

PREPARATION AND STRUCTURE ELUCIDATION OF SOME N-ALKYLPYRAZINIUM
SALTS AND THEIR N-OXIDES

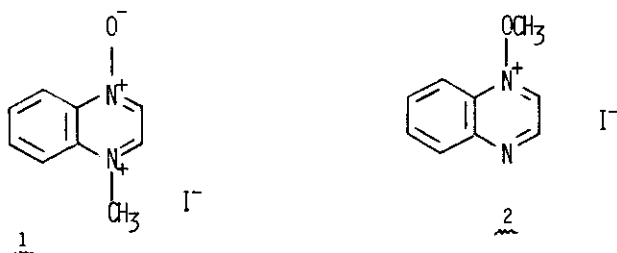
Misa V. Jovanovic

Department of Chemistry, Southern Methodist University

Dallas, Texas 75275, U.S.A.

Abstract - Several N_4 -alkylpyrazinium N-oxide salts were prepared in high yields by heating the corresponding pyrazine N_1 -oxides in the presence of alkylating reagent and solvent. The proton nmr data point to the quinoidal nature of these compounds. Pyrazine di-N-oxides deoxygenated rapidly under same reaction conditions to yield a mixture of N-alkylpyrazinium and N-alkylpyrazinium mono-N-oxide salts. Mechanism is proposed to account for these reductive deoxygenations of the pyrazine nucleus.

It is well known that pyrazine N-oxides form methiodide salts under relatively mild conditions,¹ but very few efforts were directed towards deducing whether the products were N- or O-methylated derivatives. Landquist proposed two alternative structures (i.e. 1 and 2) for the two possible isomers and suggested that 4-methylquinoxalinium 1-oxide iodide (1) is preferred over 1-methoxyquinoxalinium iodide (2) since the isolated salt does not yield formaldehyde or quinoxaline upon alkaline degradation.² The multicolored solutions which resulted (probably due to radical cation formation) discouraged further work in this field.^{1,2}



Recently, Ohta et al. showed that the methylation indeed occurs at the ring nitrogen.³ Few selected N_4 -methylpyrazinium iodide N_1 -oxides (3) were reduced with sodium borohydride at room temperature to yield N_1 -hydroxy- N_4 -methylpiperazines (4).

In our search for stable, highly charged π -deficient heterocyclic systems, we decided to prepare a number of pyrazine N-oxide methiodide salts since they are excellent models for studying N-oxide backdonation.⁴⁻⁶ (Protonated diazine N-oxides are susceptible to proton exchange equilibria and may deprotonate in solution. This renders them useless as dicationic models for ^{13}C and ^{15}N nmr studies in solution). Accordingly, several pyrazine N-oxides (5a-f) were successfully methylated with methyl iodide in acetone or absolute ethanol in a sealed tube to yield the quaternary salts 6a-f as orange or brown solids which were recrystallized to give bright yellow needles.

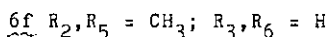
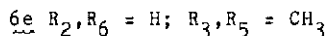
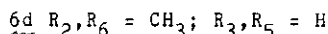
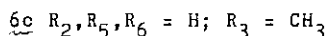
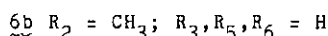
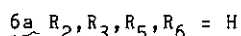
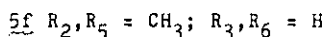
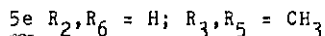
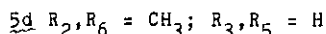
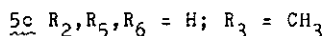
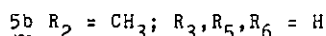
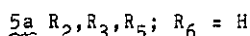
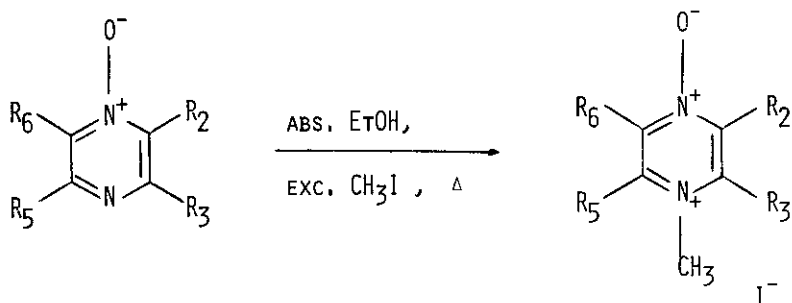


