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61. Takanobu Itai and Shozo Kamiya : Potential Anti-cancer Agents.*1 X. Syntheses and Reactions of 3- and 6-Azidopyridazine 1-Oxide.

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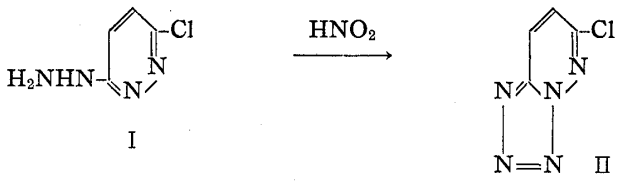
In the previous papers, syntheses of pyridine and quinoline 1-oxide having the azide group at 4-position had been reported, and their reactions were also investigated.[1] The chemical reactivities of 2-, 3-, 5-azidoquinoline 1-oxide and the quaternary salts of 4-azidoquinoline 1-oxide were studied by Kamiya.[2] It was found that some of them showed a considerable bacteriostatic action.

An attempt was made to synthesize azidopyridazine derivatives in order to examine their anti-cancer and bacteriostatic actions. This paper was dealt with syntheses and reactions of 3- and 6-azidopyridazine 1-oxides, as well as some related compounds.

Reaction of 3,6-Dichloropyridazine and Sodium Azide

It was shown by Takabayashi[3] that a treatment of 3-chloro-6-hydrazinopyridazine (I) with nitrous acid resulted in the formation of 6-chlorotetrazolo[1,5-*b*]pyridazine (II).



On the treatment with sodium azide, 3,6-dichloropyridazine (III) gave a violently explosive azide, which was identical with the product obtained by the reaction of II with sodium azide, and by the reaction of 6-hydrazinotetrazolo[1,5-*b*]pyridazine with nitrous acid. Its infrared spectrum showed a strong N_3 band as listed in Table I, and its structure was determined, by the following reactions shown in Chart 1, to be 6-azidotetrazolo[1,5-*b*]pyridazine (IV).

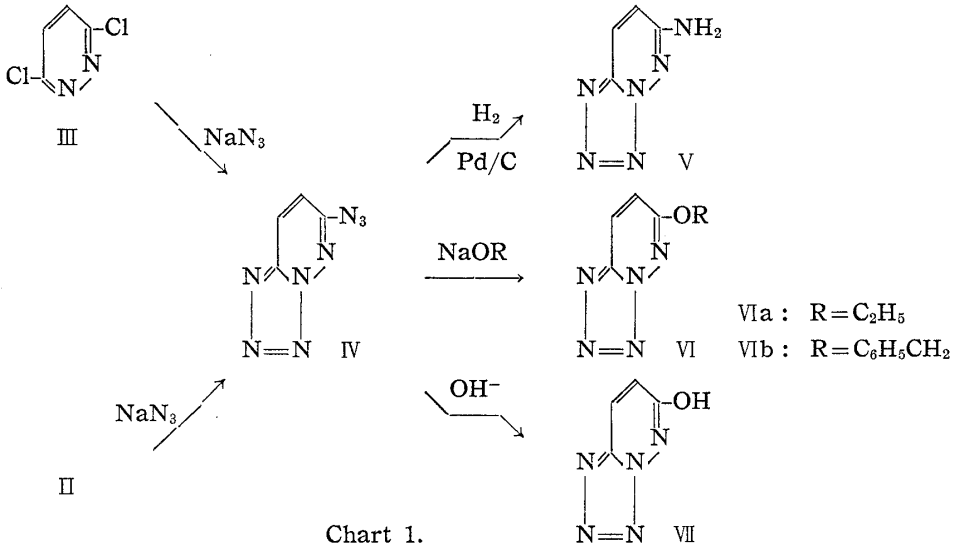


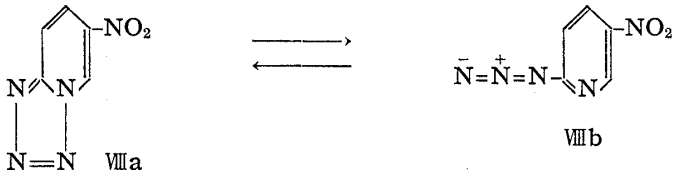
Chart 1.

*1 Part IX. T. Itai, S. Natsume : This Bulletin, **11**, 342 (1963).
*2 Tamagawa-Yoga-machi, Setagayaku, Tokyo (板井孝信, 神谷庄造).
1) T. Itai, S. Kamiya : This Bulletin, **9**, 147 (1961); *Ibid.*, **10**, 471 (1962).
2) S. Kamiya : Yakugaku Zasshi, **81**, 1743 (1962); This Bulletin, **10**, 669 (1962).
3) N. Takabayashi : Yakugaku Zasshi, **75**, 1242 (1955).

Catalytic hydrogenation of IV over palladium charcoal gave 6-aminotetrazolo[1,5-*b*]-pyridazine (V). When IV was heated with sodium alkoxides on a water bath, 6-alkoxy-tetrazolo[1,5-*b*]pyridazine (VI) was obtained, and by heating with 5% sodium hydroxide solution, the sodium salt of tetrazolo[1,5-*b*]pyridazine-6-ol (VII) was produced. These compounds were identical with the authentic samples synthesized from II. Consequently, IV was proved to be a monoazido-monotetrazolo structure.

