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Studies on the Synthesis of Pyridazine Derivatives. X.[1] Reaction of 3,6-Dimethoxy-4-nitropyridazine 1-Oxide with Alkyl Halides[2]

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Reaction of 3,6-dimethoxy-4-nitropyridazine 1-oxide (I) with alkyl halides were investigated, and following results were obtained.

1) Reaction with methyl iodide gave 1,3,4-trimethoxy-6(1*H*)pyridazinone (II).
2) Reaction with ethyl iodide gave 1,4-diethoxy-3-methoxy-6(1*H*)pyridazinone (IV).
3) Reaction with ethyl chlorocarbonate gave 1-ethoxycarbonyloxy-3-methoxy-4-chloro-(VI) and 1,4-bisethoxycarbonyloxy-3-methoxy-6(1*H*)pyridazinone (VII).
4) Reaction with ethyl bromoacetate gave 1,4-bisethoxycarbonylmethoxy-3-methoxy-6(1*H*)pyridazinone (IX).

Moreover the reaction of 4-nitropyridazine 1-oxide derivatives with methyl iodide was described.

1) Reaction with 3-methoxy-4-nitro-6-methylpyridazine 1-oxide (XIII) gave 3,4-dimethoxy-6-cyanopyridazine 1-oxide (XV) and 1-methyl-3-methoxy-6-cyano-4(1*H*)pyridazinone (XVI).
2) Reaction with 6-methoxy-4-nitropyridazine 1-oxide (XIV) gave 1,4-dimethoxy-6(1*H*)pyridazinone (XX).

In the previous paper[4] of this series, it was reported that the reaction of 3,6-dimethoxy-4-nitropyridazine 1-oxide (I) with acetylchloride gave 1-acetoxy-3-methoxy-4-chloro-6(1*H*)-pyridazinone.

This paper describes the reaction of 3,6-dimethoxy-4-nitro-(I), 3-methoxy-4-nitro-6-methyl-(XIII) and 4-nitro-6-methoxypyridazine 1-oxide (XIV) with alkyl halides.

Reaction of I with methyl iodide gave colorless prisms mp 157° in 65% yield. Its infrared absorption spectrum showed at 1668 cm^{-1} (ring carbonyl), and ultraviolet absorption spectrum showed only one absorption maximum at 290 mμ, the elemental analysis was identified with $C_7H_{10}O_4N_2$. This product was found to be identical with 1,3,4-trimethoxy-6(1*H*)pyridazinone[5] (II) by mixed melting point determination and infrared comparison. Similaly, reaction with ethyl iodide gave 1,4-diethoxy-3-methoxy-6(1*H*)pyridazinone (IV), which gave colorless needles mp 133° in 70% yield. It was found to be identical with authentic specimen which was synthesized by reaction of 3,6-dimethoxy-4-ethoxypyridazine 1-oxide (V) with ethyl iodide, by mixed melting point determination and infrared comparison. 3,6-Dimethoxy-4-ethoxypyridazine 1-oxide (V) was synthesized by treatment of I with ethanolic sodium ethylate at room temperature.

Thus, the reaction gave not halogen contained product, but alkoxy compounds, which were imported alkyl group of alkyl halides, and the position of alkoxy group retained that of nitro group. It was suggested that alkyl cation attacked to oxygen atom of nitro group initialy, following the oxygen attacked to pyridazine ring.

Reaction of I with ethyl chlorocarbonate gave a mixture of 1-ethoxycarbonyloxy-3-methoxy-4-chloro-6(1*H*)pyridazinone (VI) and 1,4-bisethoxycarbonyloxy-3-methoxy-6(1*H*)-

1) Part IX: *Chem. Pharm. Bull.* (Tokyo), **16**, 972 (1968).
2) Short communication was reported to *Yakugaku Zasshi*, **86**, 1124 (1966).
3) Location: *4-23 Bunkyo-machi, Nagasaki.*
4) M. Yanai and T. Kinoshita, *Yakugaku Zasshi*, **86**, 314 (1966).
5) T. Itai and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **11**, 1073 (1963).

