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32. Takanobu Itai and Sachiko Natsume: Potential Anticancer Agents. XIV.*1 Reaction of 3-Substituted Pyridazine 1-Oxide with Benzoyl Nitrate.

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In an earlier paper[1] dealing with the reaction between pyridazine 1-oxide (I) and benzoyl nitrate, it was reported that the formation of two kinds of nitro N-oxides, 3-nitro- (II) and 5-nitro-pyridazine 1-oxide (III) was observed in 33% and 0.8% yields respectively. The former (II) was shown to react with nucleophilic reagents, leading readily to various 3-substituted pyridazine 1-oxides, and II was proved to possess bacterio- and carcino-static activity as well. Chemical behavior and biological activity of the latter compound (III), however, have not been tested because of its poor production due to the competitive reaction with the preferential formation of 3-nitro compound (II). Thus, reactions of 3-substituted pyridazine 1-oxide with benzoyl nitrate were carried out in order to gain 5-nitro 1-oxide derivatives in better yield and to examine their properties.

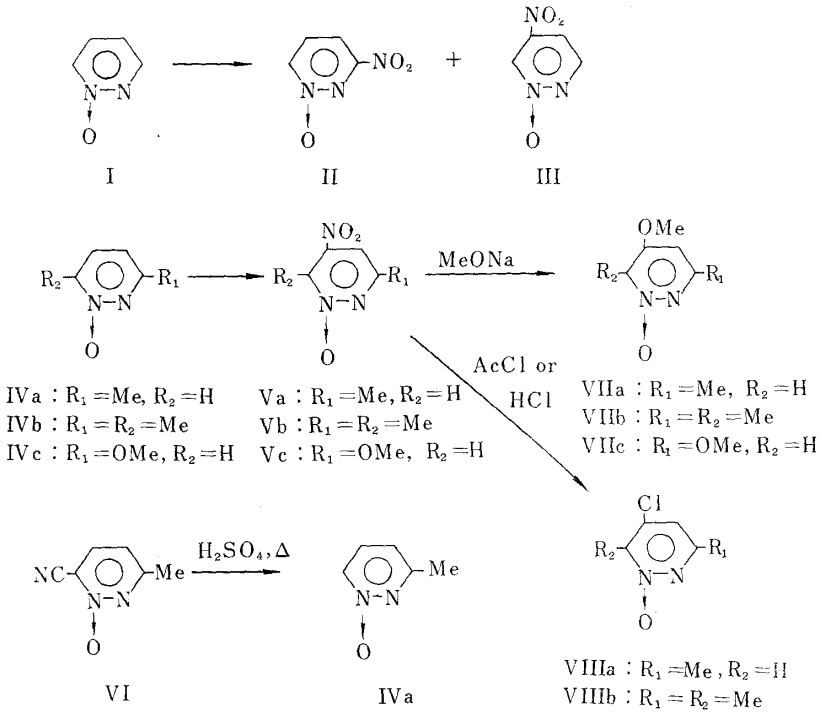


Chart 1.

Nitration of 3-Substituted Pyridazine 1-Oxides

3-Substituted pyridazine 1-oxides (IVa : R_1=Me, R_2=H; IVb : R_1,R_2=Me; IVc : R_1=OMe, R_2=H; IVd : R_1,R_2=OMe) were treated with benzoyl chloride-silver nitrate in the same manner as described in the previous paper.[1] IVa, IVb, and IVc afforded their

*1 Part XIII. T. Itai, S. Sako, G. Okusa : This Bulletin, **11**, 1146 (1963).
*2 Tamagawa-yoga, Setagaya, Tokyo (板井孝信, 夏目幸子).
1) T. Itai, S. Natsume : This Bulletin, **11**, 342 (1963).

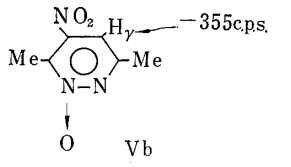
corresponding mononitro derivatives (Va, m.p. 94°, Vb, m.p. 85~86°, and Vc, m.p. 135~136°), while 3,6-dimethoxypyridazine 1-oxide (Ⅳd) formed no nitrated compound but a cleavage of one methoxyl group took place. The yields and the characters of mononitropyridazine 1-oxides synthesized here, are listed in Table I. In the case of the nitration of Ⅳb, a small amount of colorless plates (Ⅵ), m.p. 149~151°, was isolated as a by-product. It was determined to be 3-methyl-6-cyanopyridazine 1-oxide*3 on the basis of the analytical values, the infrared spectral data (ν_{CN} : 2230 cm^{-1}) and the fact that the hydrolysis including a simultaneous decarboxylation afforded 3-methylpyridazine 1-oxide (Ⅳa).

