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Studies on Pyridazine 1,2-Dioxides. IV.*,[1] Reduction and Substitution of 4-Nitro-3,6-dimethylpyridazine 1,2-Dioxide

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Catalytic reduction of 4-nitro-3,6-dimethylpyridazine 1,2-dioxide (II) over palladium-charcoal in ethanol, the reaction being stopped after absorption of four moles of hydrogen, afforded 4-amino-3,6-dimethylpyridazine 1-oxide (III) and 5-amino-3,6-dimethylpyridazine 1-oxide (IV), while after absorption of three moles of hydrogen, II gave 5-hydroxylamino-3,6-dimethylpyridazine 1-oxide (V) in 38% yield.

Heating of II with hydrochloric acid or with hydrobromic acid formed 4-chloro-3,6-dimethylpyridazine 1,2-dioxide (IXa) or 4-bromo-3,6-dimethylpyridazine 1,2-dioxide (IXb), respectively. When II was treated with acetyl chloride at room temperature for 7 days, 3,6-dimethyl-4,5-dichloropyridazine 1-oxide (X), 3-chloromethyl-4-nitro-6-methylpyridazine 1-oxide (XI) and 3-methyl-4,5-dichloro-6-cyanopyridazine 1-oxide (XII) were obtained besides IXa.

In addition to above-mentioned new pyridazine dioxide derivatives (IXa and IXb), 4-methoxy-3,6-dimethylpyridazine 1,2-dioxide (XIIIa) and 4-benzyloxy-3,6-dimethylpyridazine 1,2-dioxide (XIIIb) were synthesized.

In the previous papers, syntheses of pyridazine 1,2-dioxides[3] and electrophilic and nucleophilic reactions of 3,6-dimethylpyridazine 1,2-dioxide (I)[1] had been reported. Nitration of I was proceeded at relatively low temperature and was obtained 4-nitro-3,6-dimethylpyridazine 1,2-dioxide in good yield.

As an extension of this series, the present paper deals with reduction and substitution of 4-nitro-3,6-dimethylpyridazine 1,2-dioxide (II).

Reduction

Catalytic reduction of II over palladium-charcoal in ethanol, the reaction being stopped after absorption of four moles of hydrogen, afforded 4-amino-3,6-dimethylpyridazine 1-oxide (III) and 5-amino-3,6-dimethylpyridazine 1-oxide (IV) in 55% and 42% yields, respectively. On the other hand, when the reaction being stopped after absorption of three moles of hydrogen, II gave pale yellow precipitates (V) in 38% yield, whose analytical values corresponded to composition of $C_6H_9O_2N_3$, as shown in Chart 1. Reaction of V with a silver nitrate ammonia reagent was produced a dark turbidity by silver and catalytic hydrogenation of V over palladium-charcoal in ethanol afforded IV. Consequently, it is concluded that this compound is 5-hydroxylamino-3,6-dimethylpyridazine 1-oxide.

Although the reduction of 4-nitro-3,6-dimethylpyridazine 1-oxide (VI) to give III under the same condition over palladium-charcoal was already reported,[4] there has been no other report on the reduction of 5-nitro-3,6-dimethylpyridazine 1-oxide (VII). In order to investigate connection with the reduction of the dioxide compound, following experiment was carried out. When VII was reduced under the same condition in the case of II, a mixture of IV and V were isolated in a product ratio of 1 : 1.6.

* Dedicated to the memory of Prof. Eiji Ochiai.

1) Part III: S. Sueyoshi and I. Suzuki, *Yakugaku Zasshi*, **95**, 1327 (1975).

2) Location: *1–18–1, Kamiyoga, Setagaya-ku, Tokyo.*

3) M. Nakadate, S. Sueyoshi, and I. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **18**, 1211 (1970).

4) T. Nakagome, *Yakugaku Zasshi*, **82**, 253 (1962).

