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Studies on Pyrimidine Derivatives. XIV.[1] On the Structural Determination of Pyrimidine N-Oxides[2]

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N-Oxidation of pyrimidines having unsymmetrically substituted 4- and 6-positions with hydrogen peroxide in acetic acid gave mixture of their 1-oxides and 3-oxides. Ring transformation of these 1-oxides and 3-oxides into isoxazoles occurred on treatment with mineral acid, and provided information on the position of the N-oxide group in the pyrimidine N-oxides.

Nuclear magnetic resonance spectroscopy with a lanthanide shift reagent was also found to be useful in identifying the pyrimidine 1- and 3-oxides.

Keywords——ring transformation; unsymmetrically substituted pyrimidine N-oxides; 3,5-disubstituted isoxazoles; NMR spectra of pyrimidine N-oxides; tris(heptafluorobutanoylpivaloylmethanato)europium^{III}

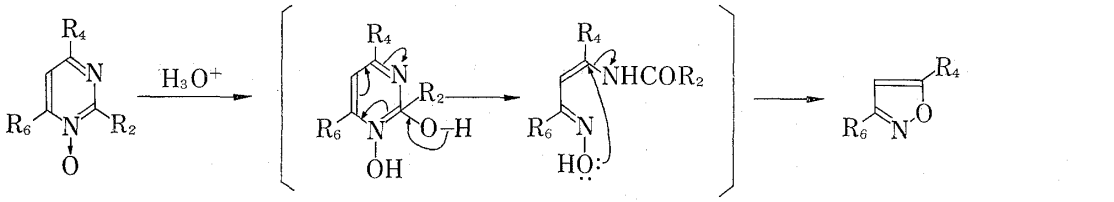
The presence of two nitrogen atoms in a pyrimidine molecule presents an obvious problem in the structural elucidation of mono-N-oxides. In 1964, Ogata *et al.*[4] reported the first separation of 4-methylpyrimidine N-oxides into the 1-oxide and the 3-oxide, using preparative gas chromatography, and they identified each N-oxide by comparing the dipole moments of the two compounds. Similarly, Otomasu *et al.*[5] confirmed that the calculated value of the dipole moment coincided with the observed value for 4-ethoxy-6-methylpyrimidine 1-oxide, which has been synthesized by one of the present authors[6] as the sole product of direct oxidation of the corresponding tertiary amine.

In contrast to the above physical method, van der Plas *et al.*[7] demonstrated by means of chemical reactions that 4-chloro-6-methylpyrimidine N-oxide, obtained by permaleic acid oxidation of the parent base, contained an N-oxide group at the 1-position.

In this paper, we report the structural differentiation of pyrimidine 1-oxides and 3-oxides by means of a particular ring transformation of pyrimidine N-oxides into isoxazole derivatives, and by nuclear magnetic resonance (NMR) spectroscopy of these N-oxides with an NMR shift reagent.

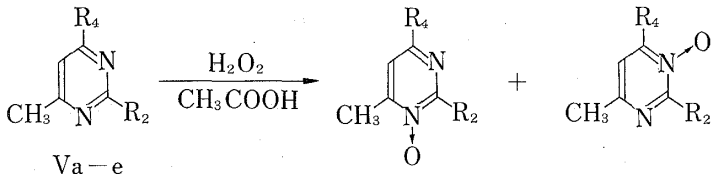
It is already known[8] that the acid hydrolysis of 4-phenylpyrimidine N-oxide (I) gives 5-phenylisoxazole (II) in good yield. In order to confirm the scope of this reaction, 4,6-dimethyl-2-phenylpyrimidine N-oxide (III) was heated in boiling dilute hydrochloric acid, and gave 3,5-dimethylisoxazole (IV), as expected. On the basis of the probable reaction mechanism, which is illustrated in the Chart, this ring transformation may be applicable to the structural determination of pyrimidine N-oxides even if the 2-position is occupied by an alkyl or aryl group.

1) Part XIII: H. Yamanaka, S. Niitsuma, and T. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **27**, 2642 (1979).
2) A part of this work has been published as a preliminary communication [T. Sakamoto, S. Niitsuma, M. Mizugaki, and H. Yamanaka, *Heterocycles*, **8**, 257 (1977)].
3) Location: *Aobayama, Sendai 980, Japan.*
4) M. Ogata, H. Watanabe, K. Tori, and H. Kano, *Tetrahedron Lett.*, **1964**, 19.
5) H. Otomasu, H. Takahashi, and M. Ogata, *Chem. Pharm. Bull.* (Tokyo), **12**, 714 (1964).
6) E. Ochiai and H. Yamanaka, *Pharm. Bull.*, **3**, 175 (1955).
7) R. Peereboom, H.C. van der Plas, and A. Koudijs, *Rec. Trav. Chim.*, **93**, 58 (1974).
8) T. Kato, H. Yamanaka, and N. Yasuda, *J. Org. Chem.*, **32**, 3788 (1967).