Table I. 3-Substituted-5-nitropyridazine 1-Oxides

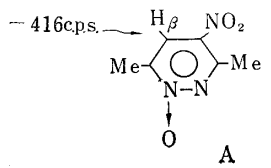
Compd. No.	Yield, % (Recovery)	m.p. (°C)	Appearance (Recryst. solvents)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Va	12 (43)	94	yellow plates ((iso-C_3H_7)$_2$O)	$C_5H_5O_3N_3$	38.71	3.25	27.09	39.20	3.53	26.86
Vb	25 (31)	85~86	yellow needles ((iso-C_3H_7)$_2$O)	$C_6H_7O_3N_3$	42.60	4.17	24.85	42.63	4.34	24.49
Vc	11 (21)	135~136	yellow prisms (benzene)	$C_5H_5O_4N_3$	35.09	2.95	24.56	35.71	3.01	24.75

Among these mononitro derivatives, Vc is apparently 3-methoxy-5-nitropyridazine 1-oxide, because its physical properties (Table I) differ from those of 4-nitro[2,3] and 6-nitro[3] derivatives, which have been derived from Ⅳ by nitration with the mixed acid and their structures have been determined chemically.[2,3]

Similarly, the structure of Vb was deduced to be 5-nitro-3,6-dimethylpyridazine 1-oxide because of no identity with the nitration product (A)[4] of Ⅳb with the mixed acid, whose structure was claimed[5] to be 4-nitro compound by Sako, based on the fact that the 1-methoxy-4(1*H*)-pyridazinone type compound could be derived from A *via* a series of reactions. Nuclear magnetic resonance spectra of Vb and Sako's compound (A) were examined in order to elucidate the structures of these conpounds.*4 When the spectra were measured in dioxane solutions containing cyclohexane as an internal standard, Vb showed a single peak assigned to a ring proton at −355 c.p.s. from cyclohexane, whereas, a ring proton signal of Sako's compound (A) appeared at −416 c.p.s. Recent reports on nuclear magnetic resonance study of pyridazine derivatives have concluded[6,7] that the introduction of N-oxide function to a pyridazine ring causes appreciable downward shift for a proton located at β-position to N-oxide group and upward shift for a γ-proton compared with those of the parent base.



Vb



A

*3 A similar formation of α-cyano N-oxide was reported as a by-product in the nitration reaction of quinaldine N-oxide with benzoyl nitrate. H. Tanida : This Bulletin, **7**, 540 (1959).

*4 Spectra were measured by a Varian Associates DP-60 NMR spectrometer with 60 c.p.s. oscillator. The authors are much indebted to Dr. Y. Kawazoe for his co-operation of NMR spectra and helpful discussion.

2) H. Igeta : This Bulletin, **8**, 550 (1960).
3) T. Nakagome : Yakugaku Zasshi, **80**, 712 (1960); *Ibid.*, **81**, 554 (1961).
4) T. Itai, S. Sako : This Bulletin, **9**, 149 (1961).
5) S. Sako : *Ibid.*, **11**, 337 (1963).
6) Y. Kawazoe, S. Natsume : Yakugaku Zasshi,, **83**, 523 (1963).
7) K. Tori, M. Ogata, H. Kano : This Bulletin, **11**, 235 (1963).

The proton signal peaks attributable to ring protons of Vb and A are reasonably interpreted by formulating their structures to be 5-nitro and 4-nitro compound respectively, and Vb having a γ-proton showed a ring proton peak in the higher field than the compound (A) having β-proton.

Ultraviolet absorption spectrum of the nitration product (Va) was compared with those of Vb and 5-nitropyridazine 1-oxide[1] (Fig. 1). An obvious resemblance of the spectral curves of these three compounds leads the conclusion that Va has to be 5-nitro N-oxide. In this connection, ultraviolet absorption spectra of 3-nitropyridazine 1-oxide[1] and 4-nitropyridazine 1-oxide derivatives*[5,4,8] are shown in Fig. 2. Characteristic curves to each 3-, 4-, and 5-nitro compound series suggest that ultraviolet spectra measurement may offer an effective clue for the structural determination of unknown nitro compound derived from alkyl pyridazine 1-oxide.