Table 1a lists the physical properties and experimental variables of N-oxide methiodide salts. In general, pyrazine N-oxides were converted to the quaternary salts within four hours in essentially quantitative yield. This is in contrast to the moderate yields (59-75%) obtained by Ohta and co-workers³ and may be due to the procedural differences (80°C, 2 h without solvent). Compounds 6d and 6f were also included since only scant information (mp,^δ N-CH_3) was quoted in the previous report.³

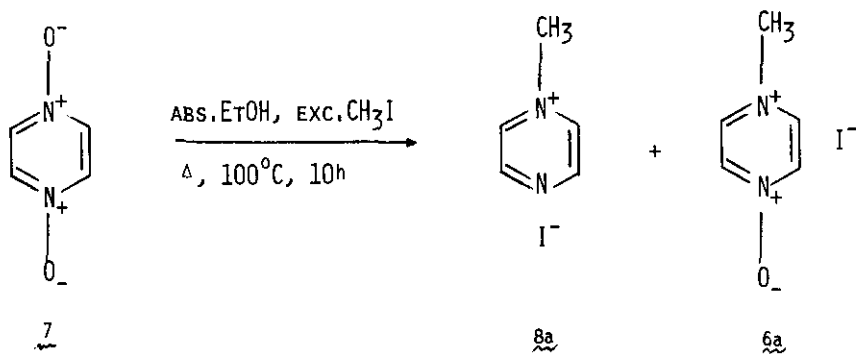
Attempted methylation of pyrazine 1,4-dioxide (7) resulted in a mixture of products. When 7 was treated with an excess of methyl iodide in absolute ethanol and heated in a sealed tube over a steam bath for 4 h, the crude reaction mixture contained N-methylpyrazinium iodide (8a), N_4 -methylpyrazinium iodide N_1 -

TABLE 1a. Physical Properties and Experimental Variables for Some Pyrazine N-Oxide Methiodide Salts.

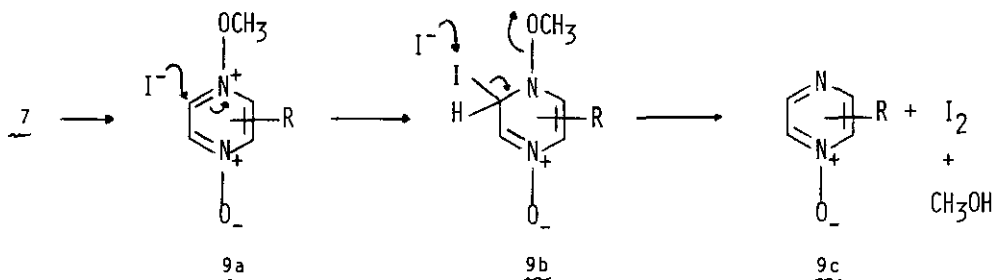
Cpd. No.	Molecular Formula	mp ^a °C	Substituent(s) R	Rxn Time(h)	Yield %	Analysis		
						Calcd (Found)	H Calcd (Found)	N Calcd (Found)
<u>6a</u>	C ₅ H ₇ IN ₂ O	202-204	R ₂ =R ₃ =R ₅ =R ₆ =H	4	98	25.23 (25.18)	2.87 (2.82)	11.77 (11.65)
<u>6b</u>	C ₆ H ₉ IN ₂ O	188-190	R ₂ =CH ₃ , R ₃ =R ₅ =R ₆ =H	4	95	28.59 (28.48)	3.60 (3.55)	11.12 (11.20)
<u>6c</u>	C ₆ H ₉ IN ₂ O	215-216	R ₃ =CH ₃ , R ₂ =R ₅ =R ₆ =H	5	92	28.59 (28.45)	3.60 (3.52)	11.12 (11.22)
<u>6d</u> ^b	C ₇ H ₁₁ IN ₂ O	235-238 (lit.244) ³	R ₂ =R ₆ =CH ₃ , R ₃ =R ₅ =H	4	97	31.59 (31.50)	4.17 (4.29)	10.53 (10.47)
<u>6e</u> ^b	C ₇ H ₁₁ IN ₂ O	238-240 (lit.235) ³	R ₃ =R ₅ =CH ₃ , R ₂ =R ₆ =H	6	89	31.59 (31.56)	4.17 (4.08)	10.53 (10.60)
<u>6f</u>	C ₇ H ₁₁ IN ₂ O	240-242 (lit.234-237) ^c	R ₂ =R ₅ =CH ₃ , R ₃ =R ₆ =H	5	94	-	-	-