Then IV was heated with sulfuric acid to give a ditetrazolo compound attached to a single pyridazine ring, but almost of the starting material was recovered unreacted, without any further secondary ring-closure.

It was reported that the azide group adjacent to the ring nitrogen often tended to cyclize to form isomeric tetrazoles. Boyer and his colleagues[4,5] recently reported that 2-azidopyridine derivative with a strong electron withdrawing group, such as a nitro group at 5-position, exist in crystalline state as pyridotetrazole (VIIIa), and in liquid state as 2-azidopyridine (VIIIb) probably together with VIIIa.



In IV, it appears most likely that the strong electron-withdrawing effect of the tetrazolo-ring diminishes the basicity of the ring nitrogen at 2-position, and any secondary ring closure will never be occurred.

Table I. Characteristic Infrared Bands of These Azides

Azide	KBr (cm^{-1})	Nujol (cm^{-1})	$CHCl_3$ (cm^{-1})
X	2120	2126, 2160	2123, 2160
XXI	2128	2120	2122
XIX	2120	2100, 2122	2122
IV	2163	—	2140

Synthesis of 3- and 6-Azidopyridazine 1-Oxide

When 3-chloropyridazine 1-oxide (IX) was heated with sodium azide at 90° in a sealed tube, an azide compound which showed infrared band at 2120 cm^{-1} was obtained in 44% yield. This product was not affected by sun light in solution, and its structure was identified to be 3-azidopyridazine 1-oxide (X) from the two experimental facts: i.e., possessing an infrared absorption band characteristic to the azide group in crystals and in solution as shown in Table I, and also some of the reactions shown in Chart 3.

X was first synthesized by Natsume[6] in our laboratory who treated at first IX with hydrazine hydrate, then diazotized the produced 3-hydrazinopyridazine 1-oxide hydrochloride without further separation and purification of the intermediate. In this case, 3-hydrazinopyridazine 1-oxide (XII) was purely obtained by refluxing 3-methoxypyridazine 1-oxide[7] (XIa) with hydrazine hydrate in ethanol. XII was yellow needles, m.p. 158~160° (decomp.), and the treatment of XII with either benzaldehyde, salicylaldehyde or acetone gave the corresponding hydrazones (XIIIa, b. c), and by heating the hydrochloride of XII with potassium thiocyanate, 3-thiosemicarbazinopyridazine 1-oxide (XIV) was obtained. XII was also converted into X with nitrous acid in 60% yield.

4) J.H. Boyer, E.J. Miller, Jr.: J. Am. Chem. Soc., **81**, 4671 (1960).
5) J.H. Boyer *et al.*: J. Org. Chem., **25**, 287, 458 (1960).
6) T. Itai, S. Natsume: This Bulletin, **11**, 342 (1963).
7) H. Igeta: *Ibid.*, **7**, 938 (1959).

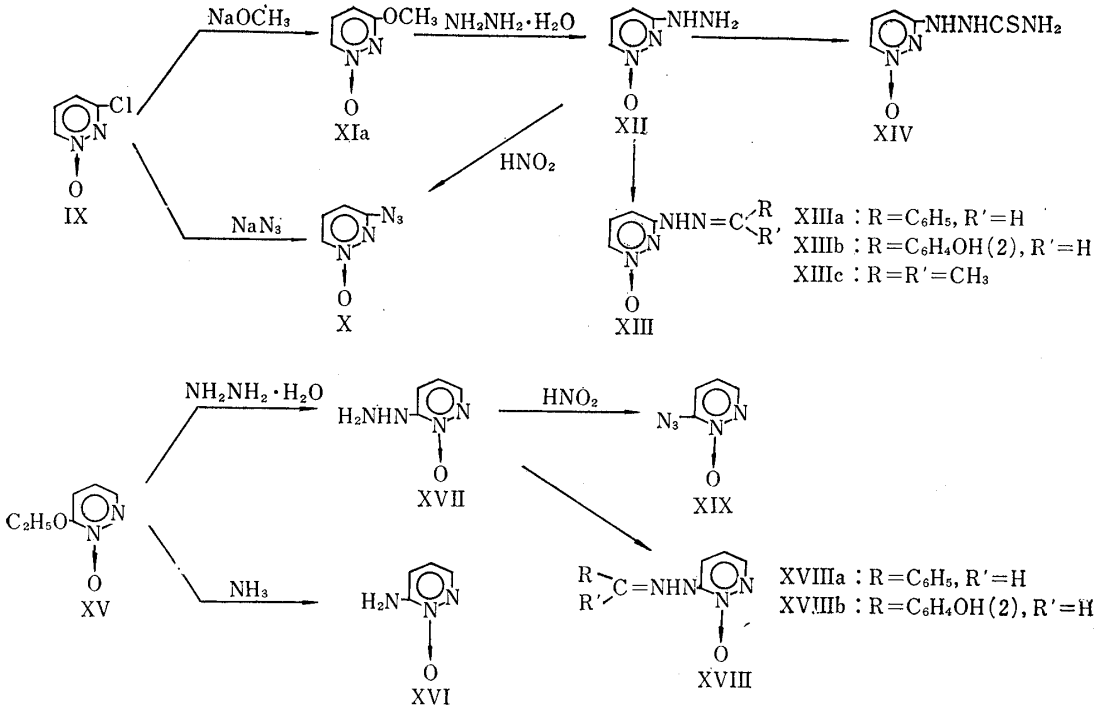


Chart 2.