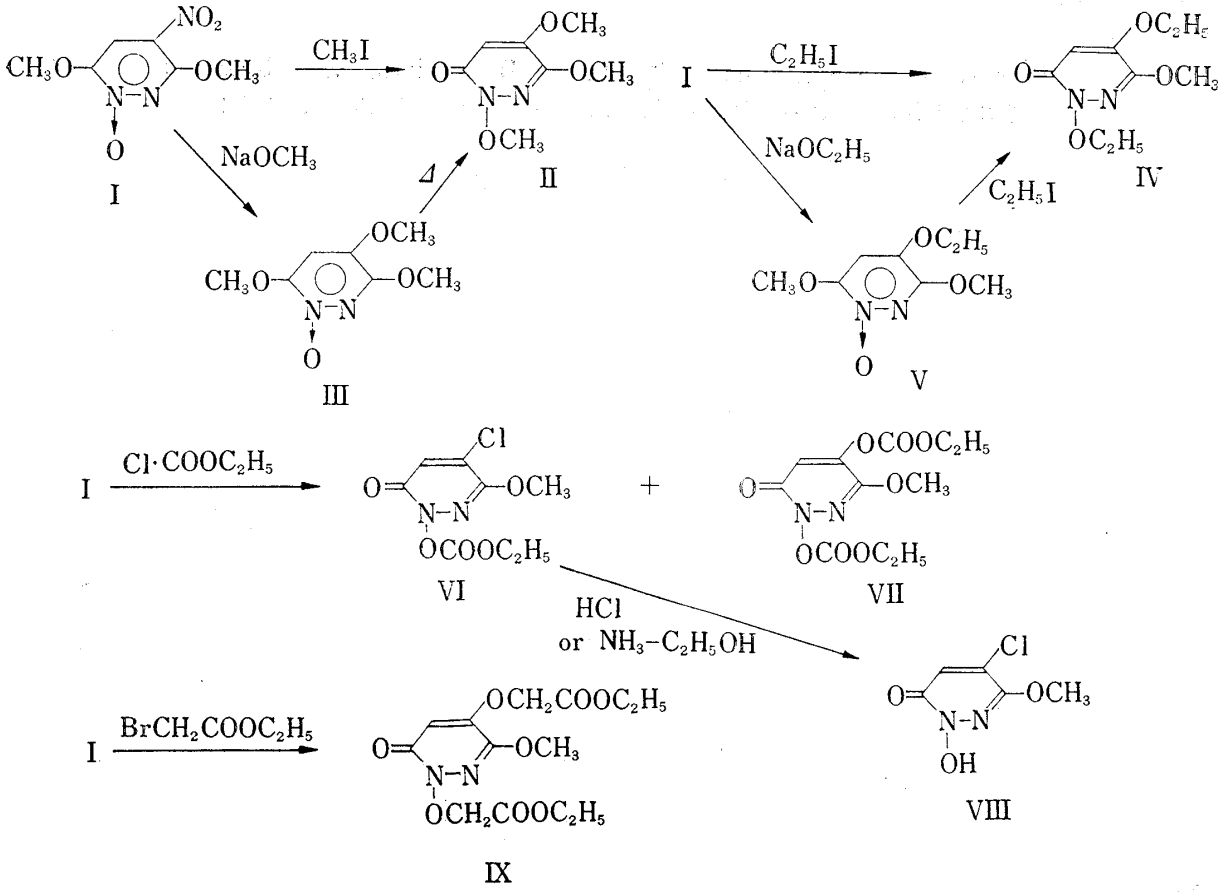

Chart 1

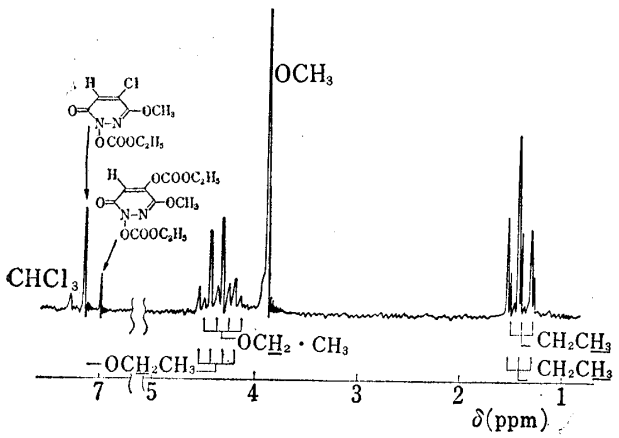

Fig. 1. Nuclear Magnetic Resonance Spectrum of Reaction Product of 3,6-Dimethoxy-4-nitropyridazine 1-oxide with Ethyl chlorocarbonate, at Mcps in $CDCl_3$ (internal standard is tetramethylsilane)

pyridazinone (VII). Their structures were identified with following methods. The infrared spectrum of the reaction product showed at 1800, 1773 and 1690 cm^{-1} for carbonyl absorption band. 1800 and 1690 cm^{-1} absorption band suggested 1-acyloxy-6(1*H*)pyridazinone,[4,6,7] 1773 cm^{-1} band corresponded to carbonyl absorption band region of vinyl esters or phenyl esters.[8] Thus 4-ethoxycarbonyloxy compound (VII) was assumed by infrared absorption spectrum. The nuclear magnetic resonance spectrum of the reaction product (Fig. 1) indicated evidently the presence of two different ring proton at δ 7.14, δ 6.98 and ethoxyl signals at δ 4.36, δ 1.41 and δ 4.29, δ 1.37, respectively. The signals of ring proton