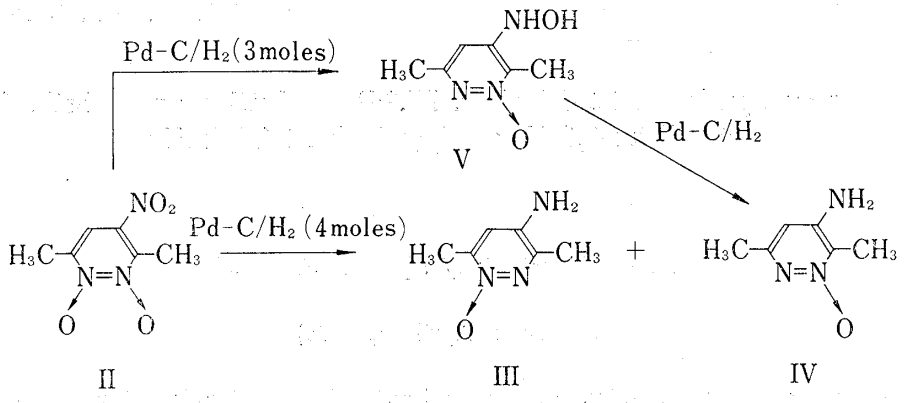

Chart 1

It has been found that one of the N-oxide group of 1,2-dioxide is easily deoxygenated, and 5-hydroxylamino compound obtained by catalytic reduction is comparatively stable.

It has already been noted that 4-nitro aromatic heterocyclic N-oxides were deoxygenated easily and produced 4-amino compounds by catalytic reduction over Raney nickel catalyst in methanol solution containing glacial acetic acid. For instance, VI afforded 4-amino-3,6-dimethylpyridazine (VIII) in 91% yield.[4] The reduction of VII under the same condition gave a mixture of IV and VIII. The similar reduction of dioxide (II) also afforded IV and VIII in 22% and 19% yields, respectively.

The catalytic reduction over palladium-charcoal or platinum dioxide, in acidic solution or ammonia-alkaline solution, resulted in the formation of mixture and attempts to isolate amino compounds by column chromatography were unsuccessful.

Halogen Substitution

Heating of 4-nitro and 5-nitropyridazine 1-oxides with hydrochloric acid resulted in the formation of 4-chloro and 5-chloro compounds,[5] respectively. In a similar manner, II, when heated in hydrochloric acid or hydrobromic acid, underwent substitution of 4-nitro group with halogen to form the corresponding 4-halo-3,6-dimethylpyridazine 1,2-dioxide in low yield, as indicated in Chart 2. However, in the case of chlorination to prepare 4-chloro-3,6-dimethylpyridazine 1,2-dioxide (IXa), good result obtained by carrying out this reaction in boiling ethanol in the presence of urea and passing dry hydrogen chloride gas through the solution, while II was brominated to 4-bromo-3,6-dimethylpyridazine 1,2-dioxide (IXb) only in 19% yield in spite of the presence of urea (Table I).