Similarly the synthesis of 6-azidopyridazine 1-oxide (XIX) was accomplished by the reaction of 6-ethoxypyridazine 1-oxide (XV) with hydrazine hydrate to form 6-hydrazinopyridazine 1-oxide (XVII), followed by the treatment of XVII with nitrous acid. XV was prepared by the treatment of 6-chloropyridazine 1-oxide[8] with sodium ethoxide. XVII is a new compound which has a strongly reductive hydrazino group adjacent to the N-oxide group. Treatment of XVII with either benzaldehyde or salicylaldehyde gave the corresponding hydrazones (XVIIIa, b). XIX was decomposed even by heating in benzene, followed by the recrystallization from chloroform.

It may be assumed that the alkoxy group in 6-alkoxypyridazine 1-oxide will be more reactive than that of 3-alkoxypyridazine 1-oxide by the polar effect of the N-oxide group. Actually the treatment of XV with ammonia ethanol in a sealed tube at 90° gave XVI in 12% yield, but in the case of XIa any reaction did not occur. It was also considered that the ethoxy group of XV seems to be more reactive than that of 4-ethoxypyridine and quinoline 1-oxides.

When 3,6-dichloropyridazine 1-oxide (XX) was heated with about 2.5 moles of sodium azide, only a monoazide was produced in 19% yield, and none of the di-azide derivatives were produced even by the elongated heating. Therefore this positon of its azide group was presumed to be 3-position according to the literatures.[9,10] Then the monoazide (XXI) was catalytically hydrogenated into 3-aminopyridazine 1-oxide (XXII). This fact also coincided with the experimental results by Sako.

Reaction of 3- and 6-Azidopyridazine 1-Oxide

Several reactions, such as substitution reaction, catalytic hydrogenation, desoxygenation, thermal decomposition etc. in Chart 3 were carried out on X and XIX.

Treatment of X and XIX with sodium alkoxides resulted in the formation of the corresponding ethers (XIa, b, c) and (XVa, b, c) with simultaneous elimination of sodium

8) S. Sako : This Bulletin, **11**, 261 (1963).
9) T. Nakagome : Yakugaku Zasshi, **82**, 244 (1962).
10) S. Sako : This Bulletin, **10**, 956 (1962).

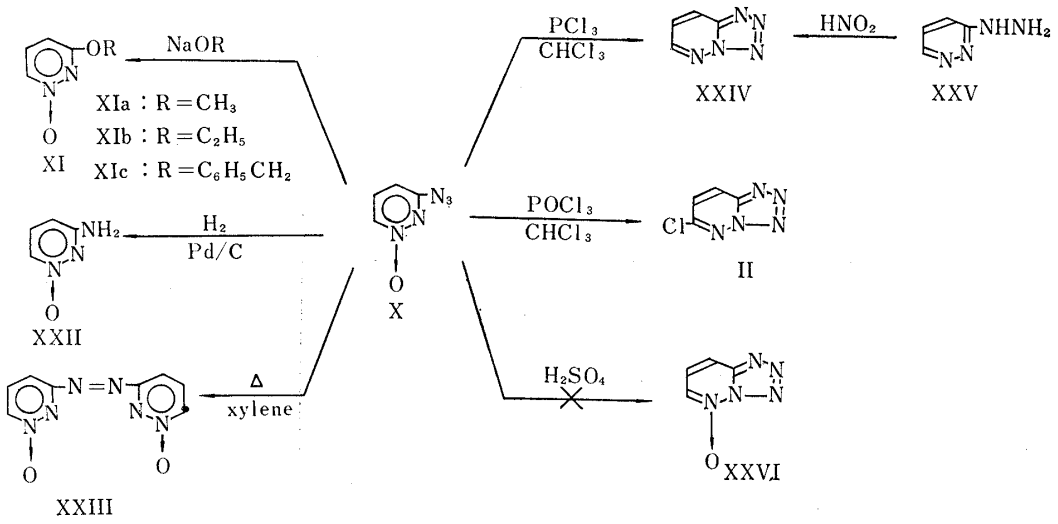


Chart 3.

azide. Their catalytic hydrogenation over palladium charcoal at room temperature gave respective aminopyridazine 1-oxide (XXII, XVI).

The azide group in X was so stable in solution that X was not thermally decomposed in either benzene or toluene, the starting material being quantitatively recovered, but a small amount of brownish powder was obtained by refluxing in xylene for five hours, thus it was considered to be 3,3′-azodipyridazine 1,1′-dioxide (XXIII) from its analytical data and high melting point. A purification of XXIII was very difficult due to its insolubility. On the contrary, XIX was decomposed even by heating in benzene into a small amount of XVI and an oily product which has not been identified yet.