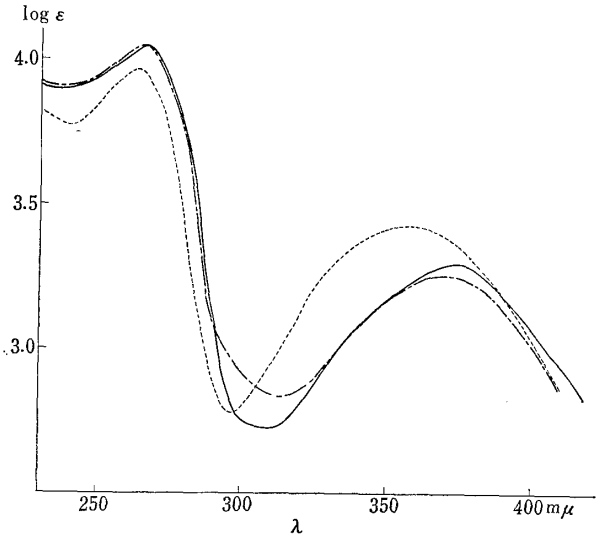


Fig. 1. Ultraviolet Absorption Spectra (in 95% ethanol)

——— 5-nitropyridazine 1-oxide (III)
-·-·- 3-methyl-5-nitropyridazine 1-oxide (Va)
- - - - - 5-nitro-3,6-dimethylpyridazine 1-oxide (Vb)

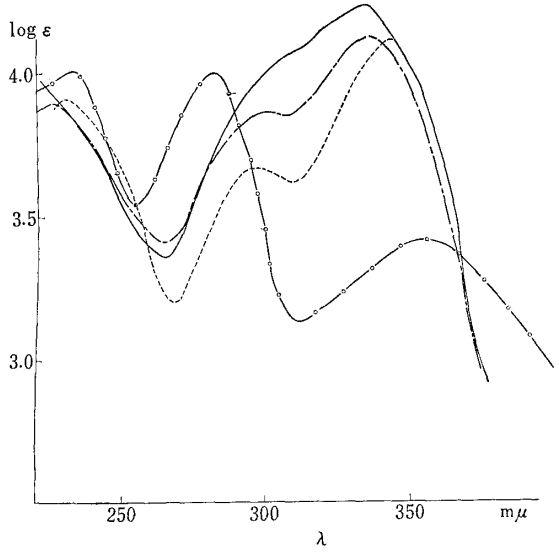


Fig. 2. Ultraviolet Absorption Spectra (in 95% ethanol)

——— 4-nitropyridazine 1-oxide
-·-·- 3-methyl-4-nitropyridazine 1-oxide
- - - - - 4-nitro-3,6-dimethylpyridazine 1-oxide
○—○ 3-nitropyridazine 1-oxide (II)

The structure of Va was confirmed by the chemical reaction which correlated Va with 5-nitro-3,6-dimethyl pyridazine 1-oxide (Vb), as discussed in the next section.

Reactions of 5-Nitropyridazine 1-Oxides

Reactions of 5-nitro group on the compounds prepared above were examined under the similar condition to the case of 4-nitro- and 3-nitro-pyridazine 1-oxide described in the previous papers.[1,8] By treatment with sodium methoxide at room temperature, all of 5-nitropyridazine 1-oxide derivatives examined here, afforded readily their corresponding 5-methoxypyridazine 1-oxides derivatives (VIIa, m.p. 112°; VIIb, m.p. 142°[5]; VIIc, m.p. 131°) in good yields (Table II). Measurement of ultraviolet absorption spectra on VIIa and comparison with those of 5-, 4-, and 6-methoxypyridazine 1-oxide provides another structural confirmation that VIIa belongs to 5-substituted series (Fig. 3).

Concentrated hydrochloric acid reacted with Va and Vb with an evolution of nitrogen dioxide. The latter (Vb), gave 5-chloro-3,6-dimethyl pyridazine 1-oxide (VIIIb)[5] in

*5 T. Nakagome : Yakugaku Zasshi, **81**, 1817 (1961); This Bulletin, **11**, 726 (1963). The samples of 3-methyl-4-nitropyridazine 1-oxide was supplied by Dr. T. Nakagome. We wish to thank him for kindness.

8) T. Itai, S. Natsume : This Bulletin, **11**, 83 (1963).

9) *Idem* : *Ibid.*, **10**, 643 (1962).

69% yield by heating at 100°, while, the former (Va) was chlorinated to 3-methyl-5-chloropyridazine 1-oxide (VIIIa) only in 7% yield, accompanied by recovery of 67% of the starting material. Vc did not afford the corresponding 5-chloro 1-oxide under the same condition.