a. Melting points are not corrected, b. Elemental analyses were included since melting points differ from those reported in reference 3. c. Prepared in DMF.¹³

oxide (6a), and some starting material (7). When the same reaction was repeated and run for 10 h, no starting material was recovered and only 8a and 6a were isolated in approximately equal amounts. The reduction of pyrazine N-oxides is of particular interest to us since we have observed earlier that pyrazine and other diazine and triazine N-oxides also partially or completely deoxygenate

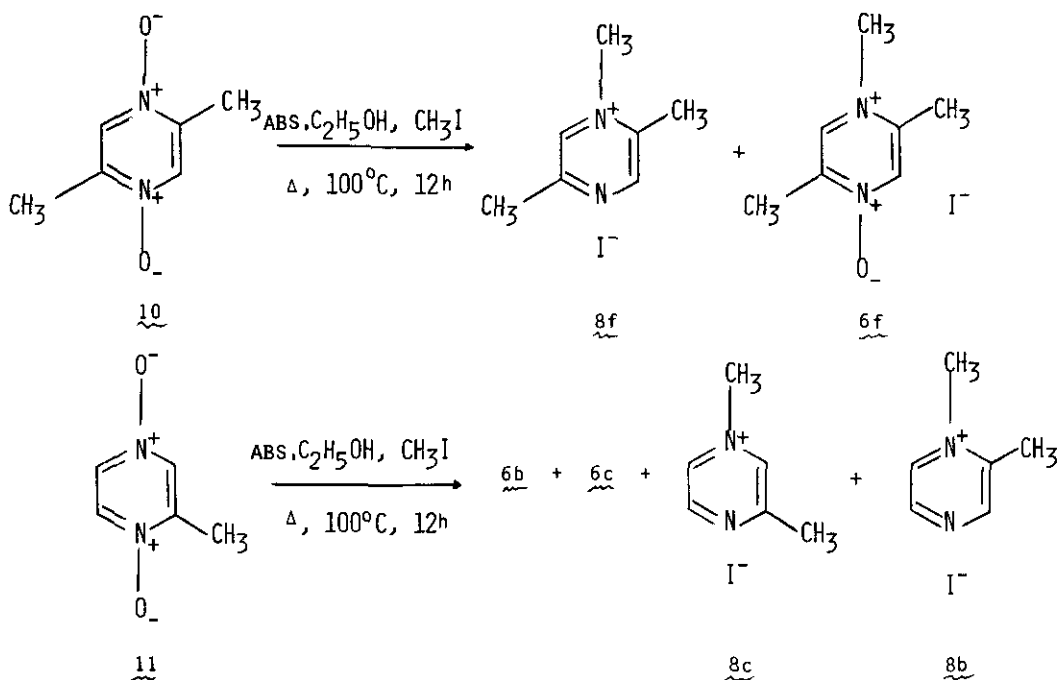


during bromination,⁷ iodination,⁸ diazotization,^{9,10} and hydroxylation¹⁰⁻¹² of the heterocyclic six-membered ring. Failure of 7 and other dimethylpyrazine dioxides to react under reaction conditions described by Ohta³ is probably due to the lack of solvent. Furthermore, polar solvents, such as ethanol, promote deoxygenation and aprotic solvents such as acetone only afford the quaternized salts. It is possible that the solvent serves a dual purpose; as a proton source and to stabilize the charged transition intermediates such as 9a and 9b.