Tetrazolopyridazine (XXIV) was obtained by refluxing X or XIX with a large amount of phosphorus trichloride in chloroform. Besides, XXIV was also produced by the treatment of 3-hydrazinopyridazine (XXV) with nitrous acid in 55% yield.

On the other hand, the treatment X with phosphorus oxychloride resulted in the formation of 6-chlorotetrazolo[1,5-*b*]pyridazine (II) in 57% yield. These reactions were considered to cyclize immediately into the tetrazolopyridazines, when they were desoxygenated to either 3-, 6-azidopyridazine, or 3-azido-6-chloropyridazine.

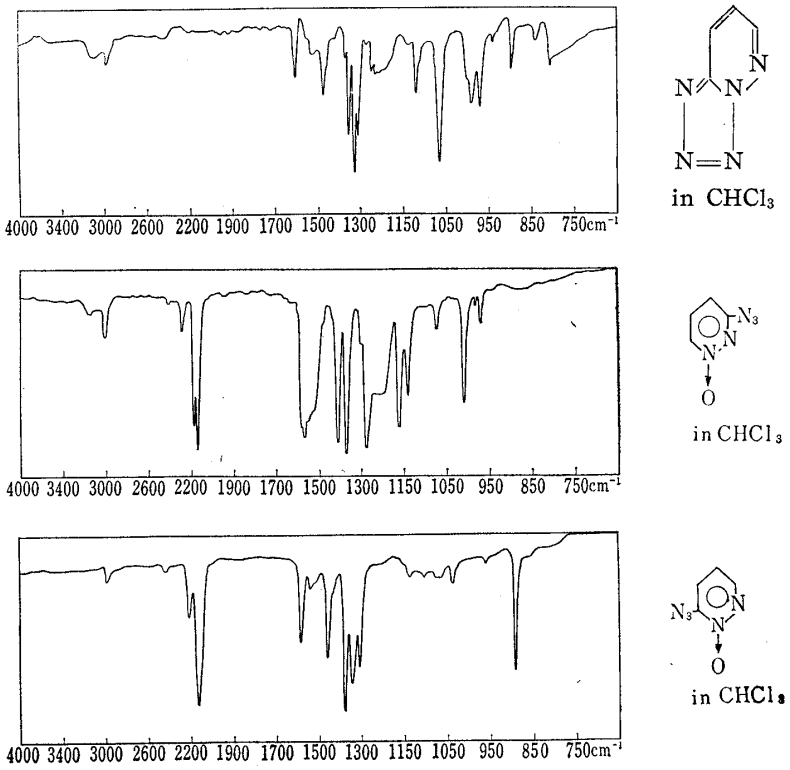
In order to prepare the tetrazolo isomer (XXVI), X was heated in conc. sulfuric acid on a water bath for ten hours, but only the starting material was recovered quantitatively.

Consequently it was known that a presence of the 1-oxide group in X prevents its tetrazolo-ring closure. However, when the 1-oxide group has been removed, the cyclization may occur immediately and these facts may agree with the fact that no di-N-oxide in a pyridazine nucleus has been obtained yet. The reason why the cyclization in X does not occur, is now being investigated.

From reactions above-mentioned, the ionic reactivity of 3- and 6-azide group in pyridazine 1-oxide were almost equal, but in radical reactivity 6-azide group was more reactive than 3-azide group. Further a comparison of the radical reactivity of 3- and 6-azide group was made by the reaction with diphenylpicrylhydrazyl (DPPH).

DPPH is a stable nitrogen free radical, having characteristic purple in solution. If other radicals are released in its solution, the purple color will gradually fade or disappear due to the reaction each other.

Considering from the reactions of X and XIX with DPPH, it was also concluded that the azide group at 6-position in pyridazine 1-oxide was more reactive than that of at 3-position.



Experimental*3

6-Azidotetrazolo[1,5-*b*]pyridazine (IV)——1) Reaction of 3,6-dichloropyridazine (III) and sodium azide: A mixture of 4.0 g. of III, 4.0 g. of NaN_3, 22 cc. of EtOH and 12 cc. of H_2O was heated in a sealed tube at 90° for 8 hr. on a water bath. Pale brownish needles that separated out were collected, and recrystallized from a mixture of EtOH and H_2O to white needles, m.p. 128~129° (decomp.). Violently explosive! *Anal.* Calcd. for $C_4H_2N_8$: N, 69.12. Found: N, 69.55. Yield, 2.55 g. (42%).

2) Reaction of 6-hydrazinotetrazolo[1,5-*b*]pyridazine[3] and nitrous acid: To a solution of 0.10 g. of 6-hydrazinotetrazolo[1,5-*b*]pyridazine, m.p. 238~240° (decomp.) in 5 cc. of 10% HCl, a solution of 50 mg. of $NaNO_2$ in 3 cc. of H_2O was added dropwise under cooling, the reaction mixture was allowed to stand for 30 min., basified with $NaHCO_3$, and extracted with $CHCl_3$. After drying over Na_2SO_4, the solvent was evaporated to dryness, and the residue was recrystallized from a mixture of EtOH and H_2O to white leaves, m.p. 125° (decomp.), undepressed with the product obtained in 1. Yield, 84 mg. (79%).