6) L.A. Paquette, *J. Am. Chem. Soc.*, **87**, 5186 (1965).
7) *a*) T. Nakagome, *Yakugaku Zasshi*, **82**, 1005 (1962); *b*) M. Yanai, T. Kinoshita, and M. Yamaguchi, *ibid.*, **86**, 81 (1966).
8) L.J. Bellamy, "The Infrared Spectra of Complex Molecules," second edition, Methuen Co., Ltd., London, 1958, p. 182.

equivalent to ring proton of 1-acetoxy-3-methoxy-4-chloro-6(1*H*)pyridazinone (δ 7.18)[9] and 1,3-dimethoxy-4-methyl-6(1*H*)pyridazinone (δ 6.80[10]), respectively.

Moreover, hydrolysis of the product with ethanolic ammonia or 10% hydrochloric acid gave 1-hydroxy-3-methoxy-4-chloro-6(1*H*)pyridazinone (VIII). In general, 1-acyloxy-6(1*H*)pyridazinone types are hydrolyzed[6,11] with acids, alkalis and even alcohols, easily. It was indicated that VIII was obtained by hydrolysis of VI, but hydrolyzed product of VII was not obtained, it was probably very hygroscopic material.

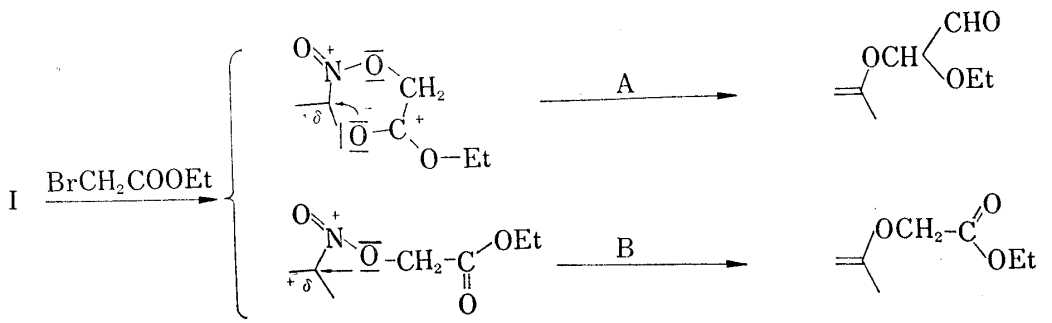

Chart 2

These results suggested that the reaction product consisted of 1-ethoxycarbonyloxy-3-methoxy-4-chloro-6(1*H*)pyridazinone (VI) and 1,4-bisethoxycarbonyloxy-3-methoxy-6(1*H*)pyridazinone (VII). The mixed ratio of the product (VI: VII=1.7 : 1.0) was determined by measure of weight of methylen signals of nuclear magnetic resonance spectrum. The elemental analysis accorded with the mixed ratio of $C_8H_9O_5N_2Cl$: $C_{11}H_{14}O_8N_2$=1.7:1.0.

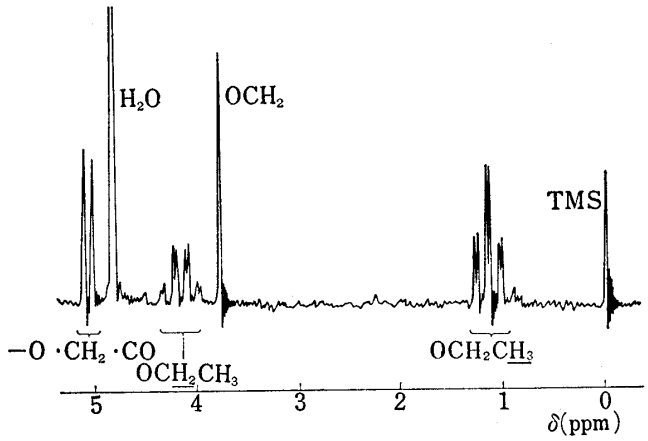

Fig. 2. Nuclear Magnetic Resonance Spectrum of 1,4-Bisethoxycarbonylmethoxy-3-methoxy-6(1*H*)-pyridazinone (IX) at 60 Mcps in Pyridine (internal standard is tetramethylsilane)

By reaction with ethyl bromoacetate, I gave 1,4-bisethoxycarbonylmethoxy-3-methoxy-6(1*H*)pyridazinone (IX), colorless needles mp 119.5—121°. Its structure was identified with elementary analysis and nuclear magnetic resonance spectrum, which showed no signal of aldehyde. It was pointed out that a reaction route was not A, but B (Chart 2).

