The authors wish to express their gratitude to Prof. T. Yoshida, Dr. H. Satoh, and Mr. H. Imamura for their advice and collaboration especially in the animal experiments. The authors are also indebted to Miss M. Aoshima for assisting them in synthetic works.

Summary

1,1-Bis(2-chloroethyl)hydrazine and its hydrazide- and hydrazone-type derivatives were prepared and investigated as to their chemical reactivity and anti-tumor activity against the Yoshida sarcoma.

(Received November 4, 1959)

UDC 547.852.2.07

96. **Hiroshi Igeta**: Syntheses of Pyridazine Derivatives. V.[1] Nitration of 3-Methoxypyridazine 1-Oxide.

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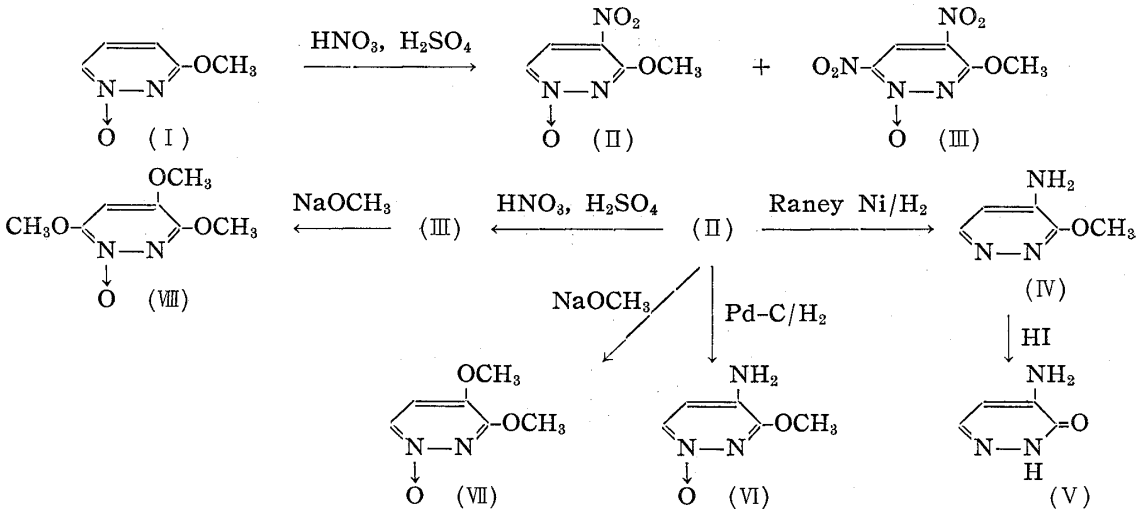
In a previous work,[2] the structure of 3-methoxypyridazine N-oxide was proved to be 3-methoxypyridazine 1-oxide. Nitration of 3-methoxypyridazine 1-oxide (I) was investigated in the present work.

Treatment of this 1-oxide compound (I) with excess of nitric acid in a sulfuric acid solution at 50~55° gave a mononitro compound (II), m.p. 103°, a dinitro compound (III), m.p. 130°, some yellow oils, and a small amount of the starting material.



Catalytic hydrogenation of the mononitro compound (II) with Raney nickel in methanol gave an amino-methoxypyridazine (IV), m.p. 127°, and this was hydrolyzed with hydriodic acid to produce an aminophenol compound (V), m.p. 230°, undepressed on admixture with 4-amino-3-pyridazinol,[3] m.p. 229~230°.[*2] This shows that the nitro group

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*2 This sample was sent from Dr. T. Kuraishi of the University of Nagasaki, to whom the author wishes to express thanks.

1) Part IV: This Bulletin, 8, 368(1960).

2) Part III: *Ibid.*, **7**, 938(1959).

3) T. Kuraishi: *Ibid.*, **6**, 331(1958).

of the mononitro compound (II) is in a position *para* to the N-oxide group.

Nitration of (II) afforded a dinitro compound (III). Furthermore, by reaction with 2 moles of sodium methoxide, the dinitro compound (III) was converted into a trimethoxyl compound (VIII), m.p. 117°, which was proved to be identical with 3,4,6-trimethoxypyridazine 1-oxide,[4] m.p. 117°, derived from 3,6-dimethoxypyridazine 1-oxide[4] via its nitro compound,[4] by admixture.

These facts indicated that the *ortho* and *para* positions of 3-methoxypyridazine 1-oxide are reactive to electrophilic substitution.

Catalytic hydrogenation of (II) over palladium-carbon gave 4-amino-3-methoxypyridazine 1-oxide (VI), m.p. 176° (decomp.). Reaction of (II) with sodium methoxide yielded 3,4-dimethoxypyridazine 1-oxide (VII).

From these results, 3,4,6-trimethoxypyridazine 1-oxide and consequently 3,6-dimethoxy-4-nitro-pyridazine 1-oxide, whose structures were tentatively postulated in Part II of this series,[4] were also confirmed experimentally.

Experimental

Nitration of 3-Methoxypyridazine 1-Oxide (I)—To a solution of 10 g. of (I) dissolved in 50 cc. of conc. H_2SO_4, 25 cc. of HNO_3 (d=1.5) was added at 50~55° and the mixture was allowed to stand for 1.5 hr. at the same temperature. The mixture was poured on ice, the pale yellow precipitate that separated out was collected, and recrystallized from MeOH to yellow crystals (III), m.p. 130°. Yield, 1.11 g. *Anal.* Calcd. for $C_5H_4O_6N_4$: N, 25.92. Found: N, 26.28.