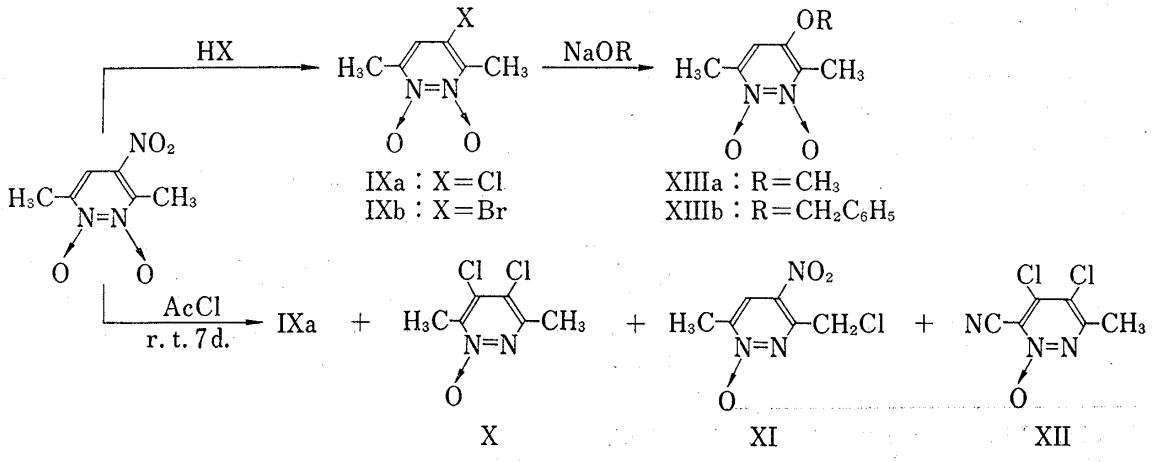

Chart 2

5) T. Itai, "Heterocyclic Compounds," Vol. 28, John Wiley & Sons, Inc., New York, 1973, p. 675.

When II was refluxed with acetyl chloride for 2 hours, IXa was isolated in 39% yield. As shown in Chart 2, when II was allowed to stand with acetyl chloride at room temperature for 7 days, IXa was obtained in 8% yield and three kinds of compounds were isolated by preparative thin layer chromatography (X: colorless scales, mp 104—109°, $C_6H_6ON_2Cl_2$; XI: yellow needles, mp 94—95°, $C_6H_6O_3N_3Cl$; XII: colorless scales, mp 178—179°, $C_6H_3ON_3Cl$).

The structure of X confirmed as 3,6-dimethyl-4,5-dichloropyridazine 1-oxide consistent with its nuclear magnetic resonance (NMR) spectrum, which shows two singlets due to two methyl groups at 2.58 ppm and 2.60 ppm, and vanishes the aromatic proton.

Compound XI has the empirical formula $C_6H_6O_3N_3Cl$, and its structure was elucidated to be 3-chloromethyl-4-nitro-6-methylpyridazine 1-oxide by infrared (IR) and NMR spectroscopy. Namely, IR spectrum of XI in nujol shows the presence of nitro group at 1324 cm^{-1} and 1575 cm^{-1}. The NMR spectrum of XI shows three singlets due to the methyl group at 2.52 ppm, the methylene group at 4.91 ppm and the aromatic proton at 8.27 ppm. The chemical shift of the aromatic proton of XI is similar to that of the aromatic proton of VI (8.20 ppm) than VII (7.15 ppm). The position of the N-oxide of XI was confirmed by its conversion to 4-amino-3,6-dimethylpyridazine 1-oxide with catalytic hydrogenation over palladium-charcoal in methanol.

The analytical values of XII corresponded to $C_6H_6O_3NCl_2$, and a band at 2330 cm^{-1} in IR spectrum was attributable to cyano group and the NMR spectrum only shows a singlet due to the methyl protons at 2.66 ppm and vanishes the aromatic proton, so that XII was obviously 3-methyl-4,5-dichloro-6-cyanopyridazine 1-oxide. The position of the N-oxide was proved as follows. On heating XII with phosphoryl oxychloride, 90% of the starting material was recovered and did not obtained 3-chloromethyl compound, and Itai, *et al.*,[6] reported that the production of cyano group in similar reaction of 3,6-dimethylpyridazine 1-oxide derivatives seemed to be concerned with methyl group adjacent to the N-oxide function.

In contrast to the reaction with acetyl chloride, II hardly react with phosphoryl oxychloride. The above-mentioned experimental results were summarized in Table I.