Analogous products were obtained by reaction of I with *n*-propyl-, iso-propyl-, *n*-butyl-, iso-butyl iodide (Table I). Their structure were determined by measurement of elementary analyses infrared (ring carbonyl at 1665—1677 cm^{-1}[12]), ultraviolet (only one maximum absorption band at 292—294 mμ[12]) and nuclear magnetic resonance spectra.

In order to prove the relation between structure and reactivity, following materials were treated with methyl iodide, 4-nitropyridazine 1-oxide (X), 4-nitro-3-methoxy-6-chloropyridazine 1-oxide (XI), 4,6-dinitro-3-ethoxypyridazine 1-oxide (XII),[13] 4-nitro-3-

9) M. Yanai, T. Kinoshita, not published.
10) M. Yanai, T. Kinoshita, not published.
11) F. Yoneda and Y. Nitta, *Chem. Pharm. Bull.* (Tokyo), **11**, 269 (1963); T. Nakagome, *Yakugaku Zasshi*, **83**, 934 (1963).
12) M. Yanai and T. Kinoshita, *Yakugaku Zasshi*, **85**, 344 (1965).
13) We will report in the near future.

Table I. Reaction of 3,6-Dimethoxy-4-nitropyridazine with Alkyl Halides

Starting materials (g)	RI (ml)	Reaction Temp. (°C)	Reaction Time (hr)	R	mp (°C)	Yield (%) (g)	UV λ_{max}^{EtOH} mμ (log ε)	IR ν^{KBr} cm^{-1} (C=O)
0.50	MeI	95—100	7	Me	156.5—157	0.30 (65)	290 (3.43)	1668
0.50	EtI	95—100	4	Et	132.5—133	0.37 (70)	291.5 (3.44)	1667
0.50	nor-PrI	125—135	6	nor-Pr	81—82	0.30 (50)	239 (3.76)	1670
							292.5 (3.49)	
1.00	iso-PrI	125—135	7	iso-Pr	81—82	0.90 (75)	239 (3.76)	1677
							294 (3.44)	
0.50	nor-BuI	125—135	7	nor-Bu	77—78	0.35 (52)	239 (3.76)	1665
							293 (3.46)	
2.00	iso-BuI	125—135	8	iso-Bu	93.5—94.5	0.25 (9.3)	239 (3.82)	1665
							293.5 (3.43)	

methoxy-6-methylpyridazine 1-oxide (XIII) and 4-nitro-6-methoxypyridazine 1-oxide (XIV).

95% of starting material was recovered by reaction of X with methyl iodide in a sealed tube by heating at 100° for 26 hours. Similarly, 90% were recovered by reaction of XI or XII, in a sealed tube by heating at 130° for 7 hours, respectively.

In the reaction of XIII, starting material was recovered by heating at 100° for long time, while colorless plates mp 201.5° (XV) and colorless prisms mp 199° (XVI) were obtained by heating at 130° for 5 hours. The elemental analysis of XV was identified with $C_7H_7O_3N_3$, infrared spectrum showed at 2220 cm^{-1} ($\nu_{C\equiv N}$), 1380 cm^{-1} ($\nu_{N\to O}$), nuclear magnetic resonance spectrum (dimethylsulfoxide) showed at δ 7.98 (ring proton, 1H, singlet), δ 3.97 ($3CH_3O$-, 3H, singlet), δ 3.88 ($4CH_3O$-, 3H, singlet), it was suggested that XV was 3,4-dimethoxy-6-cyanopyridazine 1-oxide. XVI corresponded to $C_7H_7O_2N_3$, infrared spectrum showed at 2225 cm^{-1} ($\nu_{C\equiv N}$), 1630 cm^{-1} ($\nu_{C=O}$). The ring carbonyl absorption band corresponded to 4(1*H*)pyridazinone region,[14] not 3(2*H*)pyridazinone.[7b] In general, the γ-position ring carbonyl of nitrogen containing heterocyclic compounds show lower wave number than α-position.[15]

Nuclear magnetic resonance spectrum (pyridine) showed at δ 3.82 (CH_3O-, singlet), 3.78 (CH_3N-, singlet) respectively. On the other hand, reaction of XIII with ethyl iodide gave colorless needles mp 165° (XVII), which elemental analysis corresponded to $C_8H_9O_2N_3$, infrared spectrum showed at 2220 cm^{-1} ($\nu_{C\equiv N}$), 1642 cm^{-1} ($\nu_{C=O}$), ultraviolet spectrum was very similar to that of XVI (Fig. 3). Nuclear magnetic resonance spectrum (pyridine) showed at δ 3.84 (CH_3O-, singlet), δ 4.15 ($CH_3\underline{CH_2}N$-, quartet), 1.33 ($\underline{CH_3}CH_2$-, triplet). These results suggested that XVI and XVII were 1-methyl-, 1-ethyl-3-methoxy-6-cyano-4(1*H*)-pyridazinone, respectively.