It is unlikely that di-N-oxide would actually form the O-methylated product 9a and it is probably protonated instead; subsequent loss of water molecule would also yield 5. At this point, it is difficult to substantiate this claim since both, water and methanol, were observed as reaction byproducts. (Methanol could also be produced from the hydrolysis of methyl iodide). However, our preliminary results on the reduction of various heterocyclic N-oxides by hydroiodic acid strongly suggest that the reaction is first order with respect to HI and support the above argument.¹³ The preferred dehalogenation rather than deprotonation of 9b was discussed elsewhere⁸ and will not be commented on in this communication.

The deoxygenation reaction is general and gave consistent results with other substituted pyrazine dioxides. For instance, symmetrical pyrazines such as 2,5-dimethylpyrazine 1,4-dioxide (10) was reduced after 12 h to 6f and 1,2,5-trimethylpyrazinium iodide (8f). On the other hand, 2-methylpyrazine 1,4-dioxide (11) produced a mixture of two isomeric N-oxide methiodides 6b and 6c and methiodide salts 8b and 8c. The products were not isolated; they were identified by comparing the proton nmr spectra with ¹H chemical shifts of authentic samples (Tables 2 and 3). The most useful resonances for this purpose were the signals of the N-methyl group (see NMR section).



The authentic *N*-methylpyrazinium iodides (8a-f) were prepared in nearly quantitative yields by simple alkylation procedure (see Experimental and Table 1b).

In the case of 2-methylpyrazine (12), two isomeric methiodide salts 8b and 8c were formed in nearly equal quantities. Similarly, 2,6-dimethylpyrazine (13) also produced two isomers but in this instance, the 1,3,5-trimethylpyrazinium iodide (8e) was formed in much higher yield (> 90% product distribution ratio) than the 1,2,6-isomer (8d). This could probably be attributed to the steric effect which the two *ortho*-methyl groups have on the adjacent nitrogen atom.

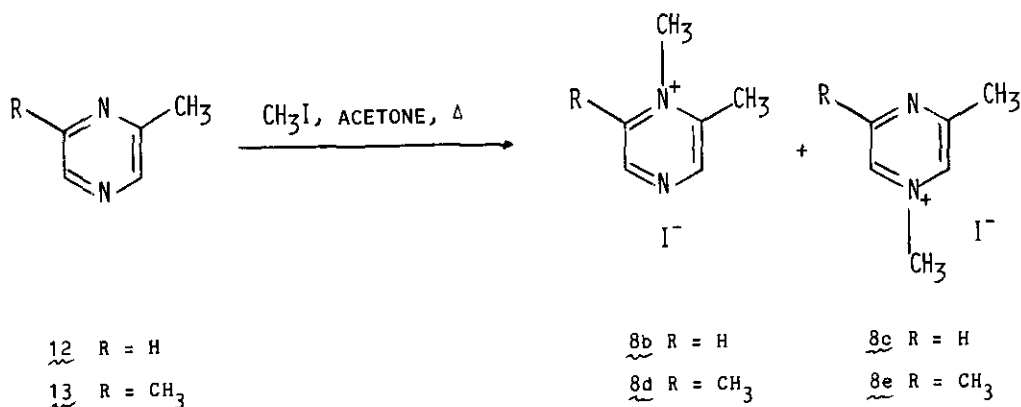


TABLE 1b. Physical Properties and Experimental Variables for Some
N-Methylpyrazinium Iodides.