Reactions of 6-Azidotetrazolo[1,5-*b*]pyridazine (IV)——1) Catalytic hydrogenation: Formation of 6-aminotetrazolo[1,5-*b*]pyridazine (V): A solution of 0.20 g. of IV in 20 cc. of MeOH was submitted to a reduction over Pd-charcoal, prepared from 5.0 cc. of 1% $PdCl_2$ and 0.2 g. of charcoal. After a complete absorption of H_2, the reaction mixture was heated to boil, and filtered immediately. The filtrate was concentrated and cooled. Yellow crystals (from MeOH), m.p. 293~295° (decomp.) were separated out. *Anal.* Calcd. for $C_4H_4N_6$: C, 35.29; H, 2.96; N, 61.75. Found: C, 34.92; H, 2.89; N, 61.51. Yield, 65 mg. (39%).

2) C_2H_5ONa and $C_6H_5CH_2ONa$: Formation of 6-alkoxytetrazolo[1,5-*b*]pyridazine (VI): To a solution of 30 mg. of Na in 15 cc. of abs. EtOH, 0.20 g. of IV was added, and the mixture was refluxed on a water bath for 2 hr. The EtOH was distilled off and the residue was extracted with $CHCl_3$, which was evaporated to dryness after drying over Na_2SO_4. White needles (from EtOH), m.p. 98°. *Anal.* Calcd, for $C_6H_7ON_6$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.68; H, 4.32; N, 42.48. Yield, 0.12 g. (59%).

Similarly 6-benzyloxytetrazolo[1,5-*b*]pyridazine was obtained by the treatment of IV with sodium benzylate as described in 2. White needles (from EtOH), m.p. 164~165°. *Anal.* Calcd. for $C_{11}H_9ON_5$: C, 58.14; H, 3.99; N, 30.82. Found: C, 57.75; H, 3.65; N, 31.27.

3) 5% Sodium hydroxide: Formation of 6-hydroxytetrazolo[1,5-*b*]pyridazine. A mixture of 0.20 g. of IV and 5 cc. of 5% NaOH was heated on a water bath, the mixture became clear after about 10

*3 All melting point are uncorrected.

min. and heated further 10 min. After cooling, the solution was neutralized with AcOH, and a small amount of EtOH was added. Pale yellow plates that separated out were collected, and dried *in vacuo*. As they were Na salt of tetrazolo[1,5-*b*]pyridazin-6-ol, m.p. 314°(decomp.), heating them with conc. HCl on a water bath, after cooled, afforded white prisms, m.p. 230~231° (decomp.) in a quantitative yield. *Anal.* Calcd. for $C_4H_3ON_5$: C, 35.04; H, 2.21; N, 51.09. Found : C, 34.69; H, 2.51; N, 52.07. The IR spectrum was identical with that of the authentic sample.

3-Hydrazinopyridazine 1-Oxide (XII)——A mixture of 1.0 g. of 3-methoxypyridazine 1-oxide, 5.0 cc. of 80% $NH_2NH_2 \cdot H_2O$ and 5.0 cc. of EtOH was refluxed on a water bath for 3 hr. The reaction mixture was evaporated to dryness under a reduced pressure, and the residue was solidified on standing. The crude product was recrystallized from a mixture of benzene and EtOH to give pale yellowish needles, m.p. 158~160°(decomp.). Yield, 0.26 g.(26%). *Anal.* Calcd. for $C_4H_6ON_4$: C, 38.09; H, 4.80; N, 44.43. Found : C, 37.29; H, 5.23; N, 44.51.

1. Benzaldehyde hydrazone of XII : Pale yellowish needles (from EtOH), m.p. 246~247°(decomp.). *Anal.* Calcd. for $C_{11}H_{10}ON_4$: C, 61.67; H, 4.71; N, 26.16. Found : C, 61.67; H, 4.43; N, 26.41.

2. Acetone hydrazone of XII : Brownish neeldes (from EtOH), m.p. 200°. *Anal.* Calcd. for $C_7H_{10}N_4$: C, 50.59; H, 6.06; N, 33.72. Found : C, 50.30; H, 5.58; N, 33.95.

3-Thiosemicarbazinopyridazine 1-Oxide (XIV)——A mixture of 0.87 g. of 3-hydrazinopyridazine 1-oxide hydrochloride, 0.6 g. of KSCN, 15 cc. of EtOH, and 5 cc. of H_2O was refluxed for 5 hr. on a water bath. After cooling, the yellow crystals separated were collected, washed with MeOH, and recrystallized from a mixture of EtOH and H_2O to slightly yellowish fine prisms, m.p. 232°(deccmp.). Yield, 0.68 g.(69%). *Anal.* Calcd. for $C_5H_7ON_5S$: C, 32.42; H, 3.81; N, 37.82. Found : C, 32.67; H, 4.15; N, 37.01.

