Chem. Pharm. Bull.
21(1) 125—129 (1973)

UDC 547.852.2.04

Studies on Pyridazines. XX.[1] Syntheses of 1,2-Bis(3′-pyridazinyl)-ethenes, -ethanes, and Their Di-N-oxides

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(Received June 20, 1972)

The compounds, in which two pyridazine rings are combined through two carbon atoms, were synthesized. 3-Methylpyridazine 2-oxide (I) was condensed with 3-formylpyridazine 2-oxide (II) to give 1,2-bis[3′-(2′-oxido)-pyridazinyl]-ethene (III). Reaction of III with PCl_3 in $CHCl_3$ afforded the deoxygenated compound, 1,2-bis(3′-pyridazinyl)-ethene (IV). Oxidation of IV with H_2O_2 in AcOH gave 1′1′-di-N-oxide (V). Catalytic hydrogenation of III with Pd-C afforded 1,2-bis(3′-pyridazinyl)-ethane (VI). Oxidation of VI afforded three kinds of di-N-oxides, *i.e.*, 1′,1′-di-N-oxide (VII), 1′,2′-di-N-oxide (VIII), and 2′,2′-di-N-oxide (IX). Wurtz's reaction of chloromethylpyridazines was also carried out, affording the corresponding ethane (XI) and ethene (XII) derivatives.

We have been investigating the syntheses and reactions of bimolecular compounds of pyridazines and have already reported on those of 3,3′-bipyridazines.[3,4]

The present paper deals with the syntheses of the compounds, in which two pyridazine rings are combined through two carbon atoms, *i.e.*, ethylene and vinylene groups.

Analogous compounds of other aromatic amines are already known, including those of pyridines and quinolines. Namely, 2- or 4-methylquinoline N-oxide was allowed to react[5] with nitrobenzene or nitrosobenzene in the presence of alkali to afford the corresponding ethene and ethane derivatives. In the case of 3-methyl-4-nitropyridine and its N-oxide, they were treated with alkali,[6] whereas 4-methylpyridazine was heated with sulfur.[7] But, application of these procedures to the methylated pyridazines and their N-oxides was proved to be unsuccessful.

On the other hand, the methyl groups of α- or γ-positions to the nitrogen atoms of aromatic amines and their N-oxides are known to be easily oxidized[8] with SeO_2 to afford the aldehyde, with which the starting methyl compounds are condensed to form ethene derivatives.[9]

Methyl groups on the ring of pyridazine N-oxide have also been known to be sensitive to condense with benzaldehyde.[10] Thus, we have undertaken to get the desired compounds by condensation of methyl and formyl groups. But, reaction of 3-formylpyridazine[11] with 3-methylpyridazine ended in a failure.

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[2] Location: *Hatanodai, Shinagawa-ku, Tokyo.*

[3] H. Igeta, T. Tsuchiya, M. Nakajima, and H. Yokogana, *Tetrahedron Letters*, **1969**, 2667; H. Igeta, T. Tsuchiya, M. Nakajima, C. Okuda, and H. Yokogawa, *Chem. Pharm. Bull.* (Tokyo), **18**, 1228 (1970).

[4] H. Igeta, T. Tsuchiya, C. Okuda, and H. Yokogawa, *Chem. Pharm. Bull.* (Tokyo), **18**, 1340 (1970); *idem, ibid.*, **19**, 1297 (1971).

[5] M. Colonna, *Gazz. Chim. Ital.*, **91**, 1178 (1960).

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[7] T.L. Tolbert and J. Preston, *J. Heterocyclic Chem.*, **6**, 963 (1969).

[8] D. Jerchel, J. Heider, and H. Wagner, *Ann.*, **613**, 153 (1958); M. Katada, *Yakugaku Zasshi*, **68**, 123 (1948); M. Hamana, S. Saeki, Y. Hatano, and M. Nagakura, *ibid.*, **83**, 348 (1963).

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[11] M. Kumagai, *J. Chem. Soc. Japan*, **81**, 492 (1960).

Then, 3-methylpyridazine 2-oxide[12] (I) was oxidized with SeO_2 in pyridine to 3-formylpyridazine 2-oxide (II), mp 167—169°, which was heated under reflux with equimolar starting material (I) and CH_3ONa in abs. CH_3OH to afford 1,2-bis[3′-(2′-oxide)-pyridazinyl]ethene (III), mp 270°. In the case of this reaction, isolation and purification of the aldehyde (II) led to lowering the yield (*ca.* 20%). Therefore, after oxidation with SeO_2 and removal of the solvent, without isolation of I and II, a solution of CH_3ONa dissolved in abs. CH_3OH was added to the mixture and heated under reflux to give III in a moderate yield of 40—50%.