I : $R_2=R_6=H$, $R_4=C_6H_5$
III : $R_2=C_6H_5$, $R_4=R_6=CH_3$

II : $R_4=C_6H_5$, $R_6=H$
IV : $R_4=R_6=CH_3$

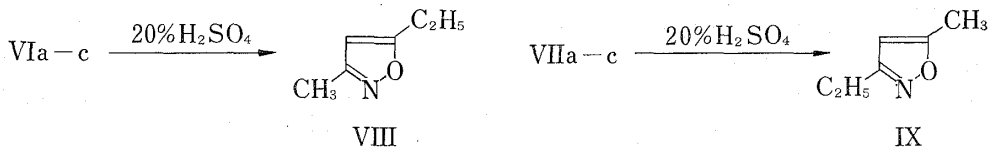


Va－e

a : $R_4=C_2H_5$, $R_2=CH_3$
b : $R_4=C_2H_5$, $R_2=CH(CH_3)_2$
c : $R_4=C_2H_5$, $R_2=C_6H_5$
d : $R_4=CH_2C_6H_5$, $R_2=CH_3$
e : $R_4=C_6H_5$, $R_2=CH_3$

VIa－e

VIIa－e



VIII

IX

Chart 1

From this point of view, 4-ethyl-2,6-dimethylpyrimidine (Va) was oxidized with hydrogen peroxide in acetic acid to give a mixture of two isomeric N-oxides in 55% yield.[9] The mixture was chromatographed on basic alumina (ether), yielding the 1-oxide (VIa) and the 3-oxide (VIIa) of the parent base (Va). Gas chromatography showed the VIa/VIIa ratio to be 6 : 5. The results of elemental analysis and the NMR spectra of VIa ($C_8H_{12}N_2O \cdot 1/4H_2O$, bp 92°/2 mmHg) and VIIa ($C_8H_{12}N_2O$, mp 79—81°) revealed that they were isomeric 2,6-dimethyl-4-ethylpyrimidine mono-N-oxides.

One of the N-oxides (VIa) was then heated in 20% sulfuric acid for 7 hr to give 5-ethyl-3-methylisoxazole (VIII) in 42% yield (81% conversion yield), together with recovery of the starting N-oxide (VIa). The other N-oxide (VIIa) was similarly hydrolyzed to 3-ethyl-5-methylisoxazole (IX) in 43% yield (73% conversion yield). The structures of the resulting isoxazoles (VIII, IX) were confirmed by comparison of their spectral data with those of authentic specimens.[10]

Based on these results it is clear that VIa is the pyrimidine 1-oxide and VIIa is the 3-oxide. Similar results regarding the structural identification of pyrimidine mono-N-oxides were obtained generally for unsymmetrically substituted pyrimidine derivatives, as summarized in Tables I, II, III. Cross-reactions (*i.e.* VIa→IX and VIIa→VIII) were not ovserved, so this ring transformation should be of wide applicability for the structural elucidation of alkylpyrimidine N-oxides even when only one of the isomeric N-oxides is isolated.

9) When this type of pyrimidine is heated with excess hydrogen peroxide in acetic acid under drastic conditions, the pyrimidine ring is oxidatively cleaved and N_1,N_3-dioxides are not obtained.
10) H. Heuer and S. Markofsky, *J. Org. Chem.*, **29**, 935 (1964).

Table I. Yields, Melting Points (or Boiling Points), and Elemental Analyses of Pyrimidine N-Oxides

No.	Yield (%)	mp or [bp(mmHg)] (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ⅲ	45	91—92	$C_{12}H_{12}N_2O$	71.98	6.04	13.99	71.81	5.88	13.78
VIa	30[a]	[92(2)]	$C_8H_{12}N_2O\cdot 1/4H_2O$	61.32	8.04	17.88	61.17	7.95	18.10
VIIa	25[a]	79—81	$C_8H_{12}N_2O$	63.13	7.95	18.41	63.43	7.88	18.77
VIb	28[a]	[100—102(1)]	$C_{10}H_{16}N_2O$	66.63	8.95	15.54	66.56	9.23	15.60
VIIb	18[a]	[93—95(1)]					66.26	9.03	15.70
VIc	22[a]	56—62	$C_{13}H_{14}N_2O$	72.87	6.59	13.08	72.92	6.53	13.01
VIIc	12[a]	56—57					72.65	6.55	13.02
VId	18	91.5—94.5	$C_{13}H_{14}N_2O$	72.87	6.59	13.08	72.65	6.59	13.01
VIId	15	73.5—76					72.58	6.59	13.08
VIe	40	98—100	$C_{12}H_{12}N_2O$	71.98	6.04	13.99	71·78	6.00	14.33
VIIe	0.6	94—96.5					72.07	6.19	13.87

a) Yields were determined by gas chromatography.

Table II. Transformation of Pyrimidine N-Oxides into Isoxazoles

Pyrimidine N-oxide	Yield of isoxazole (VIII) (%)	Pyrimidine N-oxide	Yield of isoxazole (IX) (%)
VIa	42(81[a])	VIIa	43(73[a])
VIb	67(75[a])	VIIb	77
VIc	64	VIIc	69

a) Conversion Yield.

