

SYNTHESIS OF PYRIDAZINE 1,2-DIOXIDES

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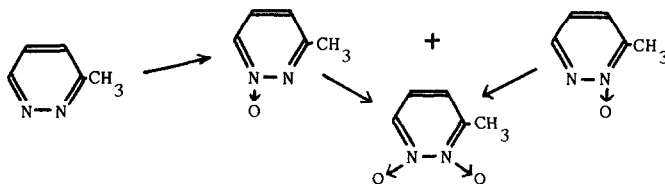
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Although the preparation of cinnoline 1,2-dioxide and 4-methylcinnoline 1,2-dioxide was previously reported both by Suzuki, et al. (1), and Palmer and Russell (2), there have been no references concerning the synthesis of any pyridazine 1,2-dioxides. We wish to report the preparation of pyridazine 1,2-dioxide and methylpyridazine 1,2-dioxides.

When pyridazine (Ia), 3-methylpyridazine (IIa), 4-methylpyridazine (IIIa), and 3,6-dimethylpyridazine (IVa) were refluxed with 50% hydrogen peroxide in acetic acid for 24 to 48 hours and the products were chromatographed on an alumina column, the corresponding dioxides i.e., pyridazine 1,2-dioxide (Ib), 3-methylpyridazine 1,2-dioxide (IIb), 4-methylpyridazine 1,2-dioxide (IIIb), and 3,6-dimethylpyridazine 1,2-dioxide (IVb) were isolated, besides their mono-N-oxides, in poor yields. By the same method Ib and IVb could be obtained from pyridazine 1-oxide (Ic) and 3,6-dimethylpyridazine 1-oxide (IVc), respectively. Further 3-methylpyridazine 1-oxide (IIc) and 3-methylpyridazine 2-oxide (IIId) afforded IIb, and 4-methylpyridazine 1-oxide (IIIc) and 4-methylpyridazine 2-oxide (IIId) afforded IIIb, respectively.

The N-oxidation reaction can be represented by the following scheme taken 3-methylpyridazine as an example.



Yields, melting points, and analytical data are summarized in Table I.

TABLE I
Yields, Melting Points, and Analytical Data of Pyridazine Dioxides

Dioxide*	M.p.**	Yield*** %	Formula	Calcd.	Found
Ib	222° decomp.	1.1 (from Ia)	$C_4H_4N_2O_2$	C: 42.86	43.11
		1.0 (from Ic)		H: 3.60	3.74
IIb	156-157°	1.2 (from IIA)	$C_5H_6N_2O_2$	N: 24.99	25.28
		1.0 (from IIC)		C: 47.62	47.40
IIIb	150-150.5°	0.8 (from IID)	$C_5H_6N_2O_2$	H: 4.80	4.88
		0.9 (from IIIA)		N: 22.22	22.46
IVb	216° decomp.	0.8 (from IIIC)	$C_5H_6N_2O_2$	C: 47.62	47.77
		0.8 (from IIID)		H: 4.80	4.85
		9.7 (from IVA)	$C_6H_8N_2O_2$	N: 22.22	22.03
		8.0 (from IVc)		C: 51.42	51.22
				H: 5.75	5.54
				N: 19.99	20.34

* Ib, IIb, and IIIb : Colorless needles. IVb : Colorless prisms.

** All melting points are uncorrected.

*** Monoxides used as the starting material were recovered in low yields.

The polarographic reduction of pyridazine dioxides was examined and the values of the half-wave potentials, $-E_{1/2}$, at pH 10.0 are summarized in Table II.

TABLE II
Half-wave Reduction Potentials* ($-E_{1/2}$ in V) of Pyridazine Dioxides

Pyridazine	1.39	3,6-Dimethylpyridazine	1.40
Pyridazine 1-oxide	1.51	3,6-Dimethylpyridazine 1-oxide	1.61
Pyridazine dioxide	1.14, 1.53	3,6-Dimethylpyridazine dioxide	1.27, 1.63
3-Methylpyridazine	1.41	4-Methylpyridazine	1.44
3-Methylpyridazine 1-oxide	1.55	4-Methylpyridazine 1-oxide	1.59
3-Methylpyridazine 2-oxide	1.58	4-Methylpyridazine 2-oxide	1.57
3-Methylpyridazine dioxide	1.19, 1.60	4-Methylpyridazine dioxide	1.20, 1.61

* Each half-wave reduction potential was measured against Hg pool electrode at 25°.

