QUATERNIZATION OF PYRAZINE MONOXIDES, AND REDUCTION OF 1-METHYL-4-OXIDOPYRAZINIUM IODIDES WITH SODIUM BOROHYDRIDE

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Quaternization of some methyl- and phenyl-pyrazine 1-oxides with methyl iodide was investigated. The 1-methyl-4-oxidopyrazinium iodides obtained were treated with sodium borohydride to give N-hydroxypiperazines. The effect of substituents on the quaternization and reduction was discussed.

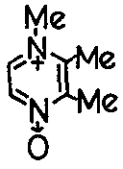
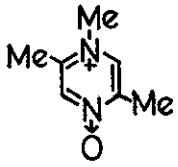
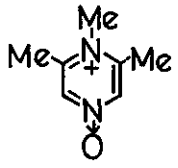
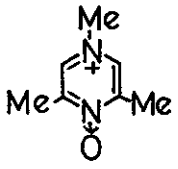
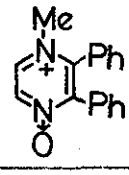
Although Koelsch and Gumprecht[1] prepared 1,2,5-trimethyl-4-oxidopyrazinium iodide, its structure was not always completely elucidated. Kasaga, et al[2] prepared some 1-amino-4-oxidopyrazinium salts, but little attention has been paid to quaternized pyrazine N-oxides. During the course of our investigation on pyrazines, we found that some dimethyl- and diphenyl-pyrazine monoxides were converted to the corresponding quaternary salts which were reduced with sodium borohydride to N-hydroxypiperazines. These results will be described briefly in this report.

A mixture of some methyl- or phenyl-pyrazine monoxides and methyl

iodide was heated at 80° for ? hr in a sealed tube. The reaction mixture colored brown-red, and in the case of dimethylpyrazine monoxides, the quaternary salts precipitated as yellow needles.

In the case of four dimethylpyrazine monoxides,[1,3] the reaction mixture was evaporated to dryness and the resultant brown-red solid was purified by recrystallization from ethanol to furnish yellow needles. These results are shown in Table I.

Table I. Some 1-Methyl-4-oxidopyrazinium Iodides

Compound (iodide)		mp (°C)	Yield (%)	PMR(DMSO) N-CH_3(ppm)
I		201 - 203	68	4.16
II		229 - 231(dec.)	75	4.04
III		235(dec.)	59	3.91
IV		244(dec.)	70	4.16
V		230	19	3.83

On the other hand, reaction of phenylpyrazine monoxides resulted in various ways. Namely, 3-phenyl-,[4] 2,5-diphenyl-,[5] and 3,5-diphenyl-pyrazine 1-oxides[6] could not be quaternized because basicity of their ring nitrogen would be decreased due to the electron-withdrawing effect[7] of phenyl groups. However, 2,3-diphenylpyrazine 1-oxide[8] was led to the corresponding salts, though in a poor yield, after being purified by column chromatography on silica gel with a mixture of chloroform and methanol as an eluent. It would seem reasonable to assume that the basicity of 2,3-diphenylpyrazine 1-oxide is a little stronger than that of other phenylpyrazine 1-oxides because the pyrazine ring and two phenyl groups are not able to be in one plane due to mutual steric hindrance of two phenyl groups, and consequently, the electron-withdrawing effect of the phenyl group will be decreased.

In the quaternization reaction, there might be two points of attack for an electrophile, namely, the unoxidized nitrogen or the oxygen of the N-oxide group. However, an attempt to determine the point of attack of methyl iodide was not possible through PMR studies as will be described below.

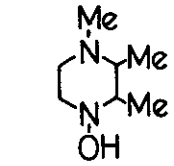
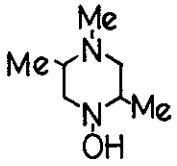
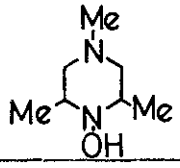
The chemical shifts of newly incorporated methyl protons of the quaternized salts are listed in Table I. 1-Methyl protons of 1,2,3-, 1,2,5-, and 1,3,5-trimethylpyrazinium iodide appeared at 4.24, 4.22, and 4.32 ppm, respectively. Namely, the methyl protons which were newly incorporated by the quaternization of dimethylpyrazine 1-oxides appeared as a singlet in a lower field than the 1-methyl protons of the above-mentioned trimethylpyrazinium iodides. However, methyl protons of 1-methoxyquinolinium and 1-methyl-

quinolinium iodides were observed at the nearly same point (4.66 and 4.62 ppm) in their PMR spectra. It was, therefore, assumed that the decision of the quaternization point cannot be made on the basis of these PMR data.