Reaction of III with PCl_3 in $CHCl_3$ gave the deoxygenated compound, *i.e.*, 1,2-bis(3′-pyridazinyl)-ethene (IV), mp 219—220°, in a yield of *ca.* 20%. This compound (IV) was also obtained by oxidation of 1,2-bis(3′-pyridazinyl)ethane (VI) with SeO_2 in relatively high yield of 75%.

Oxidation of the compound (IV) with H_2O_2 in AcOH afforded its di-N-oxide (V), mp 300—302°, in 60% yield. Comparison of V with III by nuclear magnetic resonance (NMR) spectra taken in CF_3COOH revealed that they were not identical. Thus, V was proved to be 1′,1′-di-N-oxide. Catalytic hydrogenation of V with Pd-charcoal gave VI. And catalytic hydrogenation of III with Pd-charcoal proceeded hardly under neutral and alkaline

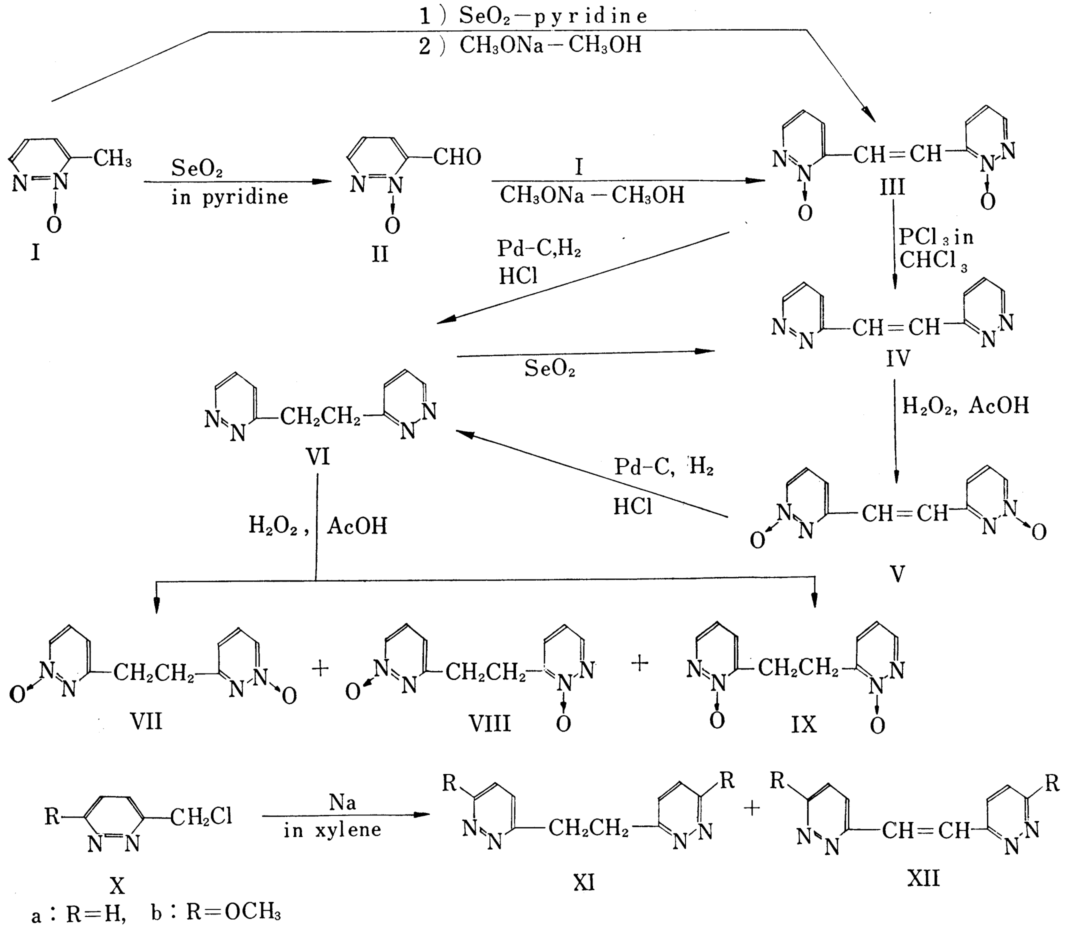

Chart 1

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[12] M. Ogata and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 29 (1963).