Dioxides were reduced more easily than bases, and the first half-wave potentials for dioxides may correspond to the reduction of dioxides to monoxides, and the half-wave potentials of second wave for dioxides nearly coincide with the half-wave potentials of monoxides. The similar trend has been also obtained from the reduction of dioxides of cinnoline (1), benzo(c)cinnoline (3), and phenazine (4). In view of above facts, dioxides were reduced first to monoxides (probably Ic, IId, IIc, and IVc) which were reduced to end products.

As shown in Table III, the ultraviolet spectra of these dioxides show a blue shift on increasing polarity of solvent (5).

TABLE III
Spectral Properties of Pyridazine Dioxides

Dioxide	Solvent	λ max $m\mu$ (log ϵ)		ν_{N-O}			
				CHCl ₃ sol.		KBr disk	
Ib	H ₂ O	241 (4.45)	288 (3.81)	1380	1328	1350	1320
	EtOH	244 (4.44)	297 (3.84)				
	Dioxane	247 (4.43)	305 (3.91)				
IIb	H ₂ O	241 (4.46)	287 (3.87)	1375	1310	1360	1300
	EtOH	244 (4.47)	296 (3.84)				
	Dioxane	248 (4.37)	305 (3.83)				
IIIb	H ₂ O	244 (4.54)	287 (3.92)	1370	1308	1365	1305
	EtOH	246 (4.52)	296 (3.89)				
	Dioxane	249 (4.45)	305 (3.89)				
IVb	H ₂ O	239 (4.48)	286 (3.84)	1372	1315	1364	1312
	EtOH	243 (4.48)	295 (3.86)				
	Dioxane	247 (4.43)	304 (3.85)				

Infrared spectra of pyridazine dioxides showed no bands due to hydroxy and carbonyl groups. In cinnoline 1,2-dioxide (1) and 4-methylcinnoline 1,2-dioxide (2), two bands at 1403 and 1343 cm^{-1} , and at 1399 and 1342 cm^{-1} were assigned to the N-O stretching vibration of dioxide group, respectively. As shown in Table III, pyridazine dioxides exhibit two kinds of characteristic bands at around 1300-1380 cm^{-1} which may be assignable to the N-O stretching vibration of dioxide group. These bands shift to lower frequency by addition of methanol to chloroform solution (6).

TABLE IV
Nuclear Magnetic Resonance Spectral Parameters for Pyridazine Dioxides

	τ_3	τ_4	τ_5	τ_6	τ_{CH_3}	$J_{3,4}$	$J_{3,5}$	$J_{3,6}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$
Ib	1.85	2.92	2.92	1.85	—	—	—	—	—	—	—
IIb	—	2.90	2.95	1.86	7.44	$\sim 0.4^*$	—	$\sim 0.6^*$	8.1	2.4	6.1
IIIb	1.93	—	3.02	1.89	7.65	$\sim 0.8^*$	2.4	0.7	$\sim 0.7^*$	—	6.8
IVb	—	3.04	3.04	—	7.47	$< 0.2^*$	—	—	—	—	$< 0.2^*$

Chemical Shift (τ), Coupling Constant, J (Hz)

* CH_3 -H coupling

The 100 MHz nmr spectral parameters of dioxides in CDCl_3 (TMS as internal standard) are summarized in Table IV. The spectrum of Ib consists of two symmetrical quartets of an A_2B_2 type. The spectra of IIb and IIIb display peaks of ABX and ABC type, respectively. The observed nmr spectra of these compounds are interpreted as di-N-oxide structure by comparing with the spectra of the parent bases and those of monoxides which have been interpreted by Tori, et al. (7), (8).

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