

PROTON MAGNETIC RESONANCE SPECTRA OF SOME ALKYLPIRIDINE AND
ALKYLPYRAZINE N-OXIDES

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In the PMR spectra of some 2-alkylpyridine 1-oxides and 2,5-dialkylpyrazine 1-oxides, except α -picoline 1-oxide and 2,5-dimethylpyrazine 1-oxide, the signals of the α -protons of the side chain at C-2 appeared in a lower field than those of the parent amines. It is concluded that this shift to the lower field is caused by the anisotropic effect of the N-O group.

It is already well known¹ that signals of the methyl protons and H-6 of α -picoline 1-oxide appear in a higher field than those of the amine due to the electronic effect of the N-O group. In the course of an investigation on alkylpyrazines, we observed that N-oxidation of 2,5-diisopropylpyrazine shifts the methine protons to a lower field than where those of the original resonate. This fact was contrary to our expectation. Therefore, in an effort to clarify the effect of the N-O group on the 2-alkyl group, PMR spectra of some 2-alkylpyridine and 2,5-dialkylpyrazine

N-oxides were compared with those of the parent amines. Its results are briefly presented in this paper.²

In Table 1, difference in chemical shifts of H-6 and α -protons of the 2-alkyl group between some 2-alkylpyridine 1-oxides³ and their parent amines is listed. The signals of H-6 in pyridine 1-oxides appeared in a higher field than those of the parent amines by about 0.25 ppm in all cases. This phenomenon may be due to the electron-donating effect of the N-O group.

Table 1. PMR Spectra of 2-Substituted Pyridines and their N-Oxides

	α -protons of the side chain			H-6		
	parent amines δ ppm(a)	N-oxides δ ppm(b)	a-b*	parent amines δ ppm(a)	N-oxides δ ppm(b)	a-b*
H				8.56	8.24	+0.32
CH ₃	2.56	2.52	+0.04	8.50	8.28	+0.22
C ₂ H ₅	2.82	2.96	-0.14	8.50	8.24	+0.26
n-C ₃ H ₇	2.76	2.92	-0.16	8.52	8.30	+0.22
iso-C ₃ H ₇	3.08	3.80	-0.72	8.52	8.26	+0.26
iso-C ₄ H ₉	2.64	2.80	-0.16	8.50	8.22	+0.28

* + denotes shift to a higher field and - to a lower field.

On the other hand, α -protons of the side chain at C-2 behaved in various ways. Although the signal of the methyl protons of α -picoline 1-oxide appeared in a slightly higher field than that of α -picoline, methylene and methine protons of other pyridine 1-oxides examined resonated in a lower field than those of the parent amines. As shown in Table 1, the difference in chemical shifts of methine protons between 2-isopropylpyridine and its

1-oxide was the largest (0.72 ppm) among the observed values. This shift to the lower field might be attributed to the anisotropic effect of the N-O group.^{4,5} With an increase in size of the alkyl group, the free rotation of the bond between C-2 and α -carbon of the side chain will be restricted. As shown in Fig. 1, H-3 may bisect the angle of CH₃-C-CH₃ of the isopropyl group, and consequently the methine proton will be under the influence of the N-O group. If the anisotropic effect the N-O group is similar to that of a carbonyl group,⁴ it is reasonable to assume that the methine proton of 2-isopropylpyridine 1-oxide might appear in a relatively low field by this effect.

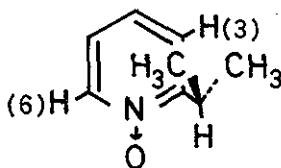


Fig. 1

PMR spectra of 2,5-dialkylpyrazines and their N-oxides⁶ were also examined and its results are shown in Table 2. The two ring-protons of 2,5-dialkylpyrazine 1-oxide resonated naturally at different chemical shifts. The signal, which appeared at the higher field, might be ascribed to H-6, because this signal disappeared more rapidly by the deuterium exchange experiment,⁷ in the presence of sodium deuterioxide in heavy water.⁸

The α -protons of the side chains in 2,5-dialkylpyrazine 1-oxides behaved interestingly, similar to 2-alkylpyridine 1-oxides. In the PMR spectrum of 2,5-dimethylpyrazine 1-oxide, two singlets were observed. The one observed in a higher field disappeared more rapidly by deuteration and is therefore due to the methyl

protons on C-2.