Cpd. No.	Molecular Formula	mp ^a °C	Substituent(s) R	Rxn Time(h)	Yield %	Analysis		
						Calcd (Found)	Calcd (Found)	Calcd (Found)
<u>8a</u>	C ₅ H ₇ IN ₂	139-140	R ₂ =R ₃ =R ₅ =R ₆ =H	5	95	lit. ¹⁴ mp 136°C		
<u>8b</u>	C ₆ H ₉ IN ₂ ^b	130-133	R ₂ =CH ₃ , R ₃ =R ₅ =R ₆ =H	4	55 ^c (97)	30.53 (30.77)	3.84 (3.87)	11.87 (11.80)
<u>8c</u>	C ₆ H ₉ IN ₂ ^b	129-130	R ₃ =CH ₃ , R ₂ =R ₅ =R ₆ =H	4	45 ^c (97)	30.53 (30.62)	3.84 (3.80)	11.87 (11.88)
<u>8d</u>	C ₇ H ₁₁ IN ₂ ^d	-	R ₂ =R ₆ =CH ₃ , R ₃ =R ₅ =H	6	8 ^c (93)	-	-	-
<u>8e</u>	C ₇ H ₁₁ IN ₂	226-228	R ₃ =R ₅ =CH ₃ , R ₂ =R ₆ =H	6	92 ^c (93)	33.62 (33.85)	4.43 (4.46)	11.20 (11.25)
<u>8f</u>	C ₇ H ₁₁ IN ₂	248-250	R ₂ =R ₅ =CH ₃ , R ₃ =R ₆ =H	5	90	lit. ¹⁶ mp 230°C		

a. Melting points are not corrected. b. Reported in literature¹⁵ as a mixture of two isomers; a crude mixture of 8b and 8c were recrystallized from methanol-acetone and were separated by successive recrystallization from ethanol.

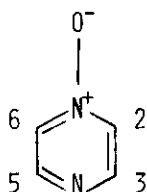
c. Isomer distribution ratios; overall yield is given in parentheses.

d. Identified by proton nmr - not isolated.

NMR DATA

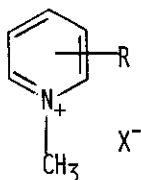
Quaternization of pyridine "like" nitrogen(s) in polyazabenzene is relatively facile process as seen by the ease with which the protonation and alkylation of these systems occur.¹⁹ The unshared electron pair of the nitrogen is orthogonal to the π -cloud and is not a part of the π -electron system. The charge generated by nitrogen quaternization is stabilized by resonance which does not affect the integrity of the aromatic ring. Thus, proton chemical shifts should reflect the increased π -deficiency of the six-membered ring. Tables 2a-c show indeed this to be the case. The chemical shifts of ring protons of N-methylated pyrazines and pyrazine N-oxides are at a much lower field (more deshielded) than those for the corresponding non-methylated compounds. Remarkably enough, the change in chemical shifts caused by nitrogen quaternization seems to be constant for many hetero-

cyclic systems. For instance, the chemical shifts of the N₁-methyl group of the 2-, 3-, 4-substituted N-methylpyridinium salts and 2- and 3-substituted N-methylpyrazinium salts are at δ 4.24 - 4.69 and δ 4.34 - 4.64 ppm, respectively (excluding substituents which do or have a potential to exist in tautomeric forms; i.e., amino or hydroxy groups).

TABLE 2a. Proton NMR Data for Some Reference Pyrazine N-oxides.^a

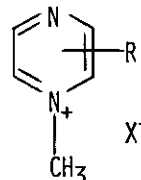
Cpd No.	Substituents				Chemical Shifts ^b			
	R ₂	R ₃	R ₅	R ₆	R ₂	R ₃	R ₅	R ₆
<u>5a</u>	H	H	H	H	8.55	8.65	8.65	8.55
					8.14 ^c	8.30	8.30	8.14
<u>5b</u>	CH ₃	H	H	H	2.07	8.32	8.18	8.00
					2.75 ^c	8.47	8.35	8.21
					2.76 ^d	9.25	8.96	8.92
<u>5c</u>	H	CH ₃	H	H	8.52	2.52	8.27	8.18
					8.36 ^c	2.54	8.02	7.98
					9.05 ^d	2.91	8.92	8.79
<u>5d</u>	CH ₃	H	H	CH ₃	2.52	8.50	8.50	2.52
<u>5e</u>	H	CH ₃	CH ₃	H	8.14	2.55	2.55	8.14
<u>5f</u>	CH ₃	H	CH ₃	H	2.60	8.66	2.65	8.43

a. All spectra were recorded as dilute solutions in D₂O unless indicated otherwise. b. δ (ppm) downfield from external TMS standard. c. In CDCl₃. d. In d₆-DMSO.



