

ON THE STRUCTURAL DETERMINATION OF PYRIMIDINE N-OXIDES

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Direct N-oxidation of 2-alkyl-4-ethyl-6-methyl-pyrimidines with hydrogen peroxide in glacial acetic acid afforded their 1-oxides and 3-oxides. Acid hydrolysis of the 1-oxides and the 3-oxides caused the ring transformation leading to 3-methyl-5-ethyl- (VII) and 3-ethyl-5-methyl-isoxazole (VIII), respectively. This result obviously demonstrated the structure of the N-oxides.

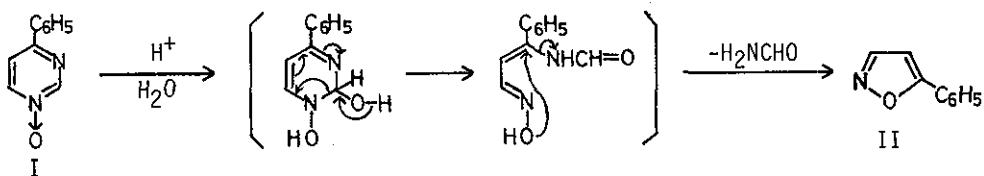
Observing displacements of signals on the NMR spectra of the N-oxides induced by adding a shift reagent, tris(heptafluorobutanoylpivaloylmethanato)europium^{III}, it is concluded that the NMR spectroscopy with the lanthanide is generally applicable to structural elucidation of pyrimidine N-oxides.

Two basic nitrogen atoms present in a pyrimidine ring pose a troublesome problem to elucidate the structure of pyrimidine mono-N-oxides. Recently, van der Plas et al.¹⁾ demonstrated 4-chloro-6-methylpyrimidine N-oxide, obtained from direct N-oxidation of

the parent base, to contain an N-oxide group at the 1-position by chemical reactions. On the other hand, there are several papers²⁾ dealing with lanthanide-induced displacements of signals in the NMR spectra of simple heteroaromatic N-oxides.

In this communication we wish to report the structural differentiation between pyrimidine 1-oxides and 3-oxides by means of a particular ring transformation of pyrimidine N-oxides and the NMR spectroscopy of these N-oxides with an NMR shift reagent.

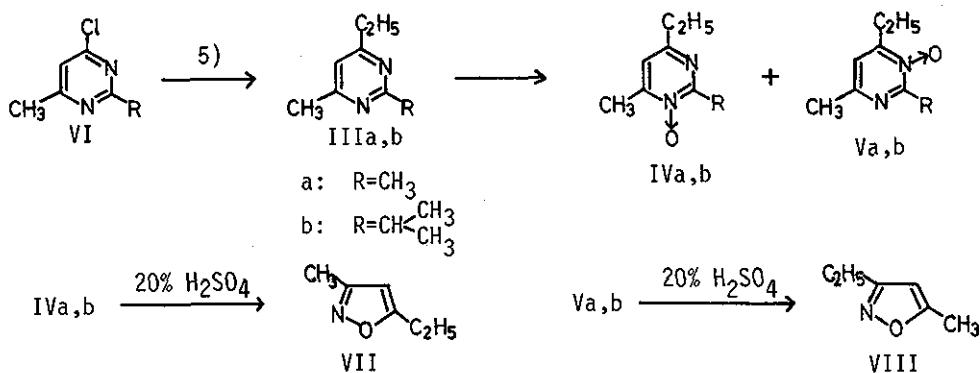
It has already been known³⁾ that acid hydrolysis of 4-phenyl-pyrimidine N-oxide (I) gave rise to 5-phenylisoxazole (II) in good yield. Furthermore, this ring transformation was shown to proceed even though the 2-position was occupied with an alkyl or aryl group.⁴⁾



According to the reaction mechanism illustrated above, this ring transformation was concluded to be applicable to structural determination of pyrimidine N-oxides. From this point of view, 2,6-dimethyl-4-ethylpyrimidine (IIIa)⁵⁾ was oxidized with hydrogen peroxide in acetic acid to give a mixture of two isomeric N-oxide in 55 % yield. The mixture was chromatographed over basic alumina (petr. ether → ether) yielding the 1-oxide (IVa) and the 3-oxide (Va) of the parent base (IIIa). A gas-chromatography showed the IVa/Va ratio to be 6:5. The elemental analyses and the NMR spectra of IVa, (C₈H₁₂N₂O, bp 96°/2 mmHg) and Va (C₈H₁₂N₂O, mp 79-81°) reveal that they are a pair of isomeric 2,6-dimethyl-4-ethylpyrimidine

N-oxides.

Then one of the N-oxides (IVa) was heated in 20 % sulfuric acid for 7-9 hr to give 3-methyl-5-ethylisoxazole (VII) in 42 % yield (81 % of conversion yield) together with the 48 % recovery of the starting N-oxide (IVa). Similarly the other N-oxide (Va) was hydrolyzed to 3-ethyl-5-methylisoxazole (VIII) in 43 % yield (73 % of conversion yield). The structure of the products (VII, VIII) were confirmed by comparison of their spectral data with those of the authentic isoxazoles.⁶⁾ Based on these results, it is obvious that IVa is the pyrimidine 1-oxide and Va is the 3-oxide.