3-Azidopyridazine 1-Oxide (X)——1) Reaction of 3-hydrazinopyridazine 1-oxide (XII) and nitrous acid: To a solution of 0.20 g. of XII in 10 cc. of 10% HCl, a solution of 0.12 g. of $NaNO_2$ in 3 cc. of H_2O was added dropwise under cooling. An excess of HNO_2 was decomposed with urea, the reaction mixture was basified with $NaHCO_3$, and extracted with $CHCl_3$, which was evaporated to dryness after drying over Na_2SO_4. The residue was recrystallized from benzene to white needles, m.p. 154~155°. *Anal.* Calcd. fro $C_4H_3ON_5$: C, 35.04; H, 2.21; N, 51.09. Found : C, 34.72; H, 2.21; N, 50.35. Yield, 0.13 g.(60%).

2) Reaction of 3-chloropyridazine 1-oxide (IX) and sodium azide : A mixture of 1.0 g. of IX, 1.0 g. of NaN_3, 20 cc. of EtOH and 4 cc. of H_2O was heated in a sealed tube at 100° for 2 hr. After cooling, the EtOH was distilled off, the residue was dissolved in a small amount of H_2O, and extracted with $CHCl_3$, which was evaporated to dryness after drying over Na_2SO_4. The residue was recrystallized from benzene to pale yellow needles, m.p. 154°. This product, on admixture with the sample prepared in 1., gave no melting-point depression. The IR spectra of these two samples were entirely identical. Yield, 0.46 g.(44%).

Reactions of 6-Ethoxypyridazine 1-Oxide (XV)——1) NH_4OH : Formation of 6-aminopyridazine 1-oxide : A mixture of 0.20 g. of XV, 2 cc. of conc. NH_4OH and 5 cc. of EtOH was heated in a sealed tube at 90° for 2 hr., and the reaction mixture was evaporated to dryness under reduced pressure. The residue was recrystallized twice from EtOH to pale yellow needles, m.p. 209°. The IR spectrum was identical with that of 6-aminopyridazine 1-oxide. Yield, 19 mg.(12%).

2) 80% Hydrazine hydrate : Formation of 6-hydrazinopyridazine 1-oxide (XVII) : A mixture of 4.0 g. of XV, 20 cc. of 80% $NH_2NH_2 \cdot H_2O$ and 20 cc. of EtOH was refluxed for 2 hr. on a water bath, the reaction mixture was evaporated to dryness under reduced pressure, and a few drops of EtOH were added to the residue. Yellow prisms separated were collected and washed with EtOH. Recrystallization from EtOH gave the product, m.p. 160°(decomp.), which was strongly oxidizable with ammoniacal silver nitrate. *Anal.* Calcd. for $C_4H_6ON_4$: C, 38.09; H, 4.80; N, 44.43. Found : C, 38.02; H, 4.76; N, 44.69. Yield, 2.00 g.(56%).

1. Benzaldehyde hydrazone of XVII : Brownish needles (from MeOH), m.p. 161~162°(decomp.). *Anal.* Calcd. for $C_{11}H_{10}ON_4$: C, 61.67; H, 4.71; N, 26.16. Found : C, 61.83; H, 4.62; N, 26.35.

2. Salicylaldehyde hydrazone of XVII : Pale yellow needles (from MeOH), m.p. 186° (decomp.). *Anal.* Calcd. for $C_{11}H_{10}O_2N_4$: C, 57.38; H, 4.38; N, 24.34. Found : C, 57.68; H, 4.64; N, 24.31.

6-Azidopyridazine 1-Oxide (XIX)——To a solution of 0.45 g. of 6-hydrazinopyridazine 1-oxide in 5 cc. of 10% HCl, a solution of 0.25 g. of $NaNO_2$ in 2 cc. of H_2O was added dropwise under cooling, and the reaction mixture was allowed to stand for 20 min. Then the solution was basified with $NaHCO_3$, extracted with $CHCl_3$, and dried over Na_2SO_4. The solvent was concentrated to about 30 cc., then the solution was passed through an alumina column, and eluted with $CHCl_3$. The $CHCl_3$ was evaporated to dryness, and the residue was solidified on standing. Recrystallization from $CHCl_3$ gave the substance, m.p. 102~104°(decomp.), sensitive to light. Pale yellow plates. *Anal.* Calcd. for $C_4H_3ON_5$: C, 35.04; H, 2.21; N, 51.09. Found : C, 35.06; H, 2.62; N, 51.40. Yield, 0.19 g.(39%).

3-Azido-6-chloropyridazine 1-Oxide (XXL) from 3,6-Dichloropyridazine 1-Oxide (XX)——a) A mixture of 0.50 g. of XX, 0.5 g. of NaN_3, 20 cc. of EtOH and 5 cc. of H_2O was heated on a water bath for 1 hr.,

then the solution turned to brown, and it was evaporated to dryness under reduced pressure, The residue was extracted with $CHCl_3$, and it was evaporated to dryness. The residue was recrystallized from a mixture of benzene and petr. benzin with charcoal to pale brownish needles, m.p. 153~154°. *Anal.* Calcd. for $C_4H_2ON_5Cl$: C, 28.00; H, 1.18; N, 40.86. Found : C, 27.71; H, 1.58; N, 40.77. Yield, 0.10 g. (19%).

b) 3-Aminopyridazine 1-oxide from (XXI) : A solution of 0.10 g. of XXI in 10 cc. of MeOH, containing 1 drop of conc. NH_4OH was submitted to reduction over Pd-charcoal, prepared from 4.0 cc. of 1% $PdCl_2$ and 0.1 g. of charcoal. After shaking in H_2 for 15 min., the catalyst was filtered off. The filtrate was evaporated to dryness, the residue was extracted with abs. EtOH, and the extract was concentrated. On standing, slightly brownish needles, m.p. 139° were obtained, and its IR spectrum was identical with that of 3-aminopyridazine 1-oxide. Yield, 19 mg. (29%).