Table 2. PMR Spectra of 2,4-Disubstituted Pyrazine 1-Oxides

	α -protons of the side chain			H-6		
	parent amines δ ppm(a)	N-oxides δ ppm(b)	a-b *	parent amines δ ppm(a)	N-oxides δ ppm(b)	a-b *
H				8.56	8.08	+0.48
CH ₃	2.52	2.42	+0.1	8.32	8.04	+0.26
C ₂ H ₅	2.82	2.88	-0.06	8.34	8.02	+0.32
n-C ₃ H ₇	2.76	2.84	-0.08	8.32	8.04	+0.28
iso-C ₃ H ₇	3.08	3.60	-0.52	8.36	8.00	+0.36
iso-C ₄ H ₉	2.64	2.72	-0.08	8.34	7.98	+0.36

* + denotes shift to a higher field and - to a lower field.

Contrary to the case of 2,5-dimethylpyrazine 1-oxide, the α -methylene and methine protons of the side chain at C-2 in other dialkylpyrazine 1-oxides resonated in a lower field than the ones of the side chain at C-5. This fact was confirmed by the deuteration experiment; i.e., the signals which appeared in a lower field disappeared faster except in 2,5-diisopropylpyrazine 1-oxide, in which the signal appearing in a higher field disappeared conversely faster than the other by the deuteration reaction. Because the methine proton of the isopropyl group at C-2 is surrounded by two methyl groups and oxygen of the N-O group, the proton might be hardly pulled out by the OD anion.

In all of the 1,4-dioxides, the singlets owing to the ring protons appeared in a higher field than those of the parent amines, while

α -protons of the side chains at C-2 appeared variously. On the basis of these data, it seems reasonable to assume that anisotropy of the N-O group is predominantly effective on the chemical shift of the methine and methylene protons in 2,5-diisopropyl-, diethyl-, and diisobutyl-pyrazine 1-oxides, and that the electron-donating effect is predominant on the chemical shifts of the methyl protons in 2,5-dimethylpyrazine 1,4-dioxides.

Table 3. PMR Spectra of 2,5-Dialkylpyrazine 1,4-Dioxides

Alkyl groups	α -protons of the side chain			H-6		
	parent amines δ ppm(a)	N-oxides δ ppm(b)	a-b *	parent amines δ ppm(a)	N-oxides δ ppm(b)	a-b *
CH ₃	2.52	2.40	+0.12	8.32	8.06	+0.26
C ₂ H ₅	2.82	2.86	-0.04	8.34	8.04	+0.30
n-C ₃ H ₇	2.76	2.76	0	8.32	8.04	+0.28
iso-C ₃ H ₇	3.08	3.54	-0.46	8.36	8.00	+0.36
iso-C ₄ H ₉	2.64	2.68	-0.04	8.34	8.04	+0.30

* + denotes shift to a higher field and - to a lower field.

In view of the above facts the most reasonable conclusion drawn from available data is that the N-O group of pyridine and pyrazine N-oxides has the electron-donating and anisotropic effects on H-6 and α -protons of the side chain at C-2. These two effects may be opposed to each other; i.e., the electron-donating effect shifts the signals of H-6 and α -protons of the side chains at C-2 to a higher field, whereas the anisotropic effect makes alkyl protons resonate in a lower field, compared with those of the parent amines. In order to clarify this anisotropy, it would be necessary to

estimate the bond length of the N-O, its neighboring C-C, and C-H. Because some of the pyrazine 1-oxides and 1,4-dioxides are conveniently solid, this point will be examined using the X-ray diffraction method.

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REFERENCES

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- 2 PMR spectra were taken in deuterated chloroform with a JEOL JNM-PS-100 spectrometer, using tetramethylsilane as an internal standard.
- 3 2-Methyl-, 2-ethyl-, and 2-propyl-pyridines were obtained commercially. 2-Isopropyl- and 2-isobutyl-pyridines were prepared by the reported method (C. Osuch and R. Levine, J. Am. Chem. Soc., 1956, 78, 1723). 2-Alkylpyridine 1-oxides were obtained by oxidation of the corresponding pyridines with peracetic or permaleic acids.
- 4 K. Tori, M. Ogata, and H. Kano, Chem. Pharm. Bull. (Tokyo), 1963, 11, 681.
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- 6 2,5-Dialkylpyrazines were obtained from chloro-2,5-dialkylpyrazines, which were prepared by treatment of the corresponding diketopiperazines with phosphoryl chloride, through hydrogenation over palladium-carbon as a catalyst. Their N-oxides were prepared

by their oxidation with peracetic or permaleic acids.

7 A. F. Thomas, "Deuterium Labeling in Organic Chemistry,"
Appleton-Century Crofts, New York, 1971, p. 64.

8 2,5-Dialkylpyrazine 1-oxides were heated in a sealed tube
at 100-170° in the presence of sodium deuterioxide. The H-D
exchange-rates measured will be reported at a later date.

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