**Summary**

The condensation reaction of acetobromoglucose with chloromercuri-4-ethoxy-2(1*H*)-pyrimidinone (I), which had been reported by Fox, *et al.*[1] to yield 1-(tetra-O-acetyl-*β*-D-glucopyranosyl)-4-ethoxy-2(1*H*)-pyrimidinone (II), was reinvestigated. It was confirmed that the main product of the reaction is not the N-glucoside (II) but the O-glucoside, 2-[(tetra-O-acetyl-D-glucopyranosyl)oxy]-4-ethoxypyrimidine (III). II was obtained as a minor product of the reaction. The O-glucoside (III) was converted to the N-glucoside (II) by the action of mercuric bromide in boiling xylene in a yield of 30~40%. This transglycosidation reaction was followed by ultraviolet absorption spectrum and by the yield of II isolated from the reaction mixture. A direct synthesis of II by the condensation of acetobromoglucose with I in the presence of mercuric bromide was described.

(Received January 28, 1963)

[Chem. Pharm. Bull. 11 (8) 1073 ~ 1077]

*UDC 615.771.7 : 547.852.2*

**Takanobu Itai and Shozo Kamiya** : Potential Anti-cancer Agents. XII.*1 Synthesis of 4-Azido-3,6-dimethoxypyridazine Derivatives.

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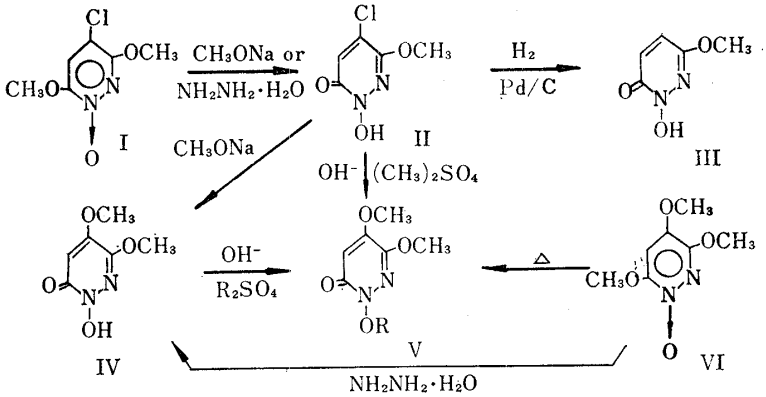
In a previous paper of this series,[1] 4-nitro-3,6-dialkoxypyridazine 1-oxides were reported to have cancerostatic and also bacteriostaic actions *in vitro* except 4-nitro-3,6-dibutoxypyridazine 1-oxide. Therefore, it was of interest for us to synthesize 4-azido-3,6-dimethoxypyridazine 1-oxide for the examination of its biological activity.

The reaction of 4-chloro-3,6-dimethoxypyridazine 1-oxide[2] (I) was examined firstly in order to synthesize 3,6-dimethoxy-4-azidopyridazine 1-oxide (XII). When I was heated with sodium azide in hydrated ethanol at 100° for 3 hours in a sealed tube, 1-hydroxy-3-methoxy-4-chloro-6(1*H*)-pyridazinone (II) was produced in 35% yield, and 60% of the starting material was recovered unchanged. The structure of II was proved as follows.




Va : R=$CH_3$ Vb : R=$C_2H_5$

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1) T. Itai, S. Sako : This Bulletin, **9**, 149 (1961).

2) T. Itai, H. Igeta : Yakugaku Zasshi, **75**, 966 (1955).

The infrared spectrum of II exhibited absorption bands at 2200~3200 and 1667 $cm^{-1}$ attributable to a hydroxamic acid. When II was catalytically hydrogenated over palladium charcoal, 1-hydroxy-3-methoxy-6(1*H*)-pyridazinone (III) was produced, which was derived from 3,6-dimethoxypyridazine 1-oxide.[3]

Igeta[4] reported that 3,4,6-trimethoxypyridazine 1-oxide (VI) could not be obtained in a reaction of I with sodium methoxide. We examined this reaction again and it was found that the 6-methoxy group adjacent to N-oxide group was almost quantitatively converted to sodium salt of a hydroxamic acid, which was led to II by acidification. Similarly, alcoholic hydrazine hydrate did not attack the 4-chloro group, but the 6-methoxy group even under cooling.