Reactions of 3-Azidopyridazine 1-Oxide (X)——1) Catalytic reduction of X : Formation of 3-aminopyridazine 1-oxide (XXII). A solution of 0.20 g. of X in 25 cc. of MeOH was submitted to reduction over Pd-charcoal, prepared from 2.0 cc. of 1% $PdCl_2$ and 0.1 g. of charcoal. After shaking in H_2 for 20 min., the reaction mixture, seperated from catalyst, was evaporated to dryness. The residue was recrystallized from a mixture of benzene and EtOH to colorless needles, m.p. 140~142°, which gave no depression in mixed melting point determination with XXII. Yield, 46 mg. (28%).

2) Sodium alkoxides : Formation of 3-alkoxypyridazine 1-oxide (XI). a. MeONa : To a solution of 10 mg. of Na in 5 cc. of abs. MeOH, 37 mg. of X was added, and the mixture was heated on a water bath for 1 hr. The MeOH was distilled off, the residue was extracted with $CHCl_3$, and it was evaporated to dryness. White plates, m.p. 79~80°. This product gave no depression in mixed melting point determination with 3-methoxypyridazine 1-oxide. Yield, 27 mg. (80%).

b. EtONa : To a solution of 20 mg. of Na in 10 cc. of abs. EtOH, 0.10 g. of X was added, and the mixture was allowed to stand overnight. The EtOH was evaporated to dryness, then residue was extracted with hot benzene, and it was evaporated to dryness. The residue was recrystallized from a mixture of benzene and petr. benzin to white prisms, m.p. 71~74°. *Anal.* Calcd. for $C_6H_8O_2N_2$: N, 19.99. Found : N, 20.22. Yield, 68 mg. (67%).

c. $C_6H_5CH_2ONa$: Similarly 3-benzyloxypyridazine 1-oxide was obtained by the treatment of X with sodium benzylate as described in b. White needles, m.p. 117°. Yield, 53%. *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.33; H, 4.98; N, 13.86. Found : C, 65.03; H, 5.35; N, 14.00.

3) Thermal decomposition of X in xylene : Formation of 3,3′-azodipyridazine 1,1′-dioxide (XXIII) : A solution of 0.5 g. of X in 20 cc. of xylene was gently refluxed for 5 hr. After cooling, a brownish precipitate that separated out was filtered, washed with benzene, and dried over P_2O_5 *in vacuo*. The black powder was dissolved in hot AcOH, filtered, then diluted with a large amount of water, and allowed to stand overnight. Reddish brown powder that separated out was filtered and dried over P_2O_5 *in vacuo* for 10 hr. at 130°. Black powder, m.p. >320°. Yield, 45 mg. *Anal.* Calcd. for $C_{12}H_6O_2N_6 \cdot \frac{1}{2}H_2O$: C, 42.29; H, 3.11; N, 37.00. Found : C, 42.69; H, 2.89; N, 37.78. From the xylene filtrate, 86 mg. (17%) of X was recovered.

Tetrazolopyridazine (XXIV) from 3-Chloro-6-hydrazinopyridazine——1) 3-Hydrazinopyridazine (XXV): A solution of 1.5 g. of 3-chloro-6-hydrazinopyridazine and 3 cc. of conc. NH_4OH in 30 cc. of MeOH was submitted to reduction over Pd-charcoal, prepared from 12 cc. of 1% $PdCl_2$ and 0.6 g. of charcoal. After H_2 was absorbed, the solution, separated from catalyst, was evaporated to dryness, and the residue was dried *in vacuo*. The residue, having hydrazine-like odor, was extracted with abs. EtOH, and the EtOH was evaporated to dryness. The residue was again extracted with $CHCl_3$, and it was evaporated to dryness in brownish oily product. Yield, 0.45. (40%). Monopicrate : Yellowish fine needles (from EtOH), m.p. 169° (decomp.). *Anal.* Calcd. for $C_4H_6N_4 \cdot C_6H_3O_7N_3$: C, 35.40; H, 2.67; N, 28.80. Found: C, 35.38; H, 2.41; N, 28.35.

2) Tetrazolopyridazine (XXIV) : To a solution of 0.20 g. of XXV in 10 cc. of 5% HCl, a solution of 0.14 g. of $NaNO_2$ in 3 cc. of H_2O was added dropwise under cooling. After 20 min., the solution was neutralized with $NaHCO_3$, then extracted with $CHCl_3$, and the extract was dried over Na_2SO_4. The $CHCl_3$ was evaporated to dryness, and the residue was recrystallized from benzene to white prisms, m.p. 108~111°. This product gave no depression in mixed melting point determination with tetrazolopyridazine, synthesized by Takabayashi's method.[3] Yield, 0.12 g. (55%).