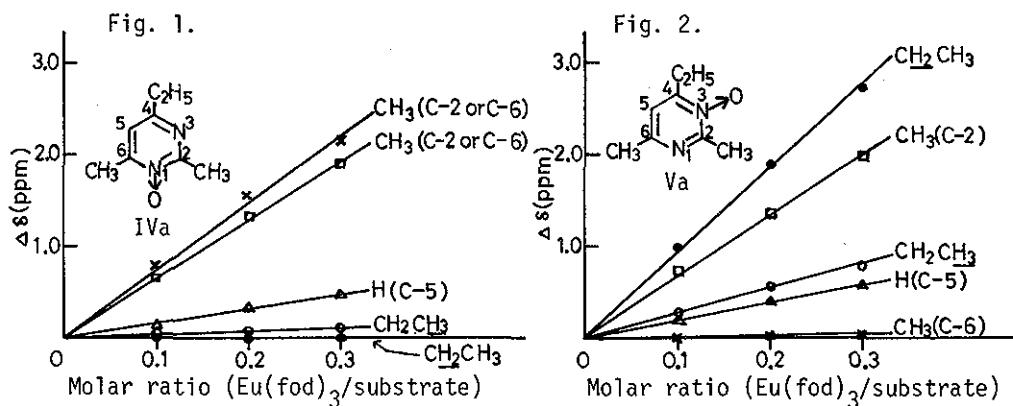
Since the cross reactions (i.e. IVa→VIII and Va→VII) were not observed, this ring transformation is of wide application to the structural determination of alkylpyrimidine N-oxides even in the cases that only one of the isomeric N-oxides was obtained.

Then an attempt was made to distinguish between the 1-oxide (IVa) and the 3-oxide (Va) with the aid of NMR spectroscopy. Although the following NMR spectra of IVa and Va are in good agreement with the pyrimidine N-oxide structure, further informations to recognize the position of N-oxide groups could not be obtained.

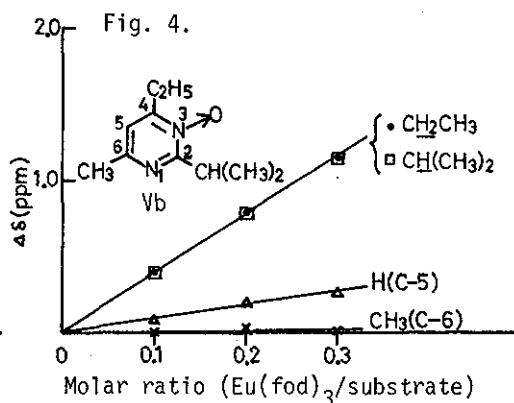
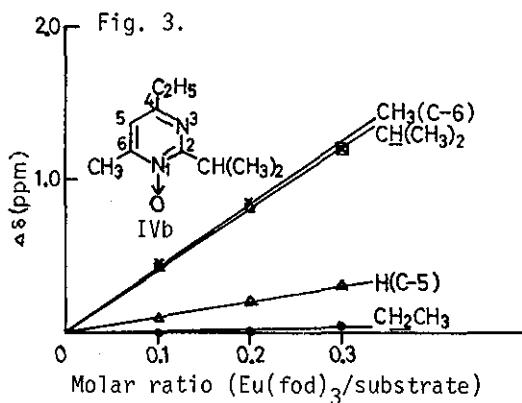
Table. The spectral data of (IIIa), (IVa), and (Va)

Compd. No.	IR(KBr) cm ⁻¹ , (ν N-O)	NMR ($CDCl_3$, TMS) ppm			
		$-CH_2CH_3$ (3H, t)	$-CH_3 \times 2$ (3H, s)	$-CH_2CH_3$ (2H, q)	ring proton (1H, s)
IIIa	—	1.24	2.43	2.64	2.69
IVa	1255	1.30	2.53	2.75	2.75
Va	1245	1.28	2.47	2.72	2.93

Thus the effect of a lanthanide reagent, tris(heptafluorobutanoylpivaloylmethanato)europium^{III} ($Eu(fod)_3$) on the NMR spectrum of the 1-oxide (IVa) has been compared with those on the spectrum of the 3-oxide (Va). In the case of IVa (Fig. 1), large displacements were observed on both of signals due to the 2- and 6-methyl groups, whereas a small displacement on the signal of the methylene protons in the ethyl group. Conversely, in the case of Va (Fig. 2), the largest effect was shown on the signal of the methylene protons and essentially no effect on the signal assignable to the 6-methyl protons. In all the cases, relationship between induced displacements of signals and reagent concentrations was recorded to be invariably rectilinear.



The similar results were obtained on 2-isopropyl-4-ethyl-6-methylpyrimidine (IIIb).⁵⁾ Namely the N-oxidation of IIIb afforded its 1-oxide (IVb) ($C_{10}H_{16}N_2O$, bp 94°/3 mmHg) and the 3-oxide (Vb) ($C_{10}H_{16}N_2O$, bp 90-94°/3 mmHg) whose yields were calculated to be 28 % and 18 % by means of gas-chromatography. Acid hydrolysis of IVb and Vb under identical conditions given for IVa, converted them into the isoxazoles (VII, VIII) in 67 % and 77 % yield, respectively. As shown below, lanthanide induced displacements of signals in the NMR spectra of IVb and Vb revealed the same tendency to those of IVa and Va.



Based on the results, the lanthanide reagent is shown to coordinate the N-oxide group predominantly. Thus it is concluded that, instead of the chemical transformation of pyrimidine N-oxides to the isoxazoles, the NMR spectroscopy with the lanthanide reagent provides a novel approach to settle the problem given at the beginning.

Although pyrimidine N-oxides have been used exclusively in this experiment, the same experimental and interpretive spectroscopy can be applied to other diazine mono-N-oxides for their structural elucidation.

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