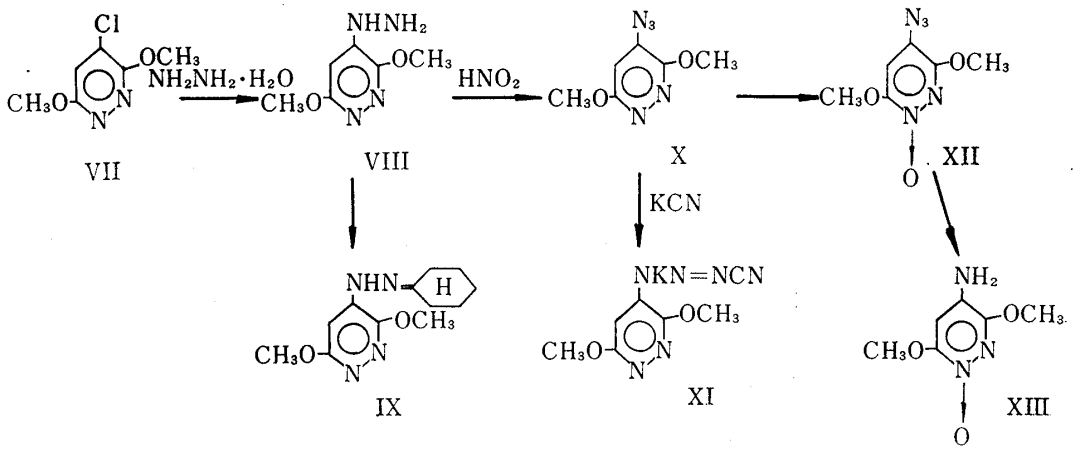
On heating II with two equimolar amounts of sodium methoxide on a water bath for 1 hour, most of the starting material was recovered unchanged. When II was heated at 150~160° in a sealed tube, 1-hydroxy-3,4-dimethoxy-6(1*H*)-pyridazinone (IV) was produced, though in a poor yield. The chlorine atom located at the 4-position in II was rather inactive.

Treatment of II with an excess of dimethylsulfate and sodium hydroxide resulted only in the formation of 1,3,4-trimethoxy-6(1*H*)-pyridazinone (Va). And Va was also identical with the product derived from IV by the same alkylation and these were different from VI.

On heating 3,4,6-trimethoxypyridazine 1-oxide (VI) at 140° for 20 minutes, rearrangement easily took place to give Va in 81% yield. However, 6-methoxypyridazine 1-oxide and 3,6-dimethoxypyridazine 1-oxide did not rearrange after keeping at their melting point for 5 minutes.

As reported in this series,[5,6] 3-, 4-, 5-, and 6-monomethoxypyridazine 1-oxides were reacted with alcoholic hydrazine hydrate to give each hydrazinopyridazine 1-oxide in 30~40% yield, however 3,6-dimethoxypyridazine or 3,4,6-trimethoxypyridazine was not changed under the same condition. On the other hand, the reaction of 3,6-dimethoxypyridazine 1-oxide or 3,4,6-trimethoxypyridazine 1-oxide (VI) with alcoholic hydrazine hydrate gave the hydrazinates of III or IV almost quantitatively, cleavaging the methoxy group in 6-position.

Therefore, XII was led from 4-chloro-3,6-dimethoxypyridazine (VII). When VII was heated with alcoholic hydrazine hydrate, 4-hydrazino-3,6-dimethoxypyridazine (VIII) was




3) T. Nakagome : Yakugaku Zasshi, **82**, 244 (1962).
4) H. Igeta : This Bulletin, **8**, 368 (1960).
5) T. Itai, S. Kamiya : *Ibid.*, **11**, 348 (1963).
6) *Idem* : *Ibid.*, **11**, 1059 (1963).

obtained. Ⅷ was converted to 4-azido-3,6-dimethoxypyridazine (X) with nitrous acid, and to 4-(2-cyclohexylidenehydrazino)-3,6-dimethoxypyridazine (Ⅸ) with cyclohexanone.

When X was treated with potassium cyanide, yellow powder, which was considered to be potassium salt of cyanotriazene derivative (Ⅺ) from its analytical data, was obtained.