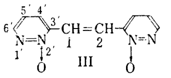
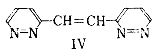
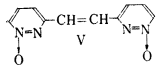
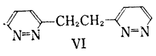
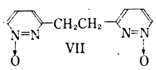
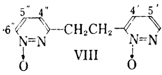
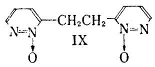
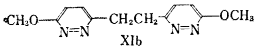
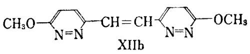
conditions, but smoothly under acidic condition to afford 1,2-bis(3′-pyridazinyl)ethene (VI), mp 106—107°, in 85% yield.

Oxidation of VI with H_2O_2 in AcOH afforded three kinds of di-N-oxides, *i.e.*, 1′,1′-di-N-oxide (VII), mp 262—263°, 1′,2′-di-N-oxide (VIII), mp 232—234°, and 2′,2′-di-N-oxide (IX), mp 285—286°, in the yields of 15%, 50%, and 5%, respectively.

Other synthetic procedure such as Wurtz Reaction was also carried out. Heating of 3-chloromethylpyridazine[13] (Xa) with Na in toluene or xylene resulted in the formation of trace amount of IV, but reaction of 3-chloromethyl-6-methoxypyridazine[14] (Xb) with Na gave 1,2-bis[3′-(6′-methoxy)-pyridazinyl]ethane (XIb), mp 160—161°, and -ethene (XIIb), mp 220° in 12% and 7% yields, respectively.

The compound (Xa) is labil and easily decomposed by being allowed to stand even at room temperature. This might be the reason why tarry substances were obtained in major in this reaction. Production of the ethene derivatives (XIIb) from Xb is rather interesting.

TABLE I. NMR Spectral Data[a] (δ in ppm)

	4′	5′	6′	1	Solvent
 III	8.65 $J^{b)}_{4',5'}=9$	7.83 $J_{5',6'}=6$	8.84 $J_{4',6'}=2$	8.32	CF_3CO_2H
 IV	7.74 $J_{4',5'}=9$	7.49 $J_{5',6'}=5$	9.12 $J_{4',6'}=2$	7.15	$CDCl_3$
 V	8.14 $J_{4',5'}=9$	8.25 $J_{5',6'}=6$	8.85 $J_{4',6'}=2$	7.88	CF_3CO_2H
 VI	7.30 $J^{c)}$	7.30	9.00	3.53	$CDCl_3$
 VII	7.18 $J_{4',5'}=9$	7.77 $J_{5',6'}=6$	8.18 —	3.13	DMSO-d_6
 VIII	7.86 (4″: 7.12) $J_{4',5'}=9$ ($J_{4'',5''}=9$)	7.15 (5″: 7.75) $J_{5',6'}=6$ ($J_{5'',6''}=6$)	8.45 (6″: 8.13) $J_{4',6'}=2.5$	3.12	DMSO-d_6
 IX	7.80 $J_{4',5'}=9$	7.14 $J_{5',6'}=5$	8.48 $J_{4',6'}=2.5$	3.16	DMSO-d_6
 XIb	6.83 $J_{4',5'}=9$	7.24	(OCH_3: 4.08)	3.39	$CDCl_3$
 XIIb	7.65 $J_{4',5'}=9$	6.93	(OCH_3: 4.14)	7.58	$CDCl_3$

a) 60M/C with TMS as internal reference.
b) Coupling constants are expressed in Hz.
c) Coupling constants in this case are undetermined.

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[13] N. Klauson-Kass and F. Limborc, *Acta Chem. Scand.*, **1**, 619 (1947); K.Y. Novitskii, N.K. Sadovaya, E.F. Kasyanova, and L.K. Semina, *Khim. Geterosikl. Soedin.*, **1970**, 412.

[14] M. Ogata and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 29 (1963).

NMR spectral data of these bis-pyridazinyl-ethenes and -ethanes are shown in Table I, indicating that these data are well in accord with their formulations. Furthermore, these ethene derivatives are all trans-isomers due to the infrared (IR) absorptions at 970—980 cm^{-1} characteristic to trans-ethenes.