Hamana, *et al.*,[16] Kato, *et al.*,[17] Ogata,[18] Itai, *et al.*[19] reported reaction of 4-nitroquinaldine 1-oxide, 4-nitro-2-picoline 1-oxide, 4-nitro-6-methyl-3-substituted pyridazine 1-oxide with acetyl chloride, in which they obtained 4-chloro-2-cyanoquinoline 1-oxide, 4-chloro-2-cyanopyridine 1-oxide and 4-chloro-6-cyano-3-substituted pyridazine 1-oxide, and corresponding aldehyde oximes, respectively.

14) A. Staehelin, K. Eichenberger, and J. Druey, *Helv. Chim. Acta*, **39**, 1741 (1956); S. Kamiya, *Yakugaku Zasshi*, **86**, 1099 (1966).
15) S.F. Mason, *J. Chem. Soc.*, **1957**, 4874.
16) M. Hamana, S. Saeki, Y. Hatano, and M. Nagakura, *Yakugaku Zasshi*, **83**, 348 (1963).
17) T. Kato and H. Hayashi, *Yakugaku Zasshi*, **83**, 352 (1963).
18) M. Ogata, *Chem. Pharm. Bull.* (Tokyo), **11**, 1511 (1963).
19) T. Itai and S. Natsume, *Chem. Pharm. Bull.* (Tokyo), **12**, 228 (1963).

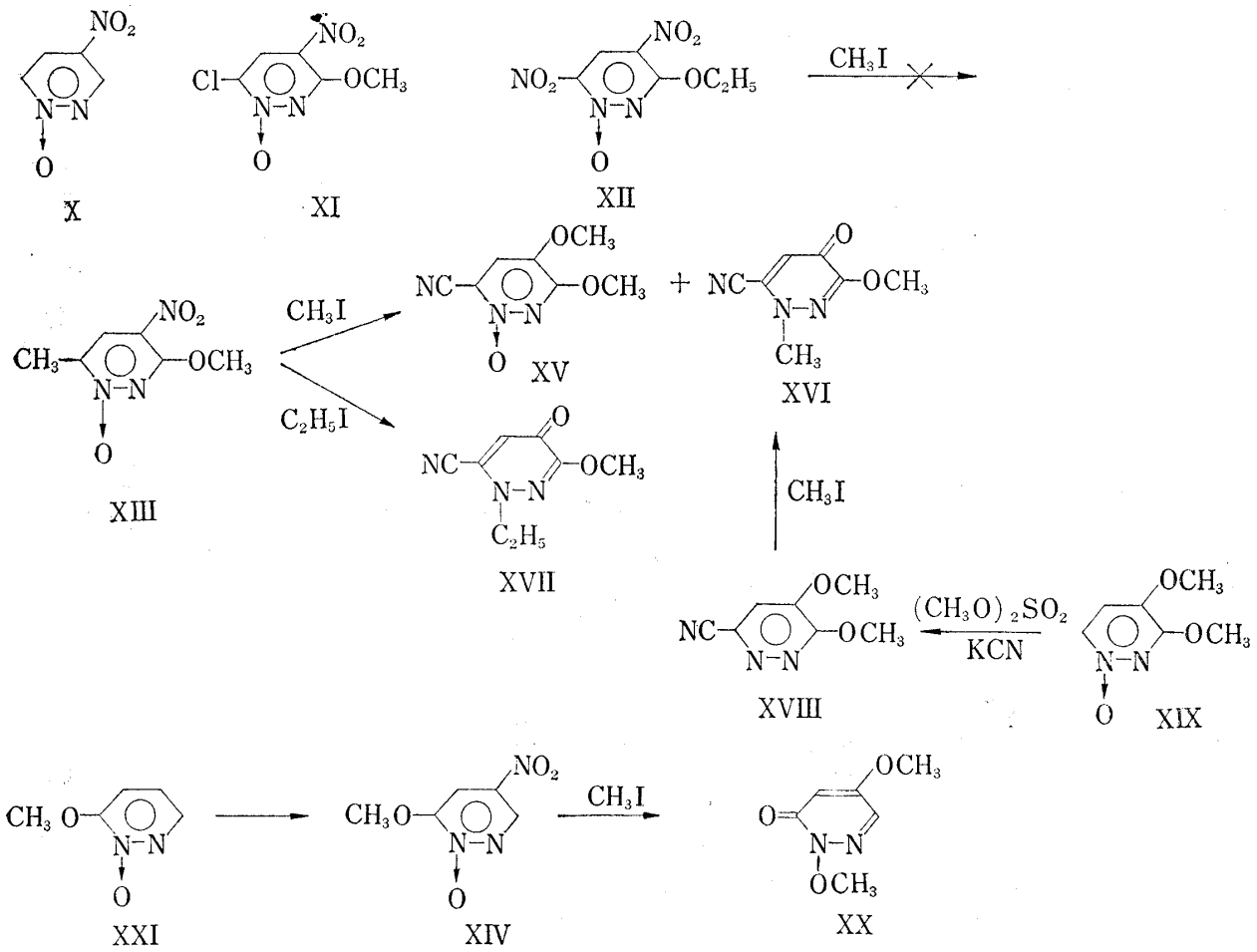

Chart 3

Hamana, *et al.*[16] and Kato, *et al.*[17] stated that the reaction would involve formation of acetyl nitrits and following nitrosation on the active methyl group. In this case, nitrosyl iodide or methyl nitrite are formed by reaction of nitro group with methyl iodide, and following attack to methy group, probably.