X was reacted with 30% hydrogen peroxide in acetic acid and a monohydrate of 4-azido-3,6-dimethoxypyridazine N-oxide was isolated from the reaction mixture as very hygroscopic, red needles, m.p. 89°(decomp.). Separation of the products in this N-oxidation was hard and a few other products were isolated, the structures of which have not been determined yet.

Position of the N-oxide group was identified to be located at 1-position by leading it to 4-amino-3,6-dimethoxypyridazine 1-oxide[2] (Ⅻ) by catalytic hydrogenation, and to 3,4,6-trimethoxypyridazine 1-oxide (Ⅵ) by treatment with sodium methoxide. In the latter reaction, 1-hydroxy-3,4-dimethoxy-6(1*H*)-pyridazinone (Ⅳ) was also isolated in 14% yield by alkaline cleavage of the 6-alkoxy group as seen in I.

Ⅻ was unstable as expected, quite sensitive to light and detonated on rapid heating. The azido group of Ⅻ was very reactive, because of being at 4-position activated with N-oxide group just like ordinary six membered heterocyclic N-oxides.

When benzene solution of Ⅻ was refluxed or exposed to sunlight, 3,3′,6,6′-tetramethoxy-4,4′-azidopyridazine 1,1′-dioxide was formed by radical reaction.

These compounds prepared in the present work have been submitted to biological tests, the results of which will be reported in future.

## Experimental*3

**Reaction of 4-Chloro-3,6-dimethoxypyridazine 1-Oxide (I) with Sodium Methylate or Hydrazine Hydrate**——1) MeONa. To a solution of 25 mg. of metallic Na dissolved in 10 ml. of anhyd. MeOH, 0.20 g. of I was added and the mixture was refluxed on a water bath for 2 hr. MeOH was evaporated under reduced pressure, the residue was dissolved in a small amount of $H_2O$ and acidified with AcOH. White needles separated out were collected by suction, m.p. 206°(decomp.). The aqueous solution of this substance colored blood red with 10% $FeCl_3$ solution. Beilstein reaction : ⊕. *Anal.* Calcd. for $C_5H_5O_3N_2Cl$ : C, 34.57; H, 2.90. Found : C, 33.91; H, 2.85. Yield, 0.16 g. (87%).

2) $NH_2NH_2 \cdot H_2O$. To a mixture of 1.0 g. of I suspended in 10 ml. of EtOH, 5 ml. of 80% $NH_2NH_2 \cdot H_2O$ was added and the mixture immediately became pasty. The paste was allowed to stand overnight with additional 5 ml. of EtOH and filtered by suction. Yield, 0.96 g. (88%). Recrystallization from MeOH gave the hydrazine salt of Ⅱ, slightly yellow needles, m.p. 190～191°(decomp.). Yield, 0.70 g. (64%). The salt was dissolved in a small amount of $H_2O$, the solution was heated with 10% HCl on a water bath, thereupon white long needles were produced. After cooling, the crystals were collected by suction. Recrystallization from a mixture of MeOH and EtOH gave white needles, m.p. 206° (decomp.). Its IR spectrum coincided with that of 1-hydroxy-3-methoxy-4-chloro-6(1*H*)-pyridazionone.

**1-Hydroxy-3-methoxy-6(1*H*)-pyridazinone (III) from 1-Hydroxy-3-methoxy-4-chloro-6(1*H*)-pyridazinone (II)**——A solution of 0.20 g. of Ⅱ dissolved in 20 ml. of MeOH was shaken in $H_2$ with a catalyst prepared from 5 ml. of 1% $PdCl_2$ solution and 0.2 g. of charcoal, and with 1 ml. of conc. $NH_4OH$. After 1 mole of $H_2$ was absorbed, the catalyst was filtered off. MeOH was evaporated, the residue was dissolved in a small amount of $H_2O$ and the solution was acidified with AcOH. White needles separated out were collected and washed with $H_2O$. m.p. 174～175°, undepressed with the authentic sample.[3] Yield, 78 mg. (48%).