Table III. Spectral Data for Pyrimidines (Va—e) and Their N-Oxides(VIa—e and VIIa—e)

No.	IR (KBr) cm^{-1} N-O	NMR ($CDCl_3$) δ (ppm) 6- and/or 2-CH_3 (s)	4-$C\underline{H}_2CH_3$ (q)	4-$CH_2C\underline{H}_3$ (t)	5-H (a)	Other protons
Va	—	2.43	2.64	2.69[a]	1.24[a]	6.81	—
VIa	1255	2.53	2.75	2.75[a]	1.30[a]	7.05	—
VIIa	1245	2.47	2.72	2.93[a]	1.28[a]	7.00	—
Vb	—	2.43	—	2.68[a]	1.23[a]	6.78	1.28 (6H, d[c]), 3.10 (1H, sep[c])
VIb	1250	2.50	—	2.70[a]	1.27[a]	6.92	1.30 (6H, d[d]), 3.92 (1H, sep[d])
VIIb	1280	2.47	—	2.92[b]	1.29[b]	6.92	1.30 (6H, d[c]), 3.95 (1H, sep[c])
Vc	—	2.54	—	2.79[a]	1.32[a]	6.91	7.40—7.63 (3H, m), 8.38—8.60 (2H, m)
VIc	1250	2.57	—	2.81[a]	1.34[a]	7.01	7.30—7.60 (3H, m), 8.30—8.70 (2H, m)
VIIc	1260	2.53	—	3.01[a]	1.34[a]	7.04	7.35—7.60 (3H, m), 8.30—8.60 (2H, m)
Vd	—	2.37	2.68	—	—	6.69	4.00 (2H, s), 7.24 (5H, s)
VId	1257	2.47	2.76	—	—	6.92	4.04 (2H, s), 7.30 (5H, s)
VIId	1255	2.37	2.77	—	—	6.67	4.25 (2H, s), 7.33 (5H, s)
Ve	—	2.42	2.65	—	—	7.21	7.28—7.50 (3H, m), 7.90—8.15 (2H, m)
VIe	1260	2.60	2.83	—	—	7.58	7.35—7.60 (3H, m), 7.90—8.15 (2H, m)
VIIe	1253	2.51	2.79	—	—	7.21	7.35—7.65 (3H, m), 7.75—8.10 (2H, m)

a) J=7.5 Hz, b) J=7.1 Hz, c) J=6.8 Hz, d) J=6.0 Hz.

On the other hand, there are several papers[11] dealing with lanthanide-induced displacements of signals in the NMR spectra of simple heteroaromatic N-oxides. Accordingly, an attempt was made to distinguish between the 1-oxide (VIa) and the 3-oxide (VIIa) with the aid of NMR spectroscopy.

Although the NMR spectra of VIa and VIIa are as expected for the pyrimidine N-oxide structure, further information regarding the position of the N-oxide group could not be obtained, as shown in Table III.

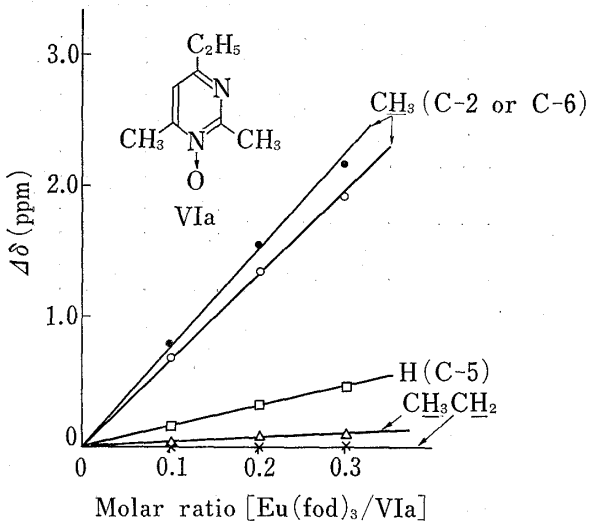


Fig. 1. $Eu(fod)_3$ Induced NMR Shifts for 4-Ethyl-2,6-dimethylpyrimidine 1-Oxide (VIa) in $CDCl_3$ Solution (0.67 M) at 34°

Thus the effect of a lanthanide reagent, tris(heptafluorobutanoylpivaloylmethanato)europium^{III} [$Eu(fod)_3$] on the NMR spectrum of the 1-oxide (VIa) was compared with that on the spectrum of the 3-oxide (VIIa). In the case of VIa (Fig. 1) large displacements were observed of the signals due to the 2- and 6-methyl groups, whereas only a small displacement of the signal of the methylene protons in the ethyl group was observed. Conversely, in the case of VIIa (Fig. 2), the largest effect was seen on the signal of the methylene protons, and essentially no effect was observed on the signal assignable to the 6-methyl protons. In both cases, the relationship between the induced displacement of signals and reagent concentration was linear.

