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4-METHYLPYRIMIDINE N-OXIDES

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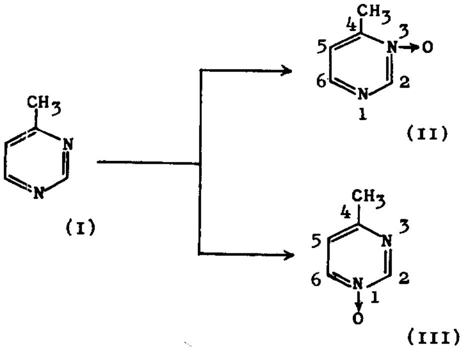
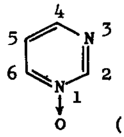
IN earlier papers dealing with the N-oxidation of monomethylpyridazines (1,2,3), it has been reported that both of the two conceivable isomers were isolated from the reaction mixture and the position of N-O group in each N-oxide was determined by the dipole moment as well as by the NMR spectrum. In this connection, it appeared of interest to extend the same procedure to the N-oxidation product of 4-methylpyrimidine (I) where only one of the two possible isomers has been isolated.

Ochiai and his coworkers oxidized I with hydrogen peroxide to obtain an N-oxide, m.p. 74-78° (4,5), which was assumed to be the 1-oxide by them as well as by subsequent workers (6,7,8,9). Otomasu, et al. (10) measured the dipole moment of the N-oxide of I obtained by Ochiai's method and concluded that the N-oxide is the 3-oxide. The present investigation was undertaken to confirm their conclusion and also to see if both of the two isomers could be obtained in a similar fashion as in the case of the 3- and 4-methylpyridazine N-oxides.

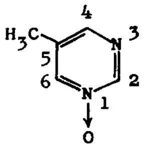
N-oxidation of I according to the known procedure (5) gave a product, which distinctly shows two spots on a thin layer alumina chromatogram (eluent, chloroform), and whose NMR spectrum indicates two set of signals due to the ring protons. This mixture was chromatographed on alumina to isolate two N-oxides. Elution with benzene gave an N-oxide II, which was recrystallized from benzene to obtain colorless and slightly hygroscopic prisms (m.p. 82-83°; λ_{max}^{EtOH} 265.5 mμ (log ε 4.06); $\nu_{N-O}^{CS_2}$ 1278 and 1270 (shoulder) cm^{-1}; picrate, m.p. 137-138°).* The eluate from chloroform was recrystallized from benzene—pet.benzin to afford another N-oxide III as colorless and very hygroscopic needles (m.p. 45-47°; λ_{max}^{EtOH} 267 mμ (log ε 4.06) and 304 mμ (log ε 3.45, shoulder); $\nu_{N-O}^{CS_2}$ 1272 (shoulder) and 1265 cm^{-1}; picrate, m.p. 104.5-105°.* Relative integrated area of the C_6-proton signals in the oxidation mixture of I showed the product ratio of II to III as 3.5:1.



(I) (II) (III)



(IV)



(V)

The dipole moments of these N-oxides and related compounds, viz. pyrimidine N-oxide (IV) (6,11) and 5-methylpyrimidine N-oxide (V) (6), were measured to determine the position of N-O group. The measurements and calculations were carried out by the same method

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* Analysis of all the compounds described satisfactorily corresponded to the calculated values.

as that described in a previous paper (2). The results are shown in Table I, in which α and β respectively denote the changes of the dielectric constant and density of solutions with the weight fraction of the solute; other notations have their usual meanings.