**1-Hydroxy-3,4-dimethoxy-6(1*H*)-pyridazinone (IV)**——1) Reaction of 3,4,6-trimethoxypyridazine 1-oxide (Ⅵ) with $NH_2NH_2 \cdot H_2O$. To a solution of 0.30 g. of Ⅵ dissolved in 5 ml. of EtOH, 1.5 ml. of 80% $NH_2NH_2 \cdot H_2O$ was added and the mixture was refluxed on a water bath for 30 min. The reaction mixture was evaporated to dryness under reduced pressure, the residue was dissolved in a small amount of $H_2O$ and acidified with HCl. Needles that separated out were collected by suction. Recrystallization from a mixture of MeOH and EtOH gave white long needles, m.p. 237～238°(decomp.). The aqueous solution of this product colored violet with 1 drop of 10% $FeCl_3$ solution. Its IR spectrum was identical with that of 1-hydroxy-3,4-dimethoxy-6-(1*H*)-pyridazinone. Yield, 0.10 g. (40%).

*3 All melting points are uncorrected.

2) Reaction of 1-hydroxy-3-methoxy-4-chloro-6(1*H*)-pyridazinone (II) with MeONa. To a solution of 25 mg. (2 equimolar amounts) of metallic Na dissolved in 20 ml. of abs. MeOH, 87 mg. of II was added and the mixture was heated in a sealed tube at 150~160° for 3 hr. MeOH was evaporated to dryness, the residue was dissolved in a small amount of $H_2O$, acidified with AcOH and separated needles were collected by suction. Recrystallization from a mixture of MeOH and EtOH gave white needles, m.p. 236° (decomp.), which were identical with the authentic sample. Yield, 16 mg.

**1,3,4-Trimethoxy-6(1*H*)-pyridazinone (Va)**——1) From 1-hydroxy-3,4-dimethoxy-6(1*H*)-pyridazinone (IV). To a solution of 0.166 g. of IV dissolved in 1 ml. of 20% NaOH aqueous solution and 2 ml. of MeOH, 0.5 g. of dimethylsulfate was added, and the mixture was heated on a water bath for 30 min. Then a few drops of 20% NaOH and a drop of phenolphthalein solution were added in order to keep the solution alkaline through the reaction. Additional 0.2 g. of dimethyl sulfate was added to the reaction mixture and heated again for 1 hr. MeOH was evaporated and the residue was extracted with $CHCl_3$. After drying over anhyd. $Na_2SO_4$, $CHCl_3$ was evaporated and the residue was recrystallized from benzene to white needles, m.p. 160°. Color reaction with $FeCl_3$ solution: ⊖. IR: $\nu_{max}^{Nujol}$ 1664 $cm^{-1}$ (CO). *Anal.* Calcd. for $C_7H_{10}O_4N_2$: C, 45.16; H, 5.41. Found: C, 45.15; H, 5.33. Yield, 0.15 g. (82%).

The same treatment of IV with diethylsulfate gave 1-ethoxy-3,4-dimethoxy-6(1*H*)-pyridazinone (Vb), white needles, m.p. 150~152° (from benzene). IR: $\nu_{max}^{Nujol}$ 1662 $cm^{-1}$ (CO). *Anal.* Calcd. for $C_8H_{12}O_4N_2$: C, 47.99; H, 6.04. Found: C, 48.06; H, 6.10. Yield, 58%.

2) From 1-hydroxy-3-methoxy-4-chloro-6(1*H*)-pyridazinone (II). The same treatment of II as described in 1) gave Va in 81% yield.

**Rearrangement Reaction of 3,4,6-Trimethoxypyridazine 1-Oxide (VI) to 1,3,4-Trimethoxy-6(1*H*)-pyridazinone (Va)**——0.50 g. of VI was gradually heated in an oil bath and perfectly melted at about 120°. Then it was left at 140° (bath) for 20 min. The melted substance gradually solidified. After cooling, the solid was recrystallized from benzene to white needles, m.p. 160°. The IR spectrum of this product was entirely identical with that of 1,3,4-trimethoxy-6(1*H*)-pyridazinone. Yield, 0.37 g. (81%).

**Reaction of 3,6-Dimethoxypyridazine 1-Oxide with $NH_2NH_2 \cdot H_2O$**——To a mixture of 1.0 g. of 3,6-dimethoxypyridazine 1-oxide suspended in 5 ml. of MeOH, 5 ml. of 80% $NH_2NH_2 \cdot H_2O$ was added and the reaction mixture was refluxed for 2 hr. on a water bath. The reaction mixture was evaporated to dryness under reduced pressure and the residue was recrystallized from EtOH to pale yellow neeldes, m.p. 160° (decomp.). *Anal.* Calcd. for $C_5H_6O_3N_2 \cdot NH_2NH_2$: C, 34.48; H, 5.79. Found: C, 34.25; H, 6.30. Yield, 0.65 g. (58%). The hydrazine salt was dissolved in a small amount of $H_2O$, acidified with HCl and needles separated out were collected by suction. Colorless pillars, m.p. 174°, undepressed with 1-hydroxy-3-methoxy-6(1*H*)-pyridazinone.[3] Yield, quantitative.