The more smooth preparation of VIIIa was achieved in good yield (63%) by treatment of Va with boiling acetyl chloride. When the reaction was carried out at 30°, the formation of VIIIa resulted in only 2% yield. These results suggest that Va has the comparable reactivity of 3-nitropyridazine 1-oxide.[1)]

On the other hand, in the reaction of Vb with acetyl chloride at 35°, the expected 5-chloro-3,6-dimethylpyridazine 1-oxide (VIIIb) was obtained only in 9% yield and the main reaction product was colorless needles (IX), m.p. 162~163°, having a positive Beilstein test. Its analytical values corresponded to $C_6H_4N_3Cl$, and a week band at 2200 cm^{-1} in the infrared spectrum was attributable to cyano group, so that IX was obviously 5-chloro-monomethyl-monocyanopyridazine 1-oxide. Its formation is reasonably explained by the attack of acetyl nitrite, which would be produced during the reaction, to the one of the two methyl groups of Vb, followed by the successive elimination of acetic acid. The similar case has been observed by Hamana[10)] and Kato[11)] independently in the reactions of 4-nitroquinaldine 1-oxide with acetyl chloride and 4-nitropicoline 1-oxide with the same reagent, and they have postulated the above reaction mechanism in view of the reasonable interpretation about the formation of the reaction products.

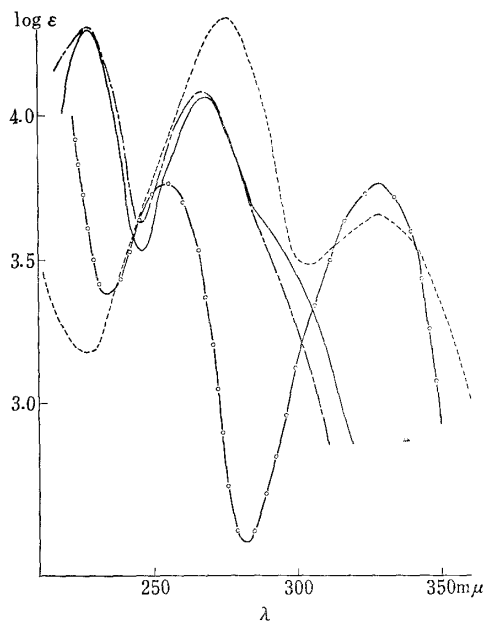


Fig. 3. Ultraviolet Absorption Spectra (in 95% ethanol)

——— 3-methyl-5-methoxypyridazine 1-oxide (VIIa)
-·-·- 5-methoxypyridazine 1-oxide
- - - - - 4-methoxypyridazine 1-oxide
○—○ 6-methoxypyridazine 1-oxide

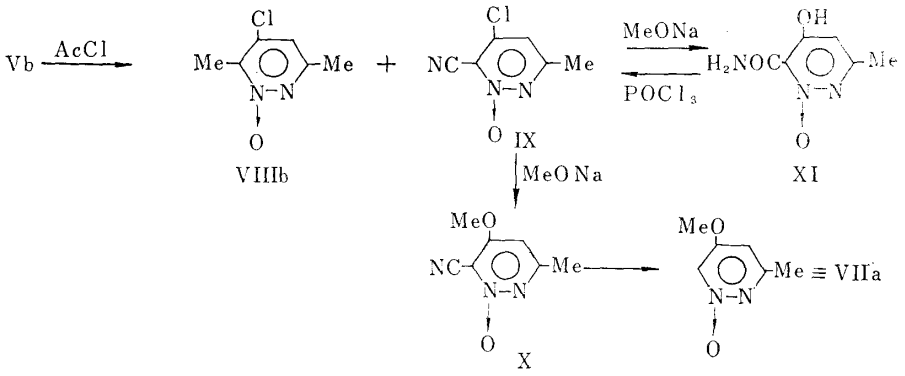


Chart 2.

The structure of 3-methyl-5-chloro-6-cyano pyridazine 1-oxide may be formulated for the cyano compound (IX) since no compound containing cyano group was detected in the similar reaction of 3-methyl-5-nitropyridazine 1-oxide (Va) and the production of

10) M. Hamana, S. Saeki, Y. Hatano, M. Nagakura : Yakugaku Zasshi, **83**, 348 (1963).
11) T. Kato, H. Hayashi : *Ibid.*, **83**, 352 (1963).

cyano group seemed to be concerned with methyl group adjacent to the N-oxide function. In order to verify this formulation the following experiments were undertaken (Chart 2). IX was treated with an equimolar amount of methanolic sodium methoxide, and the corresponding 5-methoxy derivative (X) thus obtained was hydrolyzed by refluxing with ca. 65% sulfuric acid. Simultaneous decarboxylation reaction took place and the colorless needles obtained here, m.p. 107~109°, were indentified as 3-methyl-5-methoxypyridazine 1-oxide (VIIa), derived directly from 3-methyl-5-nitropyridazine 1-oxide (Va) by methoxylation as mentioned above. Hence, the structure of IX was confirmed and, at the same time, the position of nitro group on Va was determined chemically. When two molar equivalents of sodium methoxide reacted with IX under rather drastic condition, 3-methyl-6-carboxamido-5-pyridazinol 1-oxide (XI), m.p. 220°, was isolated as a main reaction product. The structure of XI was determined on the basis of its analytical values, its infrared spectrum and the ready formation of the starting material (IX) with phosphoryl chloride.

