXXV, 1.5 ml of conc. HCl was added and heated on a boiling water bath for 3 hr. The mixture was poured onto ice and after salting out was extracted with  $CHCl_3$ . Solvent was removed, and the residue was recrystallized from AcOEt-MeOH to needles, mp 204° (decomp.). Yield 120 mg, identical with the chlorination product of III by mixed fusion.

**Nitration of 3-Hydroxy-4-methylpyridazine 1-Oxide (III): Formation of 3-Hydroxy-6-nitro-4-methylpyridazine 1-Oxide (XXXV):** To a solution of 2 g of III dissolved in 0.5 ml of  $H_2SO_4$ , 0.4 ml of fuming  $HNO_3$  was added and warmed at 45–50° for 3 hr. The mixture was poured onto ice and saturated  $Ba(NO_3)_2$  solution was added until no more precipitate was produced. The precipitate was separated by centrifugation, and water layer was evaporated to dryness *in vacuo*. The residue was extracted with AcOEt while hot, and after removal of solvent the solid was recrystallized from AcOEt to yellow crystals, mp 179° (decomp.). Yield 350 mg. *Anal.* Calcd. for  $C_5H_5O_4N_2$ : C, 35.09; H, 2.95; N, 24.56. Found: C, 35.25; H, 3.07; N, 24.60.

**3-Hydroxy-4-bromo-6-methylpyridazine 1-Oxide (XXXVI):** To a water solution of 1 g of IV bromine was added until no more precipitate was produced. Collect the precipitate and recrystallized from MeOH to crystals, mp 205–206° (decomp.). Yield 1.1 g. *Anal.* Calcd. for  $C_5H_5O_2N_2Br$ : C, 29.29; H, 2.45; N, 13.66. Found: C, 29.51; H, 2.33; N, 13.80.

**3-Hydroxy-4-mercapto-6-methylpyridazine 1-Oxide (XXXVII):** To a solution of 200 mg of XXXVI dissolved in 1 ml of dimethylformamide, 0.3 ml of 36.2% KSH alcoholic solution was added and refluxed for 2 hr. Water and 10% aq. HCl were added to make acidic, and the deposited solid was collected. Recrystallization from iso-PrOH afforded pale yellow crystals, mp 233° (decomp.). Yield 70 mg. *Anal.* Calcd. for  $C_5H_6O_2N_2S$ : C, 37.97; H, 3.83; Found: C, 38.06; H, 3.75.

**3-Hydroxy-4-chloro-6-methylpyridazine 1-Oxide (XXXVIII)—a)** Chlorination of 3-Hydroxy-6-methylpyridazine 1-Oxide (IV): To a water solution of 1 g of IV, chlorine gas was bubbled until no more precipitate was produced. Collect the precipitate and recrystallized from MeOH to colorless needles, mp 219° (decomp.). Yield 1.1 g. *Anal.* Calcd. for  $C_5H_5O_2N_2Cl$ : C, 37.40; H, 3.14; N, 17.45. Found: C, 37.57; H, 3.30; N, 17.71.

b) Formation from 3-Methoxy-4-chloro-6-methylpyridazine 1-Oxide (XXXIX): A mixture of 100 mg of XXXIX, 1 ml of MeOH, and 0.4 ml of 5% aq. NaOH was heated on a boiling water bath for 0.5 hr. The mixture was made acidic with 10% aq. HCl and extracted with  $CHCl_3$ . Solvent was removed, and the residue was recrystallized from MeOH to colorless needles, mp 219° (decomp.). Yield 60 mg, identical with the chlorination product of IV by mixed fusion.

c) Formation from 3-Hydroxy-4-nitro-6-methylpyridazine 1-Oxide (XL): To 100 mg of XL, 1 ml of conc. HCl was added and heated on a boiling water bath for 3 hr. The mixture was poured onto ice and after salting out, was extracted with  $CHCl_3$ . Solvent was removed and the residue was recrystallized from MeOH to needles, mp 219° (decomp.). Yield 60 mg, identical with the chlorination product of IV by mixed fusion.

**Nitration of 3-Hydroxy-6-methylpyridazine 1-Oxide (IV): Formation of 3-Hydroxy-4-nitro-6-methylpyridazine 1-Oxide (XL):** A mixture of 200 mg of IV and 3 ml of fuming  $HNO_3$  was allowed to stand overnight at room temperature. Water was added and evaporated to dryness *in vacuo*. The residue was recrystallized from AcOEt to yellow scales, mp 200° (decomp.). Yield 120 mg. *Anal.* Calcd. for  $C_5H_5O_4N_3$ : C, 35.10; H, 2.95; N, 24.56. Found: C, 34.83; H, 3.14; N, 24.36.

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