Reaction of 3,4-dimethoxy-6-cyanopyridazine (XVIII) with methyl iodide gave XVI, it was suggested that XV was precursor of XVI. XVIII was obtained by reaction of 3,4-dimethoxypyridazine 1-oxide (XIX) with dimethylsulfate-potassium cyanide (Okamoto-Tani's method).[20]

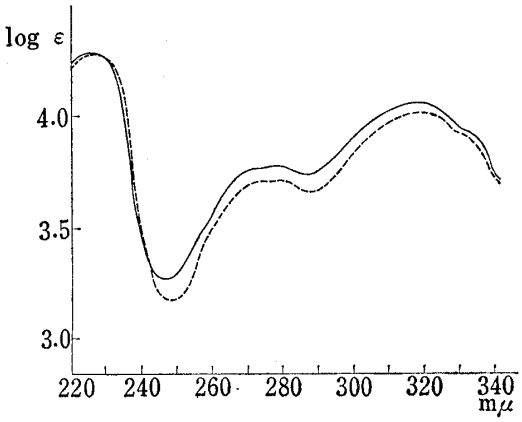

Fig. 3. Ultraviolet Spectrum of 1-Methyl-3-methoxy-6-cyano-4(1*H*)pyridazinone (XVI) and 1-Ethyl-3-methoxy-6-cyano-4(1*H*)pyridazinone(XVII) (in EtOH)

——— XVI - - - - - XVII

In the reaction of XIV with methyl iodide, starting material was mostly recovered together with small amount of colorless plates mp 158° (XX), in a sealed tube by heating at 95—100° for 7 hours. While XX was obtained in 32% yield by heating at 120—130° for 7 hours. Elemental analysis of this product corresponded to $C_6H_8O_3N_2$, and a strong absorption band

20) T. Okamoto and H. Tani, *Chem. Pharm. Bull.* (Tokyo), **7**, 130, 925 (1959).

at 1658 cm^{-1} in the infrared spectrum was attributable to ring carbonyl group. Moreover nuclear magnetic resonance spectrum (dioxane) showed doublet signals at δ 7.27, δ 6.27, their coupling constant was about 3.4 cps, whereas their ring protons were related to *meta* position each other. These results indicated that XX was obviously 1,4-dimethoxy-6(1*H*)pyridazinone.

4-Nitro-6-methoxypyridazine 1-oxide (XIV) was synthesized by treatment of 6-methoxypyridazine 1-oxide (XXI) with mixed acid in 7.5% yield by heating at 80° for 5 hours. Its elemental analysis corresponded to $C_5H_5O_4N_3$, and doublet signal at δ 9.00, δ 7.94 in nuclear magnetic resonance spectrum ($CDCl_3$) were ring proton, former was line broadening, their coupling constant was about 3.5 cps. Tori, *et al.*[21] reported that ring proton signals of H_3 and H_5 of 4-nitropyridazine 1-oxide derivatives appeared at δ 9.2, δ 8.35—8.45 region, respectively, and coupling constant was 2—3.5 cps, and by nitration, the ring proton of H_3 and H_5 shifted to lower magnetic field about 0.6—0.85 ppm. In this case, the ring protons of H_3 and H_5 of XXI appeared at δ 8.15 and δ 7.3, and by nitration, the ring protons shifted to lower magnetic field 0.85, 0.6 ppm, respectively. Itai, *et al.*[19] indicated that ultraviolet spectrum of nitropyridazine 1-oxides showed characteristic absorption curves by position of nitro group, respectively. The ultraviolet spectrum of XXI was very similar to 4-nitrocompounds. These results suggested that XXI was 4-nitro-6-methoxypyridazine 1-oxide.

Experimental

Reaction of 3,5-Dimethoxy-4-nitropyridazine 1-Oxide (I) with CH_3I——A mixture of 500 mg of I and 5.5 ml of CH_3I was heated in a sealed tube at 95—100° for 7 hr. The reaction mixture was evaporated to dryness, the residue was extracted with $CHCl_3$ and washed with Na_2SO_3 solution, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from AcOEt , to give 300 mg of colorless prisms, mp 156—157°. *Anal.* Calcd. for $C_7H_{10}O_4N_2$: C, 45.17; H, 5.41; N, 15.05. Found: C, 45.49; H, 5.25; N, 14.74.