⁺
 δ N-CH₃:

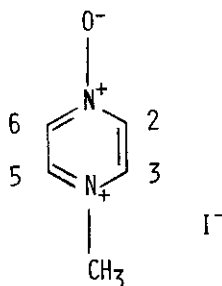
4.24 - 4.69 ppm



4.34 - 4.64 ppm

Similarly, the N-methyl singlet of N-methylpyridazinium iodide (14) and N-methyl-3-bromoquinolinium iodide (15) appear at 4.70 and 4.74 ppm. Apparently, the placement of charge onto the six-membered azaheterocycles induces changes in chemical shifts of similar magnitude. It would be of interest to see whether this observation also applies to polycyclic heteroaromatic compounds.

TABLE 2b. Proton NMR Data for Some N-Methylpyrazinium N-Oxide Salts.^a



Cpd No.	Substituents				Chemical Shifts ^b				
	R ₂	R ₃	R ₅	R ₆	R ₂	R ₃	R ₅	R ₆	N-CH ₃ ⁺
<u>6a</u>	H	H	H	H	8.75	8.89	8.89	8.75	4.30
<u>6b</u>	CH ₃	H	H	H	2.52	8.95	8.78	8.78	4.30
					2.74 ^c	9.50	9.23	9.23	4.48
<u>6c</u>	H	CH ₃	H	H	8.75	2.75	8.78	8.64	4.20
<u>6d</u>	CH ₃	H	H	CH ₃	2.52	8.83	8.83	2.52	4.27
									4.16 ^{c,d}
<u>6e</u>	H	CH ₃	CH ₃	H	8.63	2.71	2.71	8.63	4.02
									3.91 ^{c,d}
<u>6f</u>	CH ₃	H	CH ₃	H	2.75	9.02	2.88	8.78	4.16
									4.04 ^{c,d}

a. All spectra were recorded as dilute solutions in D₂O unless indicated otherwise. c. In d₆-DMSO. d. Taken from ref. 3.

Table 3 lists the chemical shifts of N-methyl group of a number of N-methylpyridinium and N-methylpyrazinium salts. The data are consistent with the predicted substituent effects. The electron-withdrawing groups, such as cyano group, exert their inductive effect relative to the distance from the N-methyl substituent so that α-cyanopyridine methiodide has the most deshielded N-methyl singlet (Δ = + 0.33 ppm) compared to β- and γ-isomers. There is apparent anomaly

for the *N*-methyl signal of 2-fluoropyridine methiodide (16) which appears at δ 3.52 ppm. We are currently investigating the ^{19}F and ^{15}N chemical shifts of 16 to determine whether polarizable structures such as 16a are responsible for such unexpected chemical shift.

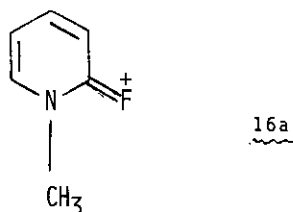
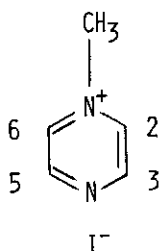


Table 2c. Proton NMR Data for Some Reference *N*-Methylpyrazinium Iodide Salts.^a