Experimental

3-Formylpyridazine 2-Oxide (II)——To a solution of 3-methylpyridazine 2-oxide (I, 1.7 g) dissolved in pyridine (10 ml), SeO_2 (1.1 g) was added and the mixture was heated under reflux for 6 hr. After cool, the reaction mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in benzene and purified by column chromatography on alumina. From the eluate with CH_2Cl_2, a solid was obtained. Recrystallization from AcOEt gave white needles, mp 167—169° (45%). *Anal.* Calcd. for $C_5H_4O_2N_2$: C, 48.39; H, 3.25; N, 22.57. Found: C, 47.81; H, 3.21; N, 22.59. IR ν_{max}^{KBr} cm^{-1}: 1710, 2820, 2900. Mass Spectrum *m/e*: 124 (M$^+$). Phenylhydrazone, mp 277—279° (from EtOH).

1,2-Bis[3′-(2′-oxido)pyridazinyl]ethene (III)——a) To a mixture of 3-formylpyridazine 2-oxide (II, 0.4 g) and 3-methylpyridazine 2-oxide (I, 0.45 g) was added a solution of Na (0.5 g) dissolved in abs. CH_3OH (20 ml) and heated under reflux for 1 hr. After cool, the deposited yellow crystals were collected and washed with ether. Recrystallization from AcOH gave yellow needles, mp 270° (decomp.), 160 mg (21% yield based on the aldehyde). *Anal.* Calcd. for $C_{10}H_8O_2N_4$: C, 55.56; H, 3.73; N, 25.91. Found: C, 55.59; H, 3.89; N, 25.61. UV ν_{max}^{EtOH} mμ (log ε): 262 (3.26), 323 (3.04). IR ν_{max}^{KBr} cm^{-1}: 980 (*trans*-ethene). Mass Spectrum *m/e*: 216 (M$^+$). b) A mixture of I (5 g), SeO_2 (5 g) and pyridine (30 ml) was heated under reflux for 6—7 hr. The reaction mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. To the residue was added a solution of Na (1 g) dissolved in abs. CH_3OH (30 ml) and the whole was heated under reflux for 1 hr and worked up in the same manner as described for a), affording 2.4 g of III (49%).

1,2-Bis(3′-pyridazinyl)ethene (IV)——a) A mixture of III (600 mg), PCl_3 (20 ml), and $CHCl_3$ (10 ml) was heated under reflux for 48 hr. The reaction mixture was evaporated to dryness *in vacuo* and was neutralized with NH_4OH, followed by extraction with CH_2Cl_2. The CH_2Cl_2 layer was evaporated and the residue was recrystallized from benzene to dark violet crystals, mp 219—220° (decomp.), 100 mg (19%). *Anal.* Calcd. for $C_{10}H_8N_4$: C, 65.21; H, 4.38; N, 30.42. Found: C, 65.18; H, 4.54; N, 30.13. UV ν_{max}^{EtOH} mμ (log ε): 273 (4.26). IR ν_{max}^{KBr} cm^{-1}: 980 (*trans*-ethene). Mass Spectroum *m/e*: 184 (M$^+$). b) To a solution of VI (200 mg) dissolved in water (10 ml), SeO_2 (1 g) was added and heated overnight at 60—70°. The reaction mixture was filtered and the filtrate was neutralized with Na_2CO_3, followed by extraction with CH_2Cl_2. After removal of CH_2Cl_2 the residue was recrystallized from benzene, affording 150 mg of IV (75%).

1,2-Bis[3′-(1′-oxido)pyridazinyl]ethene (V)——A mixture of IV (200 mg), AcOH (5 ml), and 30% H_2O_2 (3 ml) was heated at 60—70° for 3 hr, followed by addition of 30% H_2O_2 (2 ml) and was kept at the same temperature for further 3 hr. After cool, water was added to the mixture and concentrated to a small volume. The deposited yellow crystals were collected, mp 300—302° (decomp.), 140 mg (59%). *Anal.* Calcd. for $C_{10}H_8O_2N_2$: C, 55.56; H, 3.73; N, 25.91. Found: C, 54.84; H, 4.02; N, 25.40. UV ν_{max}^{EtOH} mμ (log ε): 263 (3.43). IR ν_{max}^{KBr} cm^{-1}: 987 (*trans*-ethene). Mass Spectrum *m/e*: 216 (M$^+$).