In brief view of the reactions, it might say that the reactivity of 5-nitro group is comparable to that of 3-nitro group and lower than that of 4-nitro group qualitatively, except the case of 5-nitro-3,6-dimethyl pyridazine 1-oxide.

Treatment of 3,6-Dimethoxypyridazine 1-Oxide (IVd) with Benzoyl Chloride-Silver Nitrate

As mentioned above, 5-nitro derivatives of 3-methyl-, 3,6-dimethyl-, and 3-methoxypyridazine 1-oxide (Va, Vb, and Vc) were synthesized successfully by treating the corresponding N-oxides with benzoyl chloride-silver nitrate. However, when treated under the similar condition, 3,6-dimethoxypyridazine 1-oxide (IVd) did not form any nitrated compound, but two kinds of colorless crystals (XII, m.p. 178° and XIII, m.p. 134°) were isolated as the reaction products. One of these, XII, was found to be a hydroxamic acid type of compound from its infrared absorption spectrum (pyridone type carbonyl at 1673 cm^{-1} and a complex band at 2300~2700 cm^{-1} attributable to OH) and a positive reaction to ferric chloride test, and further, XII was determined to be 1-hydroxy-3-methoxy-6(1*H*)-pyridazinone, the hydrolysate[12] of 3,6-dimethoxypyridazine 1-oxide (IVd) with dilute hydrochloric acid. The other product, XIII, was deduced to be N-O-benzoyl derivative of XII, on the basis of the analytical values, the characteristic infrared spectrum (N-OBz at 1770 and pyridone type carbonyl at 1664 cm^{-1}) and the fact that XIII was produced by benzoylation of XII and hydrolyzed to give XII under a very mild condition. A similar cleavage of α-alkoxy N-oxide to hydroxamic acid type of compound had been reported by Ochiai and Kaneko[13] in the reaction of 2-ethoxyquinoline 1-oxide with benzoyl nitrate.

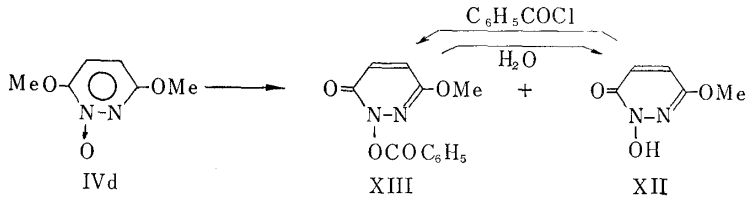


Chart 3.

Experimental

General Procedure for Nitration of 3-Substituted Pyridazine 1-Oxides (IV) with Benzoyl Chloride-Silver Nitrate——To a cold $CHCl_3$ solution of an N-oxide (IV), an equimolar amount of BzCl was added,

12) T. Nakagome: Yakugaku Zasshi, 82, 244 (1962).
13) E. Ochiai, C. Kaneko: This Bulletin, 8, 284 (1960).

followed by the addition of an equimolar amount of finely powdered $AgNO_3$ below $-10°$ with stirring. Stirring was continued for 4 hr. at the same temperature and the mixture was allowed to stand for 4 to 5 days at room temperature. AgCl which precipitated was filtered, washed with hot $CHCl_3$, and the filtrate was combined with the washings and evaporated to dryness. The residual yellow syrup was dissolved in benzene. The benzene solution was extracted with dil. HCl, the HCl layer was evaporated *in vacuo* below 50°, neutralized with $NaHCO_3$ and evaporated. The residue (A) contained the starting material mainly, accompanied by a part of 5-nitro compound. Next, the benzene layer was extracted with satd. $NaHCO_3$. The $NaHCO_3$ extract was acidified with HCl and extracted with Et_2O, and, successively with $CHCl_3$. The Et_2O layer (B) gave a nearly theoretical amount of BzOH after evaporation, and the $CHCl_3$ extract (C) gave another crop of crude 5-nitro compound.