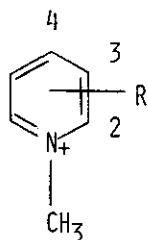
Cmpd No.	Substituents				Chemical Shifts ^b				
	R ₂	R ₃	R ₅	R ₆	R ₂	R ₃	R ₅	R ₆	⁺ N-CH ₃
<u>8a</u>	H	H	H	H	9.45	9.00	9.00	9.45	4.53 4.60 ^c
<u>8b</u>	CH ₃	H	H	H	2.82	d	d	d	4.45 4.42 ^c
<u>8c</u>	H	CH ₃	H	H	e	2.88	e	e	4.37 4.40 ^c
<u>8d</u>	H	CH ₃	CH ₃	H	8.83	2.85	2.85	8.82	4.45 4.32 ^f
<u>8e</u>	CH ₃	H	CH ₃	H	2.85	8.75	2.75	9.01	4.40 4.22 ^f

a. All spectra were recorded as dilute solutions in D₂O. b. δ (ppm) downfield from external TMS standard. d. Unresolved multiplet at δ 8.70–9.00 ppm.

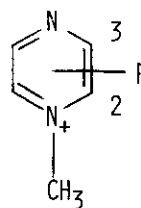
e. Unresolved multiplet at δ 8.80–9.00 ppm. c. Taken from ref. 15 (d₆-DMSO).

f. From ref. 3 (d₆-DMSO).

Table 3. Chemical Shifts of the N-Methyl Group of Some N-Methylpyridinium and N-Methylpyrazinium Salts.^{a, b}



Substitution



Substitution

Subst. R	2-	3-	4-	2-	3-
H	-	4.36	-	-	4.50
		4.47 ^c			4.60 ^c
CH ₃	4.24(-0.12) ^d	4.39(+0.03)	4.29(-0.07)	4.35(-0.15)	4.39(-0.11)
	4.35 ^c (-0.12)	4.44 ^c (-0.03)		4.42 ^c (-0.18)	4.50 ^c (-0.10)
CN	4.69(+0.33)	4.52(+0.16)	4.48(+0.12)	-	-
CONH ₂	-	4.55 ^c (+0.08)	-	-	4.53(+0.03)
					4.64 ^c (+0.04)
F	3.52 ^e (-0.84)	4.52 ^c (+0.07)	-	-	4.58 ^c (-0.02)
Cl	4.33(-0.03)	4.54(+0.18)	4.57(+0.21)	-	4.44(-0.06)
		4.47 ^c (0)			4.54 ^c (-0.06)
Br	4.37(+0.01)	4.48(+0.12)	4.54(+0.18)	-	-
		4.35(-0.01) ^f	4.67(+0.31) ^f		
I	4.37(+0.01)	-	-	-	-
NH ₂	3.65(-0.71)	4.19(-0.17)	3.87(-0.49)	3.76(-0.74)	4.24(-0.26)
	3.85 ^c (-0.62)	4.27 ^c (-0.20)		3.82 ^c (-0.78)	4.34 ^c (-0.26)
					4.27 ^g
NHCH ₃	3.79(-0.57)	-	3.88(-0.48)	-	-
N(CH ₃) ₂	4.11(-0.24)	4.18(-0.18)	3.89(-0.47)	-	-
		4.29 ^h	3.95 ^h		
OH	-	4.32(-0.04)	-	-	-
OCH ₃	-	4.47 ^c (0)	-	-	4.47 ^c (-0.13)
SCH ₃	4.07(-0.29)	-	-	-	-

a. Recorded in d_6 -DMSO unless indicated otherwise. b. δ (ppm) downfield from external TMS standard (DMSO impurity served as a double reference at δ 2.50 ppm). c. Converted from τ values from ref. 15. d. ^1H (Δ ppm) with respect to the parent heterocycle (R=H); negative sign indicates shielding. e. Shielding due to the polarizability effect of the adjacent fluoro substituent. f. N-methylpyridinium bromide salts. g. Measured in D_2O (ref. 17). h. Measured in trifluoroacetic acid (ref. 18).

Similar effect, where positively charged nitrogen atom polarizes the sigma electron system and augments the π -contribution of the halogen, may also be operative with 2-chloro- and 2-bromopyridinium salts (Scheme 1).