The filtrate was extracted with Et_2O, Et_2O extract was washed with saturated $NaHCO_3$ solution, and dried over $CaCl_2$. Evaporation of Et_2O gave 1.12 g. of yellow oil.

The aqueous layer, which was extracted with Et_2O, was extracted with $CHCl_3$, the $CHCl_3$ layer was washed with saturated $NaHCO_3$ solution, and dried over $CaCl_2$. $CHCl_3$ was evaporated to dryness and 4.68 g. of yellow crystals was obtained. This was dissolved in about 10 cc. of $CHCl_3$, passed through a column of 100 cc. of Florisil, and eluted with $CHCl_3$. $CHCl_3$ was evaporated from the initial 100 cc. of yellow eluate and 4.09 g. of yellow solid was obtained. This was recrystallized twice from MeOH to yellow needles (II), m.p. 103°. Yield, 1.96 g. *Anal.* Calcd. for $C_5H_5O_4N_3$: C, 35.09; H, 2.94; N, 24.55. Found: C, 35.43; H, 2.57; N, 25.09.

$CHCl_3$ was evaporated from the second 1 L. of the eluate and 0.36 g. of a solid was obtained, which gave $HgCl_2$-double salt of white needles, m.p. 147°, undepressed on admixture with that of (I).

3-Methoxy-4-aminopyridazine (IV)—A mixture of 200 mg. of (II), 10 cc. of MeOH, and Raney Ni prepared from 2 g. of Ni-Al alloy (1:1) was hydrogenated. After about 2 hr., 4 moles of H_2 was absorbed. The catalyst was removed by filtration and MeOH was evaporated to dryness. The residue was extracted with benzene which was filtered while hot and the filtrate was concentrated to a small volume. After cool, the deposited crystals were collected. m.p. 127°. Yield, 90 mg. *Anal.* Calcd. for $C_5H_7ON_3$: N, 33.58. Found: N, 33.83.

4-Amino-3-pyridazinol (V)—A solution of 100 mg. of (IV) dissolved in 2 cc. of HI (d=1.70) was refluxed for 1 hr. After cool, the deposited crystals were collected, dissolved in water, and then neutrallized with $NaHCO_3$. The crystals that separated out were collected and recrystallized from water to white prisms, m.p. 230°, undepressed with an authentic specimen.

3-Methoxy-4-aminopyridazine 1-Oxide (VI)—A mixture of 260 mg. of (II), 10 cc. of MeOH, and Pd-C, prepared from 0.2 g. of charcoal and 5 cc. of 1% $PdCl_2$ solution, was hydrogenated. After removal of the catalyst by filtration, MeOH was evaporated to dryness. The residue was recrystallized from $(iso\text{-}Pr)_2O$ to white prisms, m.p. 176° (decomp.). Yield, 85 mg. *Anal.* Calcd. for $C_5H_7O_2N_3$: N, 29.77. Found: N, 29.78.

3,4-Dimethoxypyridazine 1-Oxide (VII)—To a solution of 30 mg. of Na dissolved in 5 cc. of MeOH, a solution of 200 mg. of (II) dissolved in 5 cc. of MeOH was added and the mixture was refluxed for 1 hr. After evaporation of MeOH, 1 cc. of water was added and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was evaporated to dryness. The residue was recrystallized from benzene to 105 mg. of white plates, m.p. 140° when dried over P_2O_5 at 120° for 2 hr. *Anal.* Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.16; N, 17.91. Found: C, 45.86; H, 5.36; N, 17.58.

4) Part II: Yakugaku Zasshi, **75**, 996(1955).

Nitration of 3-Methoxy-4-nitropyridazine 1-Oxide (II) : Formation of 3-Methoxy-4,6-dinitropyridazine 1-Oxide (III)—To a solution of 100 mg. of (II) in 0.5 cc. of conc. H_2SO_4, 0.3 cc. of HNO_3 (d=1.5) was added, the mixture was allowed to stand at 70~75° for 2 hr., and then poured on ice. The crystals that separated out were collected and recrystallized from MeOH to yellow crystals, m.p. 130°, undepressed on admixture with (III).

3,4,6-Trimethoxypyridazine 1-Oxide (VIII)—To a solution of 43 mg. of Na dissolved in 5 cc. of MeOH, a solution of 200 mg. of (III) dissolved in 10 cc. of MeOH was added and the mixture was refluxed for 1 hr. After evaporation of MeOH, 2 cc. of water was added and then extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated. The residue was recrystallized from benzene to white crystals, m.p. 117°, undepressed on admixture with the sample obtained as described in Part II of this series.[4]

The author wishes to express his gratitude to Prof. S. Shibata and Prof. T. Okamoto of the University of Tokyo for their kind guidance, and to Dr. T. Kariyone of this Laboratory for his encouragement. He is also thankful to Mr. T. Oba of this Laboratory for the measurement of infrared spectra. Thanks are due to Miss Y. Urushibata of Kowa Chemical Laboratories and to Miss S. Nakamura of this Laboratory for elemental microanalyses.

Summary

Nitration of 3-methoxypyridazine 1-oxide (I) afforded 3-methoxy-4-nitropyridazine 1-oxide (II) and 3-methoxy-4,6-dinitropyridazine 1-oxide, showing that the positions *ortho* and *para* to the N-oxide group are reactive to electrophilic substitution.

(Received May 2, 1960)