Reaction of 3,6-Dimethoxy-4-nitropyridazine 1-Oxide (I) with C_2H_5I——A mixture of 500 mg of I and 5.5 ml of C_2H_5I was heated in a sealed tube at 95—100° for 4 hr. Reaction mixture was treated similary above. The residue was recrystallized from ether, to give 370 mg of colorless needles, mp 132—133°. *Anal.* Calcd. for $C_9H_{14}O_4N_2$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.63; H, 6.79; N, 12.83.

3,6-Dimethoxy-4-ethoxypyridazine 1-Oxide (V)——A mixture of 500 mg of I and C_2H_5ONa in C_2H_5OH (25 ml containing 65 mg of Na) was allowed to stand at room temperature for 20 min, after heated at 48° for 7 min, again allowed to stand at room temperature for 93 min. Reaction mixture was evaporated *in vacuo* at 36° for 25 min, the residue was added little water, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from AcOEt, to give 330 mg of colorless needles, mp 166—167°. *Anal.* Calcd. for $C_8H_{12}O_4N_2$: C, 47.99; H, 6.04; N, 13.99. Found: C, 47.85; H, 5.97; N, 14.01.

1,4-Diethoxy-3-methoxy-6(1*H*)pyridazinone (IV)——A mixture of 120 mg of V and 1.2 ml of C_2H_5I was placed in a sealed tube, and heated in a boiling water bath for 5.2/3 hr. The reaction mixture was evaporated to dryness, the residue was extracted with $CHCl_3$, washed with Na_2SO_3 solution, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from ether to give 135 mg of colorless needles, mp 132—133°.

Reaction of 3,6-Dimethoxy-4-nitropyridazine 1-Oxide (I) with Ethyl Chlorocarbonate——A mixture of 500 mg of I and 5 ml of ethyl chlorocarbonate was heated at 95—100° for 16 hr. The reaction mixture was evaporated to dryness *in vacuo*, the residue was added little water and allowed to stand for 30 min, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, and evaporated to dryness. The residue was dissolved in ether and poured on alumina column of chromatography, repeated chromatography, 405 mg of colorless oil was obtained. *Anal.* Calcd. for $C_8H_9O_5N_2Cl$: $C_{11}H_{14}O_8N_2$=1.7:1.0: C, 40.77, H, 4.08; N, 10.45. Found: C, 41.02; H, 3.93; N, 10.24.

Hydrolysis of Reaction Product of Above——i) A solution of 500 mg of reaction product of above and 7 ml of EtOH was chilled with ice-water, and saturated with ammonia gas. Crystals deposited, and allowed to stand in refrigerator for over night. The crystals were filtered, and recrystallized from EtOH, to give 280 mg of colorless needles, mp 202—203° (decomp.). It was not depressed on admixture, and infrared spectrum was identified with 1-hydroxy-3-methoxy-4-chloro-6(1*H*)pyridazinone.

ii) A solution of 400 mg of I and 4 ml of 10% HCl was heated at 95—100° for 80 min. After HCl was removed off under reduced pressure, the residue was added EtOH, and removed off *in vacuo* to dryness.

21) K. Tori, M. Ogata, and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 235 (1963).

The residue was recrystallized from EtOH to give 200 mg of colorless needles mp 202—203° (decomp.). It was identified with mixed melting point determination and infrared comparison with a sample obtained above.

Reaction of 3,6-Dimethoxy-4-nitropyridazine 1-Oxide (I) with Ethyl Bromoacetate——A mixture of 2.0 g of I and 8 ml of ethyl bromoacetate was heated at 125—135° for 8 hr 40 min. After ethyl bromoacetate was removed off *in vacuo*, the residue was washed ether. The insoluble residue was recrystallized from AcOEt, to give 0.47 g of colorless needles, mp 119.5—121°. *Anal.* Calcd. for $C_{13}H_{18}O_8N_2$: C, 47.27; H, 5.49; N, 8.48. Found: C, 47.18; H, 5.61; N, 9.03.

General Reaction of 3,6-Dimethoxy-4-nitropyridazine 1-Oxide (I) with *n*-PrI, iso-PrI, *n*-BuI and iso-BuI——A mixture of I and alkyl iodide was heated at 125—135° for 6—8 hr. After alkyl iodide was removed off under reduced pressure, the residue was extracted with $CHCl_3$, dried over $MgSO_4$, and evaporated to dryness. The residue was dissolved in ether or AcOEt and passed through Al_2O_3 column, eluted with same solvent. Recrystallization from ether or pet. ether gave colorless crystals, respectively.