Table I. Halogen Substitution of 4-Nitro-3,6-dimethylpyridazine 1,2-Dioxide

No.	Starting material (g)	Reagent	Reaction condition		Yield of product (%)			Method of isolation[a]
			Temp. (°C)	Time (hr)	IXa	IXb	Recovery	
1	0.2	36%HCl 4 ml	95	7	35		29	preparative TLC
2	0.2	36%HCl 4 ml	90	3	13		10	column chromatography (Alumina)
3	0.2	36%HCl 3 ml	r.t.	8 days	—		98	
4	0.2	HClgas urea 0.1g EtOH 20 ml	refl.	4.5	80		—	recrystallization
5	0.4	AcCl 4 g	50–55	2	39		11	column chromatography (Alumina)
6	0.7	AcCl 3.6 g	r.t.	7 days	8		—	recrystallization
7	0.4	$POCl_3$ 4 g	refl.	2	4		33	preparative TLC
8	0.4	$POCl_3$ 4 g	95	5	8		35	column chromatography (Silica gel)
9	0.2	47%HBr 4 ml	95	7		21	41	preparative TLC
10	0.8	47%HBr 10 ml urea 0.25 g	95	10.5		19	40	column chromatography (Florisil)

a) Preparative TLC was practiced on Silica gel GF_{254}. eluting solvent: $CHCl_3$. developing solvent: No. 1 and No. 7; $CHCl_3$: acetone: EtOH: 10: 4: 1, No. 9; C_6H_6: acetone: $CHCl_3$: hexane: 15: 10: 5: 1

6) *a*) T. Itai and S. Natsume, *Chem. Pharm. Bull.* (Tokyo), **12**, 228 (1964); *b*) M. Ogata, *ibid.*, **11**, 1511 (1963).

Ionic reaction of IXa with sodium methoxide in methanol and with sodium benzyloxide in benzyl alcohol afforded 40% of 4-methoxy-3,6-dimethylpyridazine 1,2-dioxide (XIIIa) and 5% of 4-benzyloxy-3,6-dimethylpyridazine 1,2-dioxide (XIIIb), respectively. The structure of these compounds were elucidated by means of analytical data and NMR spectroscopy.

We concluded from the preceding observations that II reacts with similar behavior as monoxides (VI and VII) in catalytic reduction and halogen substitution. Further, one of the N-oxide group of 1,2-dioxide is more reactive than another. Activities of new dioxide derivatives IXa, IXb, XIIIa, and XIIIb are now being examined.

Experimental[7]

Catalytic Reduction of 4-Nitro-3,6-dimethylpyridazine 1,2-Dioxide (II)——(i) A solution of 600 mg of II dissolved in 20 ml of EtOH, added with a catalyst prepared from 8 ml of 1% $PdCl_2$ solution and 0.2 g of charcoal, was shaken in H_2 stream. After absorption of 4 moles of H_2, the catalyst was removed and the solvent was evaporated. The residue was recrystallized from MeOH–AcOEt to white needles, 206 mg, mp 281° (decomp.), which was identified by thin-layer chromatography (TLC), IR and NMR spectra of an authentic sample III[4] prepared from VI. The mother liquid was concentrated and chromatographed on silica gel. The first fraction eluted with $CHCl_3$, gave 5-amino-3,6-dimethylpyridazine 1-oxide (IV). Colorless needles (AcOEt), mp 190—191°. Yield, 187.5 mg (42%). Color reaction for aromatic primary amino group: (+). IR (Nujol) cm^{-1}: 3360, 3200. NMR (DMSO-d_6) ppm: 2.15 (6H, s, $-CH_3$), 6.15 (1H, s, C_4–H), *ca.* 6.30 (2H, broad, $-NH_2$, changeable with D_2O). *Anal.* Calcd. for $C_6H_9ON_3$: C, 51.78; H, 6.52; N, 30.20. Found: C, 51.71; H, 6.46; N, 30.28. The second fraction eluted with the same solvent gave III. Total yield of III, 244 mg (55%).