When the spectrum of 4-ethoxy-6-methylpyrimidine 1-oxide, whose structure has been confirmed by other methods,[12] was measured under identical conditions, the results shown

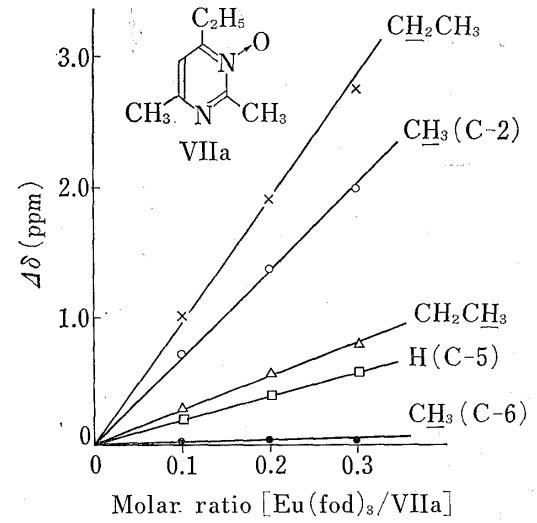


Fig. 2. $Eu(fod)_3$ Induced NMR Shifts for 4-Ethyl-2,6-dimethylpyrimidine 3-Oxide (VIIa) in $CDCl_3$ Solution (0.67 M) at 34°

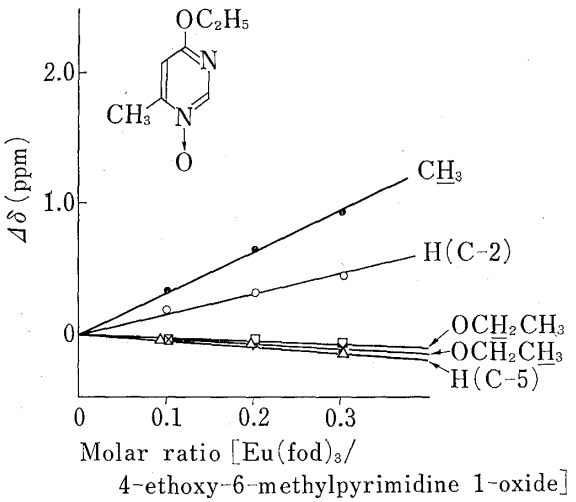


Fig. 3. $Eu(fod)_3$ Induced NMR Shifts for 4-Ethoxy-6-methylpyrimidine 1-Oxide in $CDCl_3$ Solution (0.33 M) at 34°

11) R.A. Fletton, G.F.H. Green, and J.E. Page, *Chem. Ind.* (London), **1972**, 167.
12) The treatment of 4-chloro-6-methylpyrimidine 1-oxide with sodium ethoxide in ethanol afforded 4-ethoxy-6-methylpyrimidine 1-oxide,[7] which was identical with a specimen[6] prepared by the oxidation of 4-ethoxy-6-methylpyrimidine.

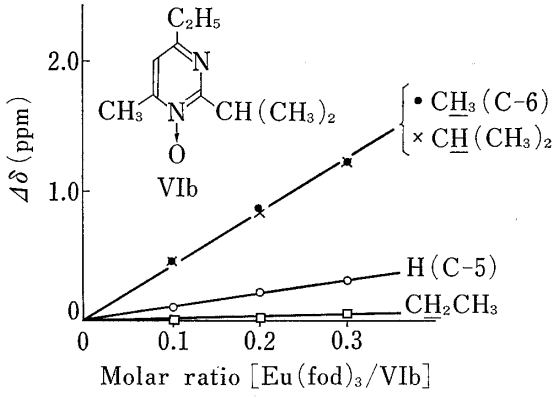


Fig. 4. Eu(fod)$_3$ Induced NMR Shifts for 4-Ethyl-2-isopropyl-6-methylpyrimidine 1-Oxide (VIb) in $CDCl_3$ Solution (0.33 M) at 34°

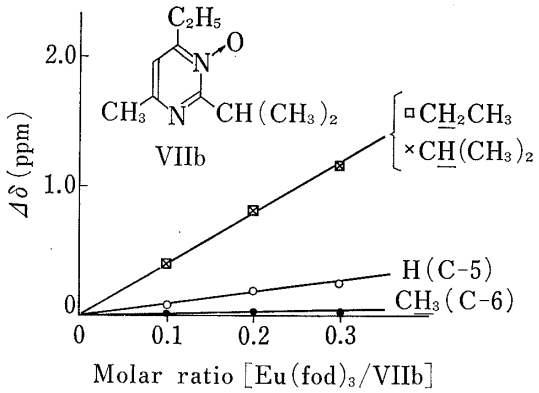


Fig. 5. Eu(fod)$_3$ Induced NMR Shifts for 4-Ethyl-2-isopropyl-6-methylpyrimidine 3-Oxide (VIIb) in $CDCl_3$ Solution (0.33 M) at 34°

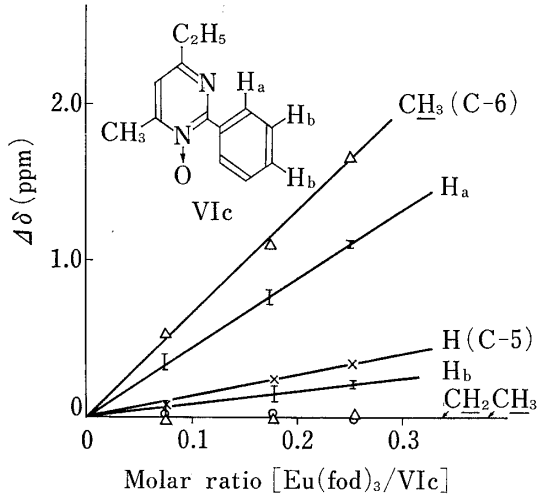


Fig. 6. Eu(fod)$_3$ Induced NMR Shifts for 4-Ethyl-6-methyl-2-phenylpyrimidine 1-Oxide (VIc) in $CDCl_3$ Solution (0.33 M) at 34°

