HETEROCYCLES, Vol. 6, No. 11, 1977

# PROTON MAGNETIC RESONANCE SPECTRA OF SOME ALKYLPYRIDINE 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 known[1] 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-oxides[3] 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 |
| $C_2H_5$ | 2.82 | 2.96 | -0.14 | 8.50 | 8.24 | +0.26 |
| n-$C_3H_7$ | 2.76 | 2.92 | -0.16 | 8.52 | 8.30 | +0.22 |
| iso-$C_3H_7$ | 3.08 | 3.80 | -0.72 | 8.52 | 8.26 | +0.26 |
| iso-$C_4H_9$ | 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 ristricted. As shown in Fig. 1, H-3 may bisect the angle of $CH_3$-C-$CH_3$ 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.

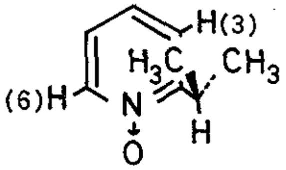

Fig. 1

PMR spectra of 2,5-dialkylpyrazines and their N-oxides[6] 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 deuteroxide 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 $\delta$ ppm(a) | N-oxides $\delta$ ppm(b) | a-b* | parent amines $\delta$ ppm(a) | N-oxides $\delta$ 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 |
| $C_2H_5$ | 2.82 | 2.88 | -0.06 | 8.34 | 8.02 | +0.32 |
| n-$C_3H_7$ | 2.76 | 2.84 | -0.08 | 8.32 | 8.04 | +0.28 |
| iso-$C_3H_7$ | 3.08 | 3.60 | -0.52 | 8.36 | 8.00 | +0.36 |
| iso-$C_4H_9$ | 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

| | α-protons of the side chain | | | H-6 | | |
|---|---|---|---|---|---|---|
| Alkyl groups | parent amines $\delta$ ppm(a) | N-oxides $\delta$ ppm(b) | a-b* | parent amines $\delta$ ppm(a) | N-oxides $\delta$ ppm(b) | a-b* |
| $CH_3$ | 2.52 | 2.40 | +0.12 | 8.32 | 8.06 | +0.26 |
| $C_2H_5$ | 2.82 | 2.86 | -0.04 | 8.34 | 8.04 | +0.30 |
| n-$C_3H_7$ | 2.76 | 2.76 | 0 | 8.32 | 8.04 | +0.28 |
| iso-$C_3H_7$ | 3.08 | 3.54 | -0.46 | 8.36 | 8.00 | +0.36 |
| iso-$C_4H_9$ | 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 anisotopic 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.

ACKNOWLEDGEMENT We are grateful to Dr. Yoji Arata, Tokyo University, for valuable discussions.

REFERENCES

1 T. J. Batterhan, ''NMR Spectra of Simple Heterocycles,'' John Wiley & Sons, Inc., New York, 1973, pp. 8 and 118.

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.

5 P. Hamm and W. von Philipsborn, *Helv. Chim. Acta*, 1971, **54**, 2362.

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 deuteroxide. The H-D exchange-rates measured will be reported at a later date.

Received, 27th June, 1977