(ii) A solution of 1.8 g of II dissolved in 150 ml of EtOH, added with a catalyst prepared from 16 ml of 1% $PdCl_2$ solution and 0.4 g of charcoal, was shaken in H_2 stream. After absorption of 3 moles of H_2, the catalyst was removed and the solvent was concentrated. The residue was filtered and the precipitate was washed thoroughly with EtOH, because it was difficult to recrystallize. 5-Hydroxylamino-3,6-dimethylpyridazine 1-oxide (V) was obtained. Pale yellow precipitate, mp 185° (decomp.). Yield, 570 mg (38%). Color reaction for aromatic primary amino group: (−). Reaction with $AgNO_3$–NH_3 reagent: (+). IR (Nujol) cm^{-1}: 3300, 2620. NMR (DMSO-d_6) ppm: 2.15 (3H, s, $-CH_3$), 2.28 (3H, s, $-CH_3$), 6.55 (1H, s, C_4–H), 8.98 (1H, s, changeable with D_2O), 9.25 (1H, s, changeable with D_2O). High Resolution Mass Spectrum: Found: 155.0723. Calcd. for $C_6H_9O_2N_3$: 155.0695.

The filtrate was evaporated and attempts to isolate crystalline by chromatography were unsuccessful.

(iii) A solution of 500 mg of II dissolved in 40 ml of MeOH and 4 ml of AcOH, added with a catalyst prepared from 1 g of Ni–Al alloy, was shaken in H_2 stream. After absorption of 360 ml of H_2, the catalyst was removed and the solvent was evaporated. To the residue a small amount of H_2O was added, the solution was neutralized with Na_2CO_3 and evaporated to dryness. The residue was extracted with hot AcOEt and the solvent was evaporated. A mixture of IV and VIII (200 mg) was obtained, and its product ratio was 1: 1.1 (calculated on NMR spectrum). The mixture was dissolved with $CHCl_3$–EtOH and chromatographed on silica gel. The first fraction eluted with $CHCl_3$ gave 70 mg (19%) of IV, which was identified by TLC and NMR spectrum of a sample obtained in (i). The second fraction eluted with $CHCl_3$–EtOH gave 74 mg (22%) of VIII, which was identified by TLC and NMR spectrum of an authentic sample[4] prepared from VI.

Reduction of 5-Hydroxylamino-3,6-dimethylpyridazine 1-Oxide (V)——A solution of 100 mg of V suspended in 30 ml of EtOH, added with a catalyst prepared from 3 ml of 1% $PdCl_2$ solution and 0.1 g of charcoal, was shaken in H_2 stream. After absorption of 40 ml of H_2, the catalyst was removed and the solvent was evaporated. Recrystallization from AcOEt gave IV, which was identical with a sample obtained in (i). Yield, 90 mg (94%).

Reduction of 5-Nitro-3,6-dimethylpyridazine 1-Oxide (VII)——(i) A solution of 260 mg of VII dissolved in 40 ml of EtOH, added with a catalyst prepared from 4 ml of 1% $PdCl_2$ solution and 0.1 g of charcoal, was shaken in H_2 stream. After absorption of 140 ml of H_2, the reaction mixture was treated as described in the case of reduction (i) of II. A mixture of IV and V was obtained (202 mg), and its product ratio was 1: 1.6 (calculated on NMR spectrum).

(ii) A solution of 90 mg of VII dissolved in 20 ml of MeOH and 1 ml of AcOH, added with a catalyst prepared from 0.5 g of Ni-Al alloy, shaken in H_2 stream. After absorption of 75 ml of H_2, the reaction

7) The following instruments were used for physical data. IR spectra: a JASCO model IR-S spectrophotometer; NMR spectra: a JEOL JNM-C-60HL spectrometer (tetramethylsilane as an internal standard); Mass spectra: a JEOL JMS-01 SG-2 spectrometer. All melting points are uncorrected.

mixture was treated as described in the case of reduction (iii) of II. A mixture (60 mg) consisting of IV and VIII was obtained, and they were identified by TLC and NMR spectroscopy.