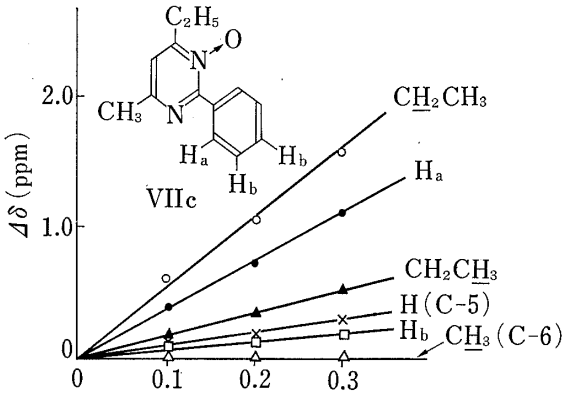


Fig. 7. Eu(fod)$_3$ Induced NMR Shifts for 4-Ethyl-6-methyl-2-phenylpyrimidine 3-Oxide (VIIc) in $CDCl_3$ Solution (0.33 M) at 34°

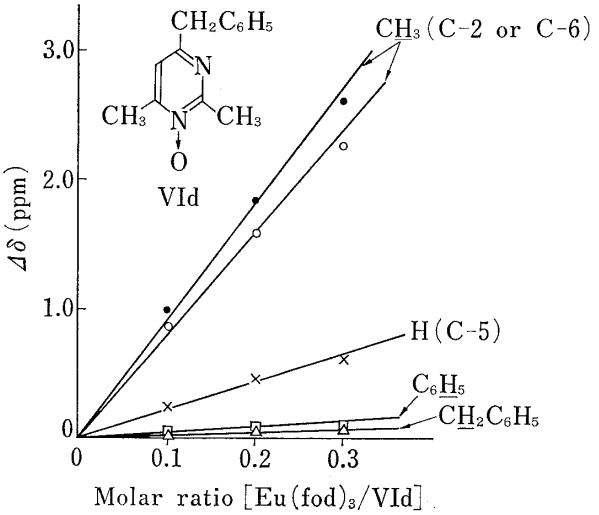


Fig. 8. Eu(fod)$_3$ Induced NMR Shifts for 4-Benzyl-2,6-dimethylpyrimidine 1-Oxide (VId) in $CDCl_3$ Solution (0.33 M) at 34°

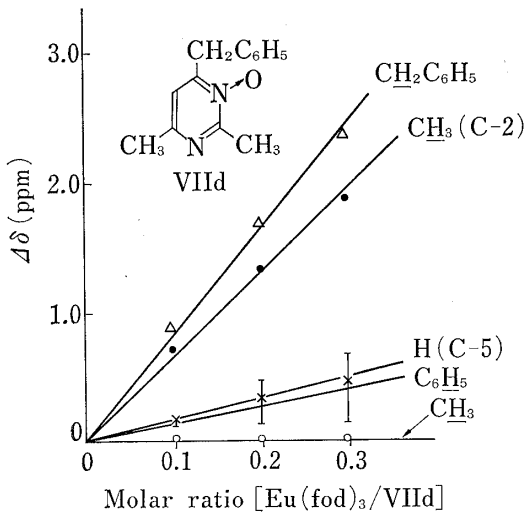


Fig. 9. Eu(fod)$_3$ Induced NMR Shifts for 4-Benzyl-2,6-dimethylpyrimidine 3-Oxide (VIId) in $CDCl_3$ Solution (0.33 M) at 34°

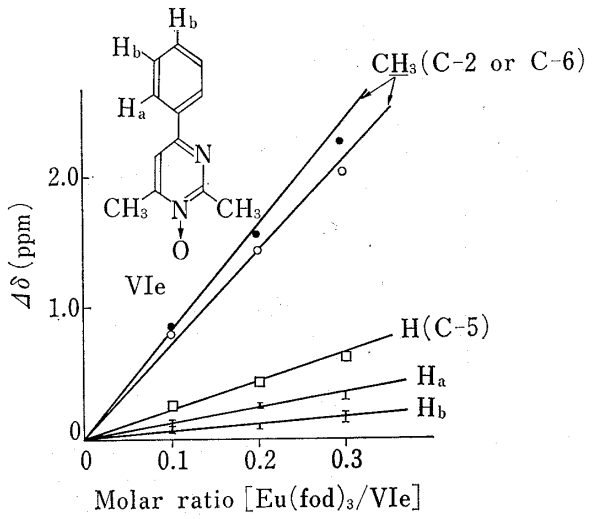


Fig. 10. $Eu(fod)_3$ Induced NMR Shifts for 2,6-Dimethyl-4-phenylpyrimidine 1-Oxide (VIe) in $CDCl_3$ Solution (0.33 M) at 34°