TABLE I

Dipole Moments of Pyrimidine N-Oxides in Benzene at 25°C

Compound	α	β (g/cc)	MR_D (cc)	Dipole moment Observed	Dipole moment Calculated	Assignment
II	13.88	0.23	30.0	3.72D	3.70D	3-oxide
III	16.70	0.40	30.0	4.05D	3.99D	1-oxide
IV	15.38	0.31	25.4	3.65D	3.67D	
V	15.53	0.29	30.0	4.03D	4.00D	

Each of the calculated moment was obtained as a vector sum of group moments. On the assumption of a regular hexagon form of the ring, the moments of IV can be calculated as 3.67D from the observed moments of pyridine, 2.22D (12), and that of its N-oxide, 4.24D (13), in benzene solution. Taking the $C\text{-}CH_3$ moment as the moment of toluene, 0.37D (14), one can easily calculate the moments of the three methyl derivatives, II, III and V. All of the observed values are in excellent agreement with the calculated moments when II is assigned to the 3-oxide and III to the 1-oxide.

Although Otomasu, et al. (10) have compared their data, 3.86D with their own calculated values of 4.15D (for 1-oxide) and 3.77D (for 3-oxide) to assign II to the 3-oxide, the discrepancy between the observed value and the calculated ones seems to leave some ambiguity in the assignment. One can find a more reliable basis for the assignment by preparing both of the two N-oxides to qualitatively compare the magnitudes of moment with a pair of the calculated ones, and the discussions described above leave no doubt that III is the 1-oxide and II is the 3-oxide.

NMR spectral data on these four pyrimidine N-oxides are listed in Table II. Their ring proton signals were easily assigned in comparison with each other and analysed by the first order treatment.

TABLE II

NMR Spectral Data[a,b]

Compound	Chemical shift (τ)				Coupling constant, J (c.p.s.)[c]					
	2-H	4-H	5-H	6-H	$J_{2,4}$	$J_{2,5}$	$J_{2,6}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$
IV	1.02	1.76	2.66	1.57	~0	1.0	2.0	4.9	1.6	6.8
III	1.10	(7.47)	2.84	1.71			2.0	(~0.5)	(~0.3)	6.6
V	1.17	1.88	(7.67)	1.71		(~0)	~2.5	(~0.7)	~1.5	(~1.5)
II	1.01	(7.47)	2.71	1.88	(~0)	~1.0	~0	(~0.4)	(~0)	5.0

[a] The spectra were observed on 10% (w/v) solutions of the samples in deuterochloroform containing tetramethylsilane as an internal standard, by using a Varian A-60 spectrometer, the calibration of which was checked according to Tiers and Hotchkiss' method (15).

[b] Values in parentheses are chemical shifts or coupling constants of methyl groups.

[c] Some of the coupling constants can not be determined owing to small broadenings in peaks arising from the proton on a carbon adjacent to a nitrogen. This fact is due to the quadrupole relaxation and spin coupling effects of N^{14} nucleus (16).

Three interesting results reached by the study of these spectra should be noted. First is the spin coupling constant $J_{2,6}$ in II, which has a larger value (2.0 c.p.s.) than that in III (~0 c.p.s.) and that in pyrimidine (17), and the oxidation of nitrogen atom between the protons in question (*meta*) may cause the increase of coupling constant. Second is the total effect of methyl substitution on the ring proton shifts (18), the effect in II (0.16 p.p.m.) being considerably smaller than those in III and V (0.40 p.p.m.). The methyl groups at an *ortho* position to the N-O group seem to have less affect than those at other positions, as reported on pyridazine

N-oxides (3). These two observations afford further evidences for the structure assignment. Third is the chemical shift of the ring protons of IV. The order of the chemical shift, $H_2 < H_6 < H_4 < H_5$, is quite different from that of the π-electron density, $C_4 < C_5 < C_2 < C_6$, obtained by a Hückel MO calculation (9).* The anisotropic effect of the N-O group and nitrogen atom (16) will give a suitable correction to fit the chemical-shift order to the π-electron density order (3,20). More detailed discussions will be appear in a forthcoming full paper.

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* Several workers have proposed that there is a quantitative relationship between the chemical shift of ring protons and the local "excess" charge density on ring carbons in aromatic molecules (19).

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