Quaternization of dimethylpyrazine dioxides did not take place under any conditions. This fact may suggest that addition of methyl iodide to dimethylpyrazine monoxides occurred at the unoxidized nitrogen.

The quaternary salts (I~V) were treated with sodium borohydride at room temperature in water or methanol solution. Although a resinous substance was obtained by the reduction of III, other salts afforded oily or crystalline products in a moderate yield, as shown in Table II.

Table II. Some 1-Hydroxypiperazines

Compound	Free base		Dipicrate
	Yield(%)	NMR($CDCl_3$) N-CH_3(ppm)	mp(°C)
	97	2.21	198 - 200
	76	2.20	225(dec.)
	74	2.22	198 - 200(dec.)

The oily products [bp ca. 130°(bath temp.)/15 Torr] derived from I, II, and IV were respectively purified by distillation and converted to picrates which were recrystallized from methanol to yellow needles. In the mass spectra of the free bases, two peaks of m/e 144 as a molecular peak and m/e 127 ($M^+ - 17$) were observed in all cases. These mass spectra may indicate the presence of one hydroxyl group in a molecule, and the occurrence of quaternization of pyrazine 1-oxides at N-4 and not at oxygen of the N-oxide group. Elemental analyses of the free bases and the picrates were also in agreement with the corresponding molecular formulae. IR (OH-band) and PMR ($N-CH_3$) spectra of the bases also agreed with those of 1-hydroxy-4-methylpiperazine structures.

The reduction of V under the same condition yielded a pale yellow solid which was purified by chromatography on a silica gel column and recrystallized from hexane to furnish pale yellow prisms, mp 123 - 124°. Although m/e 252 (M^+, $C_{17}H_{20}N_2$) and m/e 237 ($M^+ - 15$) appeared in the mass spectrum of this product, m/e 268 ($C_{17}H_{20}N_2O$) and 251 (268 − 17) were not observed. These data suggested that the hydroxyl group was not present in the product and that the N-O bond was also cleaved by the reduction. The glc (1.5% SE-30, 1.5 m) and tlc (silica gel) patterns of this product and the reduction product derived from 1-methyl-2,3-diphenylpyrazinium iodide were completely identical.

Some N-hydroxypiperazine, a new type of compounds, were consequently prepared through the reduction of pyrazinium salt N-oxides in a good yield. Investigation on stereochemistry of the products are in progress, and the results will be reported later.

REFFERENCES and NOTES

1 C. F. Koelsch and W. H. Gumprecht, J. Org. Chem., 1958, 23, 1603.

2 K. Kasuga, M. Hirobe, and T. Okamoto, Chem. Pharm. Bull.(Tokyo), 1974, 22, 1814.

3 B. Klein and J. Berkouritz, J. Am. Chem. Soc., 1959, 81, 5160. 2,3-Dimethylpyrazine 1-oxide was prepared by oxidation of 2,3-dimethylpyrazine (T. Ishiguro and M. Matsumura, Yakugaku Zasshi, 1958, 78, 229) with peracetic acid.

4 3-Phenylpyrazine 1-oxide was derived from 2-chloro-5-phenylpyrazine (S. Sugiura, S. Inoue, Y. Kishi, and T. Goto, Yakugaku Zasshi, 1969, 89, 1646) by hydrogenation and the following oxidation with permaleic acid.

5 H. Gnichtel, W. Griebenow, and W. Löwe, Chem. Ber., 1972, 105, 1865.

6 3,5-Diphenylpyrazine 1-oxide was derived from 2-hydroxy-3,5-diphenylpyrazine (G. Dunn, J. A. Elvidge, G. T. Newbold, D. W. C. Ramsay, F. S. Spring, and W. Sweeny, J. Chem. Soc., 1949, 2707) in three steps (chlorination, hydrogenation and N-oxidation).

7 The steric hindrance causing by the phenyl group might also have to be taken in consideration. However, 2,5-diphenylpyrazine gave a mono-methiodide (unpublished data), and this fact may suggest that the quaternization is affected mainly by the basicity of the ring nitrogen.

8 J. K. Landquist, J. Chem. Soc., 1956, 1885.

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