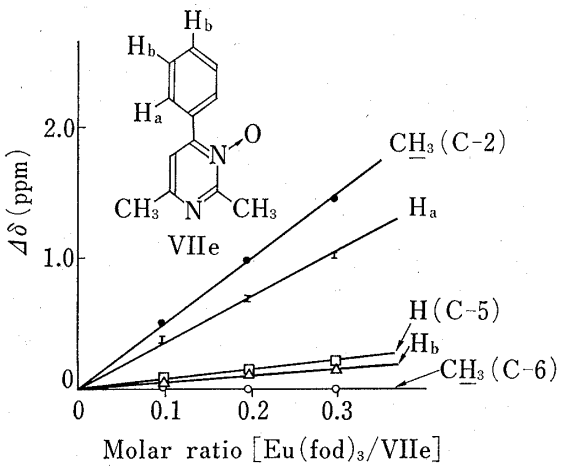


Fig. 11. $Eu(fod)_3$ Induced NMR Shifts for 2,6-Dimethyl-4-phenylpyrimidine 3-Oxide (VIIe) in $CDCl_3$ Solution (0.33 M) at 34°

in Fig. 3 was obtained. Based on these results, the lanthanide reagent is concluded to coordinate predominantly to the N-oxide group. Similar phenomena were observed with the N-oxide pairs of such compounds as 4-ethyl-2-isopropyl-6-methyl-(Vb), 4-ethyl-6-methyl-2-phenyl-(Vc), 4-benzyl-2,6-dimethyl-(Vd), and 2,6-dimethyl-4-phenyl-pyrimidine (Ve), as expected. The spectral data are illustrated in Fig. 4—11.

Accordingly it is clear that, in addition to the chemical ring transformation of pyrimidine N-oxides into isoxazoles, NMR spectroscopy with a lanthanide reagent provides a novel approach to the identification of such N-oxides. Although pyrimidine N-oxides have been used exclusively in these experiments, similar interpretative spectroscopy might be applicable to other diazine mono-N-oxides for structural elucidation.

Experimental[13]

Pyrimidines——The following pyrimidines were synthesized according to the literature; 4,6-dimethyl-2-phenyl-,[14] 4-ethyl-2,6-dimethyl- (Va),[15] 4-benzyl-2,6-dimethyl- (Vd),[15] and 2,6-dimethyl-4-phenyl-pyrimidine (Ve).[15]

4-Ethyl-2-isopropyl-6-methylpyrimidine (Vb)——A stirred solution of ethyl magnesium bromide (prepared from 4.37 g (0.18 g atom) of Mg turnings and 19.62 g (0.18 mol) of ethyl bromide) and $Ni[(C_6H_5)_2PCH_2CH_2CH_2P(C_6H_5)_2]Cl_2$ (Ni(dppp)Cl_2, 1.68 g, 0.003 mol) in anhyd. ether (80 ml) was treated with an ethereal solution (180 ml) of 4-chloro-2-isopropyl-6-methylpyrimidine (10.24 g, 0.06 mol), and the mixture was refluxed for 20 hr. After cooling, excess Grignard reagent was decomposed by adding 3 N HCl and the resulting mixture was made alkaline with conc. aq. K_2CO_3. The inorganic materials which separated were filtered off and washed with ether. The aqueous layer was extracted with ether. The combined ethereal solution was dried and concentrated to give a residue, which was purified by distillation to afford a colorless liquid, bp 91—92° (15 mmHg). Yield 5.38 g (55%). IR cm^{-1} ($CHCl_3$): 1600. *Anal.* Calcd. for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82; N, 17.06. Found: C, 73.37; H, 10.01; N, 17.06.

4-Ethyl-6-methyl-2-phenylpyrimidine (Vc)——From 4-chloro-6-methyl-2-phenylpyrimidine (14.33 g, 0.07 mol), ethyl bromide (16.79 g, 0.154 mol), Mg turnings (3.74 g, 0.154 g atom), Ni(dppp)Cl_2 (378 mg,

13) All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. NMR spectra were taken at 60 MHz with a Hitachi-Perkin-Elmer R-2 spectrometer. Chemical shifts are expressed as δ (ppm) using tetramethylsilane (TMS) as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, sep=septet, and m=multiplet.

14) A. Pinner, *Chem. Ber.*, **26**, 2122 (1898).

15) H. Yamanaka, K. Edo, F. Shoji, S. Konno, T. Sakamoto, and M. Mizugaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 2160 (1978).

0.7 mmol), and anhyd. ether (350 ml), a pale yellow liquid, bp 122—124° (2 mmHg), was obtained according to the procedure described above. Yield 11.47 g (83%). IR cm^{-1} ($CHCl_3$): 1603. *Anal.* Calcd. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.47; H, 6.97; N, 14.02.

N-Oxidation of III or Va—e——General Procedure: Aqueous hydrogen peroxide (30%; 1.0 eq.) was added to a solution of a pyrimidine (1.0 eq.) in acetic acid, and the mixture was warmed at 70—95° for 2 hr. Two further portions of 0.5 eq. of 30% hydrogen peroxide solution were added at 2 hr intervals and the whole mixture was warmed at 70—95° for an additional 3 hr (total 6 hr). The reaction mixture was concentrated under reduced pressure, water was added when the volume of the residue became small, and the resulting solution was further concentrated. This concentration procedure was repeated three times to remove as much acetic acid as possible. The residue was made alkaline by the cautious addition of conc. aq. K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated down to give a crude mixture of products. In the case of N-oxidation of Va—c, a portion of this crude mixture was analyzed with a Shimadzu GC-6A gas chromatograph (FID): column, Diasolid ZS (SILREST treatment) 2m; H_2, 0.7 kg/cm^2; air, 1.0 kg/cm^2; N_2, 60 ml/min. Column temperature, injection port and detector temperature, retention time, and ratio of N-oxides are listed in Table IV.