Reactions of 3-Azidopyridazine 1-Oxide with PCl_3 and $POCl_3$——1) PCl_3 : Formation of tetrazolopyridazine (XXIV). A solution of 0.10 g. of X and 1.5 g. of PCl_3 in 5 cc. of $CHCl_3$ was refluxed on a water bath for 3 hr. The reaction mixture was evaporated to dryness under reduced pressure, then 5 cc. of H_2O was added into the residue, and it was allowed to stand for 1 hr. The solution was basified with $NaHCO_3$, extracted with $CHCl_3$, and it was evaporated to dryness after drying over Na_2SO_4. The residue was dissolved in $CHCl_3$, the solution was passed through an alumina column, and eluted with $CHCl_3$, which was evaporated to dryness and the residue was recrystallized from benzene to colorless prisms, m.p. 109°. No depression of melting point was observed on admixture with tetrazolopyridazine. Yield, 28 mg. (32%).

2) $POCl_3$: Formation of 6-chlorotetrazolo[1,5-*b*]pyridazine (II). To a solution of 0.20 g. of X in 10 cc. of $CHCl_3$, 0.3 g. of $POCl_3$ was added dropwise, and the mixture was refluxed on a water bath for 1.5 hr. The reaction mixture was evaporated to dryness under reduced pressure. The residue was basified with $NaHCO_3$, then extracted with $CHCl_3$, the extract was passed through an alumina column after drying over Na_2SO_4, and eluted with $CHCl_3$. The solvent was evaporated to dryness and the residue was solidified on standing. Colorless leaves appeared having a melting point of 104~106°, which gave no depression in mixed melting point determination with the authentic sample. Yield, 0.13 g. (57%).

Reactions of 6-Azidopyridazine 1-Oxide (XIX)——1) Sodium alkoxides : Formation of 6-alkoxypyridazine 1-oxide. a. MeONa : To a solution of 17 mg. of Na in 10 cc. of abs. MeOH, 0.1 g. of XIX was added, and the mixture was allowed to stand overnight. The MeOH was evaporated to dryness, the residue was extracted with hot benzene, the solvent was concentrated, and white plates that separated were collected. They were identical with 6-methoxypyridazine 1-oxide by mixed melting-point determination, m.p. 126~127°. *Anal.* Calcd. for $C_5H_6O_2N_2$: N, 22.22. Found : N, 21.93. Yield, 46 mg. (50%).

b. EtONa : 6-Ethoxypyridazine 1-oxide was similarly obtained as described in a. White leaves, m.p. 51~54°. Yield, 40%.

c. $C_6H_5CH_2ONa$: To a solution of 35 mg. of Na in 10 cc. of benzyl alcohol, 0.20 g. of XIX was added, and the mixture was allowed to stand overnight. The reaction mixture was evaporated to dryness under reduced pressure. The residue was extracted with hot benzene, and the extract was passed through an alumina column after cooling. By washing with benzene the yellow band that eluted was collected, and the solvent was evaporated to dryness. The residue was recrystallized from petr. ether to white leaves, m.p. 83°. *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.33; H, 4.98; N, 13.84. Found : C, 64.86; H, 5.12; N, 13.84. Yield, 42 mg. (14%).

2) Catalytic hydrogenation : Formation of 6-aminopyridazine 1-oxide (XVI). A solution of 0.10 g. of XIX in 20 cc. of EtOH was submitted to reduction over Pd-charcoal, prepared from 5 cc. of 1% $PdCl_2$ and 0.1 g. of charcoal. After H_2 was absorbed, the reaction mixture was heated to boil, and filtered immediately. When the filtrate was concentrated and allowed to stand, white prisms, m.p. 209~211° were deposited. The IR spectrum was identical with that of XVI. Yield, 53 mg. (65%).

3) Desoxygenation : Formation of tetrazolopyridazine (XXIV). Similarly tetrazolopyridazine was produced by the treatment of XIX with PCl_3 as described in the reactions of 3-azidopyridazine 1-oxide. Pale brownish prisms (from benzene), m.p. 108°. Yield, 16 mg. (36%).

Comparison of Radical Reactivity with DPPH——Each 2.00 mg. of these azides was added into a solution of 0.50 mg. of DPPH in 5.0 cc. of anhyd. benzene, containing 3 drops of MeOH, and the purple solution was heated in a water bath at 90°. When the characteristic color was visually disappeared, its time was measured and the result was shown under. 6-Azidopyridazine 1-oxide : about 2.5 min., 3-Azidopyridazine 1-oxide : about 3.2 hr., 3-Azido-6-chloropyridazine 1-oxide : about 3.2 hr.

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Summary

Treatment of 3,6-dichloropyridazine (III) with sodium azide resulted in the formation of a mixed azido-tetrazolo compound (IV).

3-Azidopyridazine 1-oxide (X) and 6-azidopyridazine 1-oxide (XIX) were synthesized from the corresponding hydrazino compounds (XII, XVII) with nitrous acid, and also from chloro compound IX with sodium azide.

Then several reactions, such as ionic reaction, catalytic hydrogenetion, thermal decomposition, reactions with phosphorus trichloride and with phosphorus oxychloride, and reaction with DPPH of these azides were examined.

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