4-Chloro-3,6-dimethylpyridazine 1,2-Dioxide (IXa)——(i) A solution of II suspended in 36% HCl, $POCl_3$ or AcCl was heated on a water bath or an oil bath. After cooling, ice–H_2O was added to the solution and the mixture was allowed to stand for several hours. The mixture was extracted with $CHCl_3$, the $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and the solvent was evaporated. The residue was dissolved in $CHCl_3$ and chromatographed on alumina or practiced on preparative TLC.

(ii) A solution of II and urea suspended in EtOH was refluxed by passing through dry HCl gas for 4.5 hr. After cooling, the solvent was evaporated and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and dried over anhyd. Na_2SO_4. The solvent was evaporated and the residue was recrystallized from acetone to give IXa, colorless scales, mp 199—200° (decomp.). NMR ($CDCl_3$) ppm: 2.57 (3H, s, $-CH_3$), 2.68 (3H, s, $-CH_3$), 7.15 (1H, s, C_5–H). *Anal.* Calcd. for $C_6H_7O_2N_2Cl$: C, 41.24; H, 4.04; N, 16.05. Found: C, 41.08; H, 4.14; N, 16.33. The results and reaction conditions were summarized in Table I.

4-Bromo-3,6-dimethylpyridazine 1,2-Dioxide (IXb)——A solution of II suspensed in 47% HBr was treated as described in IXa. Recrystallization from MeOH gave pale yellow needles, mp 223° (decomp.). IR (Nujol) cm^{-1}: 1463, 1370, 1303. NMR ($CDCl_3$) ppm: 2.70 (3H, s, $-CH_3$), 2.53 (3H, s, $-CH_3$), 7.30 (1H, s, C_5–H). High Resolution Mass Spectrum: Found: 139.05026. Calcd. for $C_6H_7O_2N_2$: 139.05075.

Reaction of 4-Nitro-3,6-dimethylpyridazine 1,2-Dioxide (II) with AcCl——A mixture of 700 mg of II and 3.6 g of AcCl was allowed to stand for 7 days and AcCl was removed under reduced pressure. The residue was treated with ice-H_2O and extracted with ether. Ether was evaporated and the residue was extracted with hexane. After removing the solvent an yellow solid (266 mg), mp 71—74°, was obtained but the structure was not determined. The residue not extracted with hexane was dissolved in ether and practiced on preparative TLC with Silica gel GF_{254} using 50% AcOEt–C_6H_6 (developing solvent) and $CHCl_3$ (eluting solvent). Recrystallizing from C_6H_6 gave 3,6-dimethyl-4,5-dichloropyridazine 1-oxide (X), 3-chloromethyl-4-nitro-6-methylpyridazine 1-oxide (XI) and 3-methyl-4,5-dichloro-6-cyanopyridazine 1-oxide (XII). X: colorless scales, mp 105—109°. Yield, 14 mg (2%). NMR ($CDCl_3$) ppm: 2.58 (s, $-CH_3$), 2.60 (s, $-CH_3$). High Resolution Mass Spectrum: Found: 122.04801. Calcd. for $C_6H_6ON_2$: 122.04808. XI: yellow needles, mp 94—95°. Yield, 80 mg (10%). IR (Nujol) cm^{-1}: 1613, 1575, 1420, 1324, 1075, 898, 730. NMR ($CDCl_3$) ppm: 2.52 (3H, s, $-CH_3$), 4.92 (2H, s, $-CH_2-$), 8.27 (1H, s, C_5–H). *Anal.* Calcd. for $C_6H_6O_3N_3Cl$: C, 35.40; H, 2.97; N, 20.64. Found: C, 35.37; H, 2.95; N, 20.38. XII: colorless scales, mp 178—179°. Yield, 42 mg (5%). IR (Nujol) cm^{-1}: 2330, 1498, 1374, 1335, 1090, 907. NMR ($CDCl_3$) ppm: 2.70 (s, $-CH_3$). *Anal.* Calcd. for $C_6H_3ON_3Cl$: C, 35.32; H, 1.48; N, 20.60. Found: C, 35.28; H, 1.38; N, 20.64.