Table IV. Gas Chromatography of Pyrimidine N-Oxides (VIa—c and VIIa—c)

	VIa	VIIa	VIb	VIIb	VIc	VIIc
Column temp. (°C)	155		155		187	
Injec. det. temp. (°C)	220		220		280	
Retention time (sec)	80	75	110	105	82	78
Ratio (%)	55	45	60	40	66	34

4,6-Dimethyl-2-phenylpyrimidine 1-Oxide (III)——4,6-Dimethyl-2-phenylpyrimidine (7.36 g, 0.04 mol) was oxidized with 30% H_2O_2 (9.06 g, 0.08 mol) in AcOH (74 ml) according to the general procedure. The crude product was recrystallized from petr. benzine to give colorless scales. Yield 3.6 g. IR cm^{-1} (KBr): 1250. NMR δ ($CDCl_3$); 2.50 (3H, s), 2.81 (3H, s), 7.06 (1H, s), 7.30—7.80 (3H, m), 8.20—8.70 (2H, m).

N-Oxidation of Va——Va (5.45 g, 0.04 mol) was oxidized with 30% H_2O_2 (9.06 g, 0.08 mol) in AcOH (40 ml) according to the general procedure. The crude product was distilled under reduced pressure to give a yellow liquid (crude mixture of VIa and VIIa, bp 90—102° (1 mmHg), 3.34 g, 55%), which was purified by Al_2O_3 (150 ml) column chromatography using ether as an eluant. The first fraction gave a small amount of Va. The second fraction gave a colorless solid (710 mg) which was recrystallized from petr. ether to yield colorless needles (VIIa). The third fraction gave a mixture of VIa and VIIa. The fourth fraction gave a yellow liquid (680 mg) which was purified by distillation under reduced pressure and subsequent recrystallization from petr. ether to give colorless needles (VIa). VIa is hygroscopic and melts at low temperature.

N-Oxidation of Vb——Vb (6.57 g, 0.04 mol) was oxidized with 30% H_2O_2 (6.81 g, 0.06 mol) in AcOH (40 ml) according to the general procedure. The crude product was purified by Al_2O_3 (150 ml) column chromatography. The fraction eluted with ether–petr. ether (1: 5) gave Vb (66 mg). The first fraction eluted with ether–petr. ether (1: 1) gave a colorless liquid (1.08 g) which was purified by distillation under reduced pressure to yield a colorless liquid (VIIb). The second fraction eluted with ether–petr. ether (1: 1) gave a mixture of VIb and VIIb (2.27 g). The fraction eluted with ether (0.97 g) was purified by distillation under reduced pressure to afford a colorless solid (VIb). Yield of crude mixture of VIb and VIIb, 3.35 g (46%).

N-Oxidation of Vc——Vc (9.90 g, 0.05 mol) was oxidized with 80% H_2O_2 (14.16 g, 0.125 mol) in AcOH (70 ml) according to the general procedure. The crude product was purified by Al_2O_3 (200 ml) column chromatography. The fraction eluted with ether–petr. ether (1: 10) gave Vc (0.48 g, 5%). The first fraction eluted with ether gave a pale yellow solid (VIIc, 0.92 g) which was recrystallized from ether–petr. ether to afford colorless needles. The second fraction eluted with ether gave a mixture of VIc and VIIc (1.12 g). The third fraction eluted with ether gave a yellow solid (1.62 g) which was recrystallized from ether–petr. ether to give colorless needles (VIc). Yield of the crude mixture of VIc and VIIc, 3.66 g (34%).

N-Oxidation of Vd——Vd (3.97 g, 0.02 mol) was oxidized with 30% H_2O_2 (4.54 g, 0.04 mol) in AcOH (25 ml) according to the general procedure. The crude product was purified by SiO_2 (160 ml) column chromatography. The first fraction eluted with ether gave Vd (0.94 g, 24%). The second fraction eluted with ether gave a colorless solid (VIId) which was recrystallized from ether–petr. ether to give colorless prisms. Yield 645 mg (15%). The fraction eluted with acetone gave an orange liquid which was further purified by Al_2O_3 column chromatography using ether as eluant to yield colorless prisms (ether–petr. ether) (VId). Yield 789 mg (18%).

N-Oxidation of Ve——Ve (7.37 g, 0.04 mol) was oxidized with 30% H_2O_2 (9.06 g, 0.08 mol) in AcOH (50 ml) according to the general procedure. The crude product was purified by Al_2O_3 (100 ml) column

chromatography using ether as an eluant. The first fraction gave Ve (1.75 g, 24%). The second fraction gave a mixture of VIe and VIIe (228 mg). The third fraction gave a colorless solid (VIe) which was recrystallized from ether to give colorless needles. Yield 3.18 g (40%). The mother liquor was combined with the second fraction eluted with ether and further purified by SiO_2 column chromatography using ether as an eluant to yield colorless needles (ether–petr. ether) (VIIe). Yield 47 mg (0.6%).