Finally, the benzene layer was dried and evaporated. From this residue (D), 5-nitro compound was obtained mainly.

The fractions (A, B, and D) were passed through Florisil columns, if necessary. 5-Nitro compounds were obtained from the first fractions eluted with benzene, and next the starting materials were eluted in the case of Ⅳa and Ⅳc. But, in the case of Ⅳb, 3-methyl-6-cyanopyridazine 1-oxide (Ⅵ) was obtained from the fraction eluted next to the 5-nitro compound fraction and the starting material (Ⅳb) was isolated from the third fraction. (Ⅵ), colorless plate, m.p. 149~151° (from benzene). Yield, 0.8%. IR ν_{max}^{KBr} : 2230 cm^{-1}. *Anal.* Calcd. for $C_6H_5O_3N$: N, 31.10. Found : N, 31.42. The yields and the characters of 5-nitropyridazine 1-oxide are listed in Table I.

Treatment of 3-Methyl-6-cyanopyridazine 1-Oxide (VI) with Sulfuric Acid——A solution of 20 mg. of Ⅵ in a mixture of 0.5 ml. of H_2O and 1 ml. of conc. H_2SO_4 was heated at 140° for 3 hr. The mixture was poured into ice-H_2O, basified with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated. The residue was recrystallized from (iso-C_3H_7)$_2$O, to give 7 mg. of hygroscopic needles, m.p. 68°, identical with 3-methylpyridazine 1-oxide (Ⅳa) on admixture and by comparison of the IR spectra. $HgCl_2$ complex : m.p. 169°, undepressed on admixture with $HgCl_2$ salt of 3-methylpyridazine 1-oxide.*6

Reaction of 5-Nitropyridazine 1-Oxide (V) with Sodium Methoxide, General Procedure——A solution of 85~90 mg. of 5-nitropyridazine 1-oxides (Ⅴ) in 5~10 ml. of MeOH was added to a MeOH solution containing an equimolar amount of MeONa and the mixture was allowed to stand at room temperature for 1.5~3 hr. MeOH was distilled off *in vacuo*, the residue was extracted with $CHCl_3$, and $CHCl_3$ extract was dried and evaporated. The crystalline residue was recrystallized from suitable solvents. Yields and characters of 5-methoxypyridazine 1-oxides obtained here are shown in Table Ⅱ.

Table Ⅱ. 3-Substituted-5-methoxypyridazine 1-Oxides

Compd. No.	Yield (%)	m.p. (°C)	Appearance (Recryst. solvents)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ⅷa	74	112	colorless needles (benzene-benzin)	$C_6H_8O_2N_2$	51.42	5.75	19.99	51.78	5.58	20.00
Ⅷb	78	142	〃 (benzene) a)							
Ⅷc	87	131	〃 (〃)	$C_6H_8O_3N_2$	46.15	5.38	17.94	46.79	5.38	18.11

a) Ⅷb was identical with authentic 5-methoxy-3,6-dimethylpyridazine 1-oxide[5] on admixture and by comparison of IR spectra.

Reaction of V with conc. Hydrochloric Acid——i) 3-Methyl-5-chloropyridazine 1-oxide (Ⅷa) : A solution of 46 mg. of Ⅴa in 1 ml. of conc. HCl was heated at 100° for 30 min. HCl was removed under reduced pressure, the residue was basified with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated. The residue was passed through Al_2O_3 column. From the fraction eluted with benzene, the starting material (Ⅴa), m.p. 90°, was recovered (31 mg., 67%). From the fraction eluted with $CHCl_3$, 6 mg. of colorless needles (Ⅷa), m.p. 144°, was obtained after recrystallization from (iso-C_3H_7)$_2$O. Beilstein test : positive. This was identical with the reaction product of Ⅴa with AcCl by the mixed melting point determination and the comparison of IR spectra.

ii) 5-Chloro-3,6-dimethylpyridazine 1-oxide (Ⅷb) : A mixture of 70 mg. of Ⅴb and 1 ml. of conc. HCl was treated as above. After purification of the crude product by Al_2O_3 chromatography, followed by recrystallization from (iso-C_3H_7)$_2$O, 45 mg. (69%) of colorless needles (Ⅷb), m.p. 126°, was obtained.

*6 $HgCl_2$ salt of 3-methylpyridazine 2-oxide : m.p. 138°.

Beilstein test : positive. This was undepressed on admixture with authentic 5-chloro-3,6-dimethylpyridazine 1-oxide.[5] IR and UV : identical with those of the authentic sample in all respects.

iii) By treatment of Vc with conc. HCl under the above condition, 76% of the starting material was recovered and no 3-methoxy-5-chloropyridazine 1-oxide was detected.