The acidic solution was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and dried over anhyd. Na_2SO_4, and the solvent was evaporated. Recrystallization from acetone gave IXa. Yield, 55 mg (8%).

When a mixture of 2.0 g of II and 8.5 g of AcCl was reacted at room temperature for 10 days and treated as described above, X, XI and XII were obtained in 6% (126 mg), 10% (230 mg) and 13.5% (298 mg) yields, respectively.

Reduction of 3-Chloromethyl-4-nitro-6-methylpyridazine 1-Oxide (XI)——A solution of 40 mg of XI dissolved in 3 ml of MeOH, added with a catalyst prepared from 4 ml of 1% $PdCl_2$ solution and 0.1 g of charcoal, was stirred in H_2 stream for 2 hr. To the solution 0.1 ml of 28% NH_4OH was added, and the mixture was continued stirring in H_2 stream. After removal of the catalyst, the solvent was evaporated. The residue was recrystallized from MeOH–AcOEt to give III, mp 281° (decomp.), which was identified by TLC, IR and NMR spectra of an authentic sample.[4]

Reaction of 3-Methyl-4,5-dichloro-6-cyanopyridazine 1-Oxide (XII) with $POCl_3$——A solution of 50 mg of XII dissolved in 5 ml of $CHCl_3$, added with 0.5 ml of $POCl_3$, was refluxed on a water bath for 2 hr. H_2O was added to the mixture and the solution was basified with $NaHCO_3$, and extracted with $CHCl_3$. The solvent was evaporated to give XII. Recovery, 45 mg (90%). Further, 1.5 ml of $POCl_3$ was added to the recovered XII and heated at 90° for 1 hr. The reaction mixture was treated as described above. XII was recovered. 40 mg (89%).

4-Methoxy-3,6-dimethylpyridazine 1,2-Dioxide (XIIIa)——To a solution of 50 mg of metallic Na dissolved in 5 ml of MeOH, 200 mg of IXa was added, and the mixture was refluxed for 1 hr. MeOH was evaporated under reduced pressure, to the residue H_2O was added and the solution was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated. The residue was recrystallized from acetone to give XIIIa, colorless prisms, mp 221° (decomp.). Yield, 77 mg (40%). NMR ($CDCl_3$) ppm: 2.46 (3H, s, $-CH_3$), 2.57 (3H, s, $-CH_3$), 4.94 (3H, s, $-OCH_3$), 6.62 (1H, s, C_5–H). *Anal.* Calcd. for $C_7H_{10}O_3N_2$: C, 49.40; H, 5.92; N, 16.49. Found: C, 49.02; H, 5.91; N, 16.22.

4-Benzyloxy-3,6-dimethylpyridazine 1,2-Dioxide (XIIIb)——To a solution of 0.1 g of metallic Na dissolved in 5 ml of benzyl alcohol (BzOH), 0.4 g of IXa was added, and the mixture was allowed to stand for 2 days. It was extracted with ether to remove BzOH, and H_2O was added to the residue. The solution was extracted with $CHCl_3$ and the solvent was evaporated. The residue was dissolved in $CHCl_3$ and chromatographed

on silica gel. The first fraction eluted with C_6H_6 gave 180 mg of BzOH. From the second fraction eluted with $CHCl_3$, IXa was recovered. 115 mg (29%). The third fraction eluted with the same solvent gave XIIIb, colorless needles (EtOH), mp 203° (decomp.). Yield, 31 mg (5%). IR (Nujol) cm^{-1}: 1360, 1310, 1183. NMR ($CDCl_3$) ppm: 2.47 and 2.50 (6H, two singlets, two $-CH_3$), 5.07 (2H, s, $-CH_2-$), 6.60 (1H, s, C_5-H), 7.33 (5H, s, $-C_6H_5$). *Anal.* Calcd. for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73; N, 11.38. Found: C, 62.82; H, 5.54; N, 10.94.