1,2-Bis(3′-pyridazinyl)ethane (VI)——A mixture of III (200 mg), CH_3OH (70 ml), and 10% HCl (70 ml) was hydrogenated with Pd-C (5%, 500 mg). After removal of the catalyst, the filtrate was evaporated to dryness *in vacuo*, followed by neutralization with NH_4OH and extraction with CH_2Cl_2. The CH_2Cl_2 solution was dried on $MgSO_4$ and evaporated. The residue was recrystallized from benzene to colorless crystals, mp 106—107°, 160 mg (quantitative). *Anal.* Calcd. for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.50; H, 5.35; N, 30.26. UV ν_{max}^{EtOH} mμ (log ε): 251 (3.42), 255 (3.42), 315 (2.87). Mass Spectrum *m/e*: 186 (M$^+$). Hydrogenation of V (50 mg) under same condition affords VI (30 mg).

N-Oxidation of VI with H_2O_2 in AcOH——A mixture of VI (200 mg), AcOH (7 ml), and 30% H_2O_2 (3 ml) was heated at 60—70° for 3 hr, followed by addition of 30% H_2O_2 (3 ml) and was kept at the same temperature for further 3 hr. Water was added to the mixture and was concentrated to a small volume, followed by neutralization with K_2CO_3 and by extraction with CH_2Cl_2. The CH_2Cl_2 layer was dried on $MgSO_4$ and evaporated. The residue was purified by preparative thin-layer chromatography (TLC) with alumina. Solvent: CH_2Cl_2 containing 3% CH_3OH.

1,2-Bis[3′-(1′-oxido)pyridazinyl]ethane (VII): mp 262—263° (from CH_3OH), 36 mg. *Rf*: 0.40. UV ν_{max}^{EtOH} mμ (log ε): 263.5 (4.26), 316.5 (3.93). Mass Spectrum *m/e*: 218 (M$^+$). *Anal.* Calcd. for $C_{10}H_{10}O_2N_4$: C, 55.04; H, 4.60; N, 25.15. Found: C, 54.71; H, 4.60; N, 25.15.

1-(1′-Oxido-3′-pyridazinyl)-2-(2′-oxido-3′-pyridazinyl)ethane (VIII): mp 232—234° (from CH_3OH), 120 mg. *Rf*: 0.46. UV ν_{max}^{EtOH} mμ (log ε): 262 (3.90), 316 (3.59). Mass Spectrum *m/e*: 218 (M$^+$). *Anal.* Calcd. for $C_{10}H_{10}O_2N_4$: C, 55.04; H, 4.60; N, 25.15. Found: C, 54.90; H, 4.52; N, 25.31.

1,2-Bis[3′-(2′-oxido)pyridazinyl]ethane (IX): mp 285—286° (from CH_3OH), 12 mg. *Rf*: 0.51. UV ν_{max}^{EtOH} mμ (log ε): 260.5 (4.24), 316 (3.91). Mass Spectrum *m/e*: 218 (M$^+$). *Anal.* Calcd. for $C_{10}H_{10}O_2N_4$: C, 55.04; H, 4.60; N, 25.15. Found: C, 55.01; H, 4.71; N, 25.27.

Wurtz Reaction of 3-Chloromethylpyridazine (Xa)——To a solution of Xa (1 g) dissolved in xylene (10 ml) was added Na (1 g) and was heated under reflux overnight. The reaction mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in CH_2Cl_2 and purified by column chromatography on alumina. From the eluate with CH_2Cl_2, crystals were obtained, mp 106—107°, 20 mg (2.7%), which was proved to be identical with VI by mixture melting point.

Wurtz Reaction of 3-Chloromethyl-6-methoxypyridazine (Xb)——To a solution of Xb (3 g) dissolved in xylene (5 ml) was added Na (1 g) and was heated under reflux overngiht. The reaction mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was separated by column chromatography on a alumina. From the eluate with benzene, 1,2-bis[3'-(6'-methoxy)pyridazinyl]ethene (XIIb), mp 220° (from CH_3OH), 162 mg (7%), was obtained. *Anal.* Calcd. for $C_{12}H_{12}O_2N_4$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.20; H, 4.84; N, 22.84. UV $\nu_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 230 (4.07), 287 (4.58). Mass Spectrum *m/e*: 244 (M^+). Then, from the eluate with CH_2Cl_2, 1,2-bis[3'-(6'-methoxy)pyridazinyl]ethane (XIb), mp 160—161° (from iso-Pr_2O), 280 mg (12%), was obtained. *Anal.* Calcd. for $C_{12}H_{14}O_2N_4$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.43; H, 5.66; N, 22.55. UV $\nu_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 272 (3.52). Mass Spectrum *m/e*: 246 (M^+).