Reaction of V with Acetyl Chloride——i) 3-Methyl-5-chloropyridazine 1-oxide (VIIIa) : A solution of 60 mg. of Va in 2 ml. of AcCl was refluxed for 5 hr. NO_2 gas evolution was apparently observed. After AcCl was removed off under reduced pressure, the residue was basified with satd. $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated. The residue was recrystallized from (iso-$C_3H_7)_2O$ to give 35 mg. (63%) of slightly yellowish needles (VIIIa), m.p. 148°. *Anal.* Calcd. for $C_5H_5ON_2Cl$: C, 41.54; H, 3.49. Found : C, 41.63; H, 3.79. UV $\lambda_{max}^{95\%\,EtOH}$ mμ (log ε) : 268 (4.04), 317～318 (3.60).

When Va was allowed to stand at 30° for 3 hr., the major part of the starting material was recovered and 5-chloro compound (VIIIa) was isolated in only 2% yield.

ii) Reaction of 5-nitro-3,6-dimethylpyridazine 1-oxide (Vb) with AcCl : Formation of 5-chloro-3,6-dimethylpyridazine 1-oxide (VIIIb) and 3-methyl-5-chloro-6-cyanopyridazine 1-oxide (IX). A solution of 85 mg. of Vb in 1 ml. of AcCl was warmed at 35°. Immediately, precipitates deposited and yellow color of the solution faded slowly. NO_2 gas evolution was observed. During warming, the precipitate went into solution again and at the end of the reaction (after ca. 2.5 hr.), a nearly clear solution was obtained.

The reaction mixture was treated as above, the crystalline residue was recrystallized from benzene to give 40 mg. of colorless needles (IX), m.p. 162～163°. *Anal.* Calcd. for $C_6H_4ON_3Cl$: C, 42.49; H, 2.38; N, 24.78. Found : C, 42.49; H, 2.62; N, 24.70. IR : ν_{max}^{KBr} 2220 cm^{-1}(CN).

The mother liquor was passed through Al_2O_3 column. From the first fraction eluted with benzene, 8 mg. of IX was obtained. Total yield of IX, 48 mg. (60%).

From the second fraction eluted with benzene-$CHCl_3$ (1:1), 7 mg. of VIIIb, m.p. 125～127°, was obtained. Yield, 9%. This was undepressed on admixture with authentic 3,6-dimethyl-5-chloropyridazine 1-oxide.

Reaction of 3-Methyl-5-chloro-6-cyanopyridazine 1-Oxide (IX) with Sodium Methoxide——i) A suspension of 170 mg. of IX in 10ml. of abs. MeOH and a methanolic solution of MeONa prepared from 30 mg. of Na and 3 ml. of MeOH was mixed and the mixture was refluxed for 1 hr. MeOH was evaporated under reduced pressure and 3 ml. of H_2O was added to the residue. Needle-like crystals which deposited were extracted with $CHCl_3$. Evaporation of the $CHCl_3$ extract gave 145 mg. of colorless crystals, m.p. 180～185°, which was recrystallized from benzene to yield 130 mg. (75%) of colorless needles (X), m.p. 185°. *Anal.* Calcd. for $C_7H_7O_2N_3$: C, 50.91; H, 4.27; N, 25.45. Found : C, 50.59; H, 3.92; N, 25.70. IR : ν_{max}^{KBr} 2220 cm^{-1}(CN).

ii) A suspension of 0.13 g. of IX in 8 ml. of abs. MeOH was added to a MeONa solution prepared from 50 mg. of Na and 3 ml. of MeOH and the mixture was heated at 100° in a sealed tube for 6 hr. MeOH was distilled off under reduced pressure, the residue was dissolved in a small amount of H_2O and extracted with $CHCl_3$. From the $CHCl_3$ extract, only 7 mg. of colorless crystals, m.p. ca. 110°, was obtained. Acidification of the aqueous layer with HCl, followed by recrystallization of the crystalline precipitates from MeOH gave 95 mg. (73%) of colorless fine dice (XI), m.p. 220°. $FeCl_3$ test : orange. *Anal.* Calcd. for $C_6H_7O_2N_3$: C, 42.60, H, 4.17; N, 24,85. Found : C, 42.00; H, 4.32; N, 25.41. IR ν_{max}^{KBr} cm^{-1} : 3325, 3230, 2700～2600, 1663, 1628.