Reaction of 3-Methoxy-4-nitro-6-methylpyridazine 1-Oxide (XIII) with CH_3I——A mixture of 5 g of XIII and 12 ml of CH_3I was placed in a sealed tube, and heated at 120—130° for 5 hr. Reaction mixture was evaporated to dryness, the residue was extracted with $CHCl_3$, and washed with Na_2SO_3 solution, dried over $MgSO_4$, evaporated to dryness. After the residue was dissolved in AcOEt, passed through an alumina column, eluted with AcOEt. Solvent was evaporated to dryness, fractional recrystallization of the residue with MeOH gave XV, 100 mg of colorless plates mp 200—201.5° and XVI 194 mg of colorless prisms mp 198—199°. *Anal.* Calcd. for $C_7H_7O_3N_3$ (XV): C, 46.41: H, 3.90; N, 23.20. Found: C, 46.33; H, 3.80; N, 23.49. Calcd. for $C_7H_7O_2N_3$ (XVI): C, 50.91; H, 4.27; N, 25.45. Found: C, 50.86; H, 4.28; N, 25.77.

Reaction of 3-Methoxy-4-nitro-6-methylpyridazine 1-Oxide (XIII) with C_2H_5I——A mixture of 1.0 g of XIII and 5 ml of C_2H_5I was placed in a sealed tube, and heated at 120—130° for 5 hr. Reaction mixture was evaporated to dryness, and extracted with $CHCl_3$, washed with Na_2SO_3 solution, dried over $MgSO_4$, evaporated to dryness. The residue was dissolved in benzene, and poured on an alumina column for chromatography. From the first fraction eluted with benzene, 75 mg of XVII was obtained, recrystallized from iso-propyl ether to give colorless needles mp 164—165°. *Anal.* Calcd. for $C_8H_9O_2N_3$: C, 53.62; H, 5.06. Found: C, 53.90; H, 5.25.

1-Methyl-3-methoxy-6-cyano-4(1*H*)pyridazinone (XVI)——A mixture of 1.26 g of 3,4-dimethoxy-6-cyanopyridazine (XVIII) and 10 ml of CH_3I was placed in a sealed tube, and heated at 120—130° for 4 hr. Reaction mixture was evaporated to dryness, the residue was recrystallized from MeOH, to give 1.0 g of colorless prisms, mp 198—199°. It was identified with mixed melting point determination and infrared comparison with XVI.

3,4-Dimethoxy-6-cyanopyridazine (XVIII)——A mixture of 1.1 g of XIX and 0.89 g of dimethylsulfate was heated on a water bath for 4 hr. After cooling, to this salt in 15 ml of dioxane, 8 ml of H_2O and KCN solution (3 g of KCN in 8 ml) was added dropwise with stirring at 0—5°. The reaction mixture was stirred for another 30 min at room temperature and extracted with $CHCl_3$, dried over Na_2SO_4, evaporated to dryness. The residue was recrystallized from benzene or acetone, to give 0.75 g of colorless prisms, mp 200—201°. *Anal.* Calcd. for $C_7H_7O_2N_3$: C, 50.91; H, 4.27; N, 25.45. Found: C, 51.01; H, 4.26; N, 25.90.

Reaction of 4-Nitro-6-methoxypyridazine 1-Oxide (XIV) with CH_3I——A mixture of 514 mg of XIV and 5 ml of CH_3I was placed in a sealed tube, heated at 120—130° for 7 hr. Reaction mixture was evaporated to dryness, the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with Na_2SO_3 solution, dried over $MgSO_4$, evaporated to dryness. The residue was recrystallized from AcOEt, to give 150 mg of colorless plates, mp 156.5—158°. *Anal.* Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.10; H, 4.95; N, 18.19. UV λ_{max}^{EtOH} mμ (log ε), 250 (3.518), 282.5 (3.417).

4-Nitro-6-methoxypyridazine 1-Oxide (XIV)——To a cold H_2SO_4 solution of XXI (20 ml of conc.H_2SO_4 and 5 g of XXI), 5 ml of fuming HNO_3 (d. 1.52) was added, and heated at 75—80° for 2 hr, moreover added 5 ml of fuming HNO_3, and heated at 75—80° for 3 hr. After reaction mixture was poured into crashed ice, and allowed to stand for 1 hr at room temperature, extracted with $CHCl_3$, washed with 10% Na_2CO_3 solution. The $CHCl_3$ layer was dried over $MgSO_4$, evaporated to dryness, the residue was dissolved in AcOEt, and through an alumina column, eluted with AcOEt. Yellow prisms of 500 mg were obtained by concentration of eluted solution, mp 172—173° (decomp.). *Anal.* Calcd. for $C_5H_5O_4N_3$: C, 35.09; H, 2.95; N, 24.56. Found: C, 34.90; H, 3.10; N, 24.66.

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