**Reaction of 4-Chloro-3,6-dimethoxypyridazine (VII) with $NH_2NH_2 \cdot H_2O$. Formation of 4-Hydrazino-3,6-dimethoxypyridazine (VIII)**——A mixture of 0.50 g. of VII, 0.6 g. of 80% $NH_2NH_2 \cdot H_2O$ and 5 ml. of EtOH was refluxed on a water bath for 3 hr. The mixture was evaporated to dryness under reduced pressure, the residue was recrystallized from EtOH and white needles, separated out at first were filtered off. This product, m.p. 89~92°, was identical with hydrazine monohydrochloride. Concentrating the filtrate again, orange fine needles were precipitated, which collected by suction and washed with a small amount of EtOH. Twice recrystallization from EtOH gave brownish needles, m.p. 177~178° (decomp.). *Anal.* Calcd. for $C_6H_{10}O_2N_4$: C, 42.35; H, 5.92; N, 32.93. Found: C, 42.12; H, 6.27; N, 33.09. Yield, 0.12 g. (25%). The filtrate, separated from VIII, was evaporated to dryness, the residue was extracted with the mixture of benzene and $CHCl_3$ (50 ml. + 20 ml.), and the extract was passed through an $Al_2O_3$ column. 0.12 g. (24%), of the starting material was recovered from the eluant.

4-(2-Cyclohexylidenehydrazino)-3,6-dimethoxypyridazine (IX): Cream colored prisms, m.p. 143°. *Anal.* Calcd. for $C_{12}H_{18}O_2N_4$: C, 57.58; H, 7.25; N, 22.39. Found: C, 57.67; H, 6.75; N, 22.83.

**4-Azido-3,6-dimethoxypyridazine (X)**——To a solution of 0.38 g. of 4-hydrazino-3,6-dimethoxypyridazine dissolved in 10 ml. of 10% HCl, a solution of 0.16 g. of $NaNO_2$ dissolved in 3 ml. of $H_2O$ was added dropwise under cooling. The reaction mixture was basified with $NaHCO_3$, extracted with $CHCl_3$ and the extract was dried over anhyd. $Na_2SO_4$. $CHCl_3$ was evaporated, the residue was extracted again with benzene, the benzene extract was passed through an $Al_2O_3$ column and the column was eluted with benzene. Benzene was evaporated and the residue was recrystallized from hydrated EtOH to white prisms, m.p. 77~79°. IR: $\nu_{max}^{Nujol}$ 2120 $cm^{-1}$ ($N_3$). *Anal.* Calcd. for $C_6H_7O_2N_5$: C, 39.78; H, 3.89; N, 38.66. Fonnd: C, 40.22; H, 3.99; N, 38.93. Yield, 0.19 g. (47%).

Cyanotriazene potassium derivative (XI): Yellow needles (from MeOH), m.p. 213° (decomp.).

**N-Oxidation of 4-Azido-3,6-dimethoxypyridazine (X)**——To a solution of 1.0 g. of X dissolved in 20 ml. of AcOH, 2.0 ml. of 30% $H_2O_2$ was added and the mixture was heated at 70~75° for 3 hr. Further 1.0 ml. of 30% $H_2O_2$ was added and again heated at the same temperature for 2 hr. To this solution, 10 ml. of $H_2O$ was added and AcOH was evaporated to about 5 ml. in a reduced pressure. After neutralization with $NaHCO_3$ under cooling, this was extracted with $CHCl_3$ and $CHCl_3$ was evaporated after drying over anhyd. $Na_2SO_4$. The residue was left in a reduced desiccator for 2 days and