Reaction of XI with $POCl_3$: a suspension of 20 mg. of XI in 2 ml. of $POCl_3$ was heated at 100° for 30 min. All the crystals went into solution immediateiy. $POCl_3$ was distilled off under reduced pressure. The syrupy residue was basified with satd. $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried and evaporated. The residue was passed through an Al_2O_3 column using $CHCl_3$. 14 mg. of colorless crystals, m.p. 145～151°, was obtained, recrystallization of which gave colorless needles, m.p. 161°. This was identical with 3-methyl-5-chloro-6-cyanopyridazine 1-oxide (IX) by the mixed melting point determination and comparison of the IR spectra.

Reaction of 3-Methyl-5-methoxy-6-cyanopyridazine 1-Oxide (X) with Sulfuric Acid——A solution of 80 mg. of X in a mixture of 2 ml. of conc. H_2SO_4 and 1 ml. of H_2O was treated as in the case of VI (CO_2 evolution was observed). The crystalline residue, m.p. 100～105° (40 mg., 59%), was recrystallized from benzin-benzene (1:1) to colorless needles, m.p. 107～109°. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N; 19.99. Found : C, 51.88; H, 5.58; N, 19.92. This was undepressed on admixture with the above-mentioned 3-methyl-5-methoxypyridazine 1-oxide (VIIa). IR and UV : identical with those of VIIa in all respects.

Treatment of 3,6-Dimethoxypyridazine 1-Oxide (IVd) with Benzoyl Chloride-Silver Nitrate——To a solution of 0.5 g. of IVb in 10 ml. of $CHCl_3$ was added 0.4 ml. (0.46 g) of BzCl under cooling and to the mixture 0.5 g. of finely powdered $AgNO_3$ was added at −10° with stirring. Stirring was continued at the same temperature for 2 hr., and the mixture was allowed to stand for further 70 hr. at room temperature. AgCl was filtered off and the firtrate was washed with satd. $NaHCO_3$ and 5% HCl succes-

sively. After drying over Na_2SO_4, the $CHCl_3$ layer was evaporated and 0.65 g. of crystalline residue was obtained. This was recrystallized from EtOH to yield 0.44 g. (56%) of colorless dice (XIII), m.p. 133~134°. *Anal.* Calcd. for $C_{12}H_{10}O_4N_2$: C, 58.53; H, 4.09; N, 11.38. Found : C, 58.29; H, 4.14; N, 11.34. IR ν_{max}^{KBr} cm^{-1} : 1770 (N-OBz), 1685 (-N-CO-).

The mother liquor was concentrated to dryness and recrystallized from Me_2CO to yield 0.12 g. (26%) of colorless needles, XII, m.p. 178°. $FeCl_3$: reddish violet. *Anal.* Calcd. for $C_5H_6O_3N_2$: C, 42.25; H, 4.26; N, 19.71. Found : C, 42.12; H, 4.27; N, 19.38. IR ν_{max}^{KBr} cm^{-1} : 2300, 2700, 1673. No m.p. depression on admixture with 1-hydroxy-3-methoxy-6(1*H*)-pyridazinone.[12]

From HCl layer, after the neutralization with K_2CO_3 and the extraction with $CHCl_3$, 55 mg. (11%) of the starting material (IVd) was recovered.

Benzoylation of XII : To a solution of 0.1 g. of XII in 1 ml. of dehyd. pyridine was added 0.23 g. of BzCl and the mixture was allowed to stand overnight at room temperature. The mixture was poured into 3 ml. of H_2O under cooling. A reddish oil which separated was crystallized with rubbing. The crystals were collected by filtration, washed with H_2O and $CHCl_3$. 130 mg. of colorless product, m.p. 130~133°, was obtained. This was undepressed on admixture with XIII.

Treatment of XIII with H_2O at 100° : A mixture of 80 mg. of XIII in 2 ml. of H_2O was heated on a boiling water bath for 1.5 hr. H_2O was evaporated to dryness under reduced pressure, and the residue was washed with $(iso\text{-}C_3H_7)_2O$. 25 mg. of colorless needles, m.p. 175°, was obtained. This was identical with XII on admixture and by comparison of the IR spectra.

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Summary

The nitration of 3-methyl-, 3,6-dimethyl-, and 3-methoxypyridazine 1-oxide with benzoyl chloride-silver nitrate afforded their corresponding 5-nitro derivatives, while in the reaction of 3,6-dimethoxypyridazine 1-oxide with the same reagents, no nitro compound was detected but 1-hydroxy-3-methoxy-6(1*H*)-pyridazinone and its benzoyl derivative were produced. Some nucleophilic substitution reactions related to 5-nitropyridazine 1-oxides obtained here, were described.

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