4-Ethoxy-6-methylpyrimidine 1-Oxide——H_2O_2 (30%, 11.9 ml, 0.105 mol) was added to a solution of powdered maleic anhydride (87.75 g, 0.875 mol) in $CHCl_3$ (280 ml) at 2—4°. After stirring the cold solution for 2 hr, a $CHCl_3$ (9 ml) solution of 4-chloro-6-methylpyrimidine (4.50 g, 0.035 mol) was added. The solution was stirred again for 0.5 hr under ice-cooling and then allowed to stand in a refrigerator for 7 days. The precipitated maleic acid was pulverized and filtered off. The filtrate was washed several times with conc. aq. K_2CO_3 and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was dissolved in abs. EtOH (35 ml). The ethanolic solution was added to an ice-cooled ethanolic solution of sodium ethoxide (prepared from 1.61 g (0.07 g atom) of Na and 40 ml of abs. EtOH) with stirring, and the mixture was refluxed for 1 hr. After removal of the EtOH, water was added to the residue and the solution was extracted with $CHCl_3$. The $CHCl_3$ extract was dried and concentrated to give a dark brown liquid, which was purified by column chromatography (Al_2O_3). The fraction eluted with ether gave a small amount of yellow liquid. The $CHCl_3$ eluate gave a yellow solid which was recrystallized from ether as colorless leaflets, mp 117—119.5°. This compound was identified by comparison with 4-ethoxy-6-methylpyrimidine 1-oxide prepared from 4-ethoxy-6-methylpyrimidine by the method of Yamanaka.[16]

Hydrolysis of III with 3 N HCl——A mixture of III (1.0 g, 0.005 mol) and 3 N HCl (20 ml) was refluxed for 3 hr. After cooling, the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 3 N NaOH, dried, and evaporated down to give a colorless liquid, bp 55—56° (24 mmHg). Yield 0.1 g (21%). This was shown to be identical with an authentic specimen of 3,5-dimethylisoxazole.

Hydrolysis of VIa—c or VIIa—c with 20% H_2SO_4——General Procedure: VIa—c or VIIa—c was dissolved in 20% H_2SO_4 and the solution was refluxed for 7 hr. After cooling, the reaction mixture was extracted with ether. The ether extract was washed with water, dried, and evaporated down to give a colorless liquid (VIII or IX), which was purified by distillation. The 20% H_2SO_4 solution was made alkaline with conc. aq. K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried and concentrated to recover VIa—c or VIIa—c.

Hydrolysis of VIa with 20% H_2SO_4——Compound VIII was obtained from VIa (304 mg, 0.002 mol) and 20% H_2SO_4 (5 ml) according to the general procedure. Colorless liquid, bp 97—98° (85—95 mmHg). Yield 93 mg (42%). The NMR spectrum of VIII was identical with that of an authentic sample of 5-ethyl-3-methylisoxazole[10] and long-range coupling between a ring proton and $C\underline{H}_2CH_3$ in the 100 MHz NMR spectrum was confirmed by a decoupling experiment. Recovery of VIa, 145 mg (48%).

Hydrolysis of VIIa with 20% H_2SO_4——Compound IX was obtained from VIIa (304 mg, 0.002 mol) and 20% H_2SO_4 (5 ml) according to the general procedure. Colorless liquid, bp 96° (95—108 mmHg). Yield 96 mg (43%). The NMR spectrum of IX was identical with that of an authentic sample of 3-ethyl-5-methylisoxazole,[10] and long-range coupling between a ring proton and $C\underline{H}_3$ in the 100 MHz NMR spectrum, was confirmed by a decoupling experiment. Recovery of VIIa, 124 mg (41%).

Hydrolysis of VIb with 20% H_2SO_4——A colorless liquid was obtained from VIb (541 mg, 0.003 mol) and 20% H_2SO_4 (7 ml) according to the general procedure. bp 96—110° (97—110 mmHg). Yield 224 mg (67%). This compound was identical with VIII.

Hydrolysis of VIIb with 20% H_2SO_4——A colorless liquid was obtained from VIIb (360 mg, 0.002 mol) and 20% H_2SO_4 (5 ml) according to the general procedure. bp 97—104° (82 mmHg). Yield 167 mg (77%). This compound was identical with IX in all respects.

Hydrolysis of VIc with 20% H_2SO_4——A colorless liquid was obtained from VIc (214 mg, 0.001 mol) and 20% H_2SO_4 (5 ml) according to the general procedure. bp 93° (90—100 mmHg). Yield 71 mg (64%). This compound was identical with VIII.

Hydrolysis of VIIc with 20% H_2SO_4——A colorless liquid was obtained from VIIc (214 mg, 0.001 mol) and 20% H_2SO_4 (5 ml) according to the general procedure. bp 96° (100 mmHg). Yield 77 mg (69%). This compound was identical with IX.

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16) H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), **6**, 633 (1958).