the brown paste-like residue was extracted with benzene. The benzene extract was chormatographed on an $Al_2O_3$ column and eluted with benzene. 1) From the benzene eluant 12% of the starting material was recovered. 2) The column was eluted with a mixture of benzene and MeOH (50 ml.+0.4 ml.), the solvent was evaporated under reduced pressure and the residue was extracted with benzene. The benzene extract was chromatographed on an $Al_2O_3$ column. A pink band was eluted with a mixture of benzene and MeOH (50 ml.+0.4 ml.), the eluant was evaporated under reduced pressure and the residue was dried over $P_2O_5$ under reduced pressure. Red needles, m.p. 88~89° (decomp.). Very hygroscopic, explosive! IR : $\nu_{max}^{Nujol}$ 2110 $cm^{-1}$ ($N_3$). *Anal.* Calcd. for $C_6H_7O_3N_5 \cdot H_2O$ : N, 32.55. Found : N, 32.57. Yield, 0.23 g. (19%).

**Catalytic Hydrogenation of 4-Azido-3,6-dimethoxypyridazine N-Oxide**——A solution of 0.24 g. of the N-oxide dissolved in 10 ml. of EtOH, added with a catalyst prepared from 1.9 ml. of 1% $PdCl_2$ solution and 0.1 g. of charcoal, was shaken in $H_2$ stream for 10 min. The catalyst was filtered off, EtOH was evaporated, the residue was recrystallized from a mixture of benzene and EtOH to white fine needles, m.p. 168~169° (decomp.), undepressed with the authentic sample.[2] Yield, 0.16 g. (84%).

**Reactions of 4-Azido-3,6-dimethoxypyridazine 1-Oxide (XII)**——1) MeONa : To a solution of 25 mg. of metallic Na dissolved in 10 ml. of anhyd. MeOH, a solution of 0.20 g. of XII dissolved in 5 ml. of anhyd. MeOH was added and the mixture was refluxed for 1 hr. MeOH was evaporated, the residue was dissolved in a small amount of $H_2O$ and this solution was extracted with $CHCl_3$. After drying with anhyd. $Na_2SO_4$, $CHCl_3$ was evaporated and the residue was recrystallized from benzene to white fine needles, m.p. 117°, undepressed with 3,4,6-trimethoxypyridazine 1-oxide. Yield, 75 mg. (38%). The aqueous layer, extracted off with $CHCl_3$, was acidified with HCl, white long needles separated out were collected by suction and washed with $H_2O$, m.p. 238~239° (decomp.). The infrared spectrum of this product was entirely identical with that of 1-hydroxy-3,4-dimethoxy-6-(1*H*)-pyridazinone. Yield, 23 mg. (14%).

2) Thermal decomposition in benzene : A solution of 50 mg. of XII dissolved in 5 ml. of benzene was refluxed on a water bath for 2 hr. Black precipitates separated out were collected by suction, washed with benzene and recrystallized from EtOH to black purple powder, m.p. 248°. After drying at 180° for 50 hr., the sample was analyzed. *Anal.* Calcd. for $C_{12}H_{14}O_6N_6 \cdot \frac{1}{2}H_2O$ : C, 41.50; H, 4.35; N, 24.20. Found : C, 41.50; H, 4.01; N, 24.10. Yield, 15 mg. From the benzene filtrate 12 mg. of the starting material was recovered.

3) Photolysis in benzene : A solution of 100 mg. of XII dissolved in 5 ml. of benzene was exposed to sunlight for 3 hr., black fine needles gradually separated out were collected by suction and washed with benzene. On recrystallizing twice from EtOH, a black purple powder, m.p. 246°, was produced, which was identical with the authentic sample. Yield, 18 mg. From the benzene filtrate, 8 mg. of the starting material was recovered by $Al_2O_3$ chromatographic separation.

The authors express their deep gratitude to Prof. Emeritus E. Ochiai, the Director of Itsuu Laboratory and to Dr. T. Kariyone, the Director of this Institute, for the helpful advice. encouragement and They are also indebted to members of the microanalytical center of the Tokyo University for the analytical data, and to Dr. T. Oba and Mr. G. Kawabata for their co-operation in infrared absorption measurements.

## Summary

4-Azido-3,6-dimethoxypyridazine (X) was synthesized from 4-chloro-3,6-dimethoxypyridazine (VII) through the hydrazino compound and X was converted to 4-azido-3,6-dimethoxypyridazine 1-oxide (XII).

Besides, some reactions of 4-chloro-3,6-dimethoxypyridazine 1-oxide (I) and XII were examined.

(Received February 9, 1963)