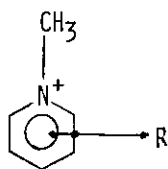
Scheme 1
Comparison of N-CH₃ Chemical Shifts of Some
N-methylhalopyridinium Salts (Δ ppm)^{a, b}

Halogen	2 - X	3 - X	4 - X
F	- 0.84	+ 0.07	
Cl	- 0.03	+ 0.18	+ 0.21
Br	+ 0.01	+ 0.12	+ 0.18

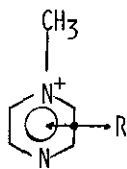
a. Data taken from table 3.

b. $\Delta \overset{+}{\text{N}}\text{-CH}_3 = \delta \overset{+}{\text{N}}\text{-CH}_3$ subst. pyridinium salt - $\delta \overset{+}{\text{N}}\text{-CH}_3$ unsubst. pyridinium salt.

The second annular nitrogen atom in N-methylpyrazinium salts acts as an independent and constant electron-withdrawing group so that substituent effects appear smaller. It represents a good example of how substituent and a ring compete for electron density and further justifies the validity of our approach to develop π_{Δ} values⁴⁻⁶ as a standard for evaluating the π -deficiency/ π -excessiveness of heterocycles. The $^{13}\rho$ value for 3-substituted N-methylpyrazinium salts is lower (0.645) as compared to the 3-substituted N-methylpyridinium salts (0.933)⁶ and shows nicely the "masking" of the substituent effects by the more π -deficient ring.

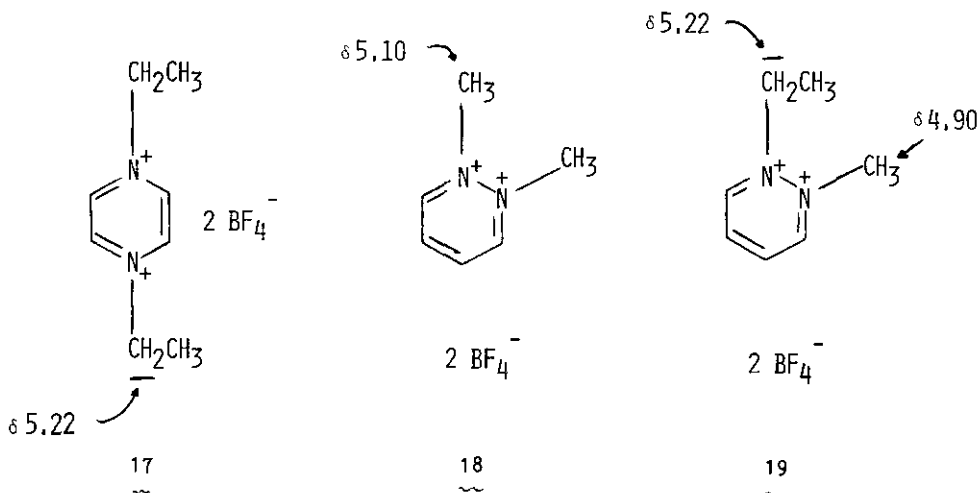


$$^{13}\rho = 0.933$$



$$^{13}\rho = 0.645$$

Methylation of pyrazine N-oxides should produce a downfield shift of the N-methyl singlet relative to N-methylpyrazinium salts by virtue of having an additional charge on the ring. Curphey has reported the chemical shifts of some diquaternary salts of diazines.²⁰ The chemical shifts of N-methyl and N-ethyl diquats are in the range of δ 5.20 ppm (in trifluoroacetic acid).

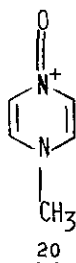


The chemical shifts of the N-CH₃ group of the methylated pyrazine N-oxides may not be as far downfield as the equivalent proton chemical shifts of the dialkylquaternary salts 17-19, because of the N-oxide backdonation, but should certainly be at the lower field than the corresponding singlet of the N-methylpyrazinium salts. However, this is not the case and the N-methyl group of pyrazine N-oxide methiodides fall well below the range δ 4.50-5.20 ppm. Table 4 shows the comparison of N-methyl chemical shifts of pyrazinium and pyrazinium N-oxide salts under identical experimental conditions (D₂O). In all instances, the effect of the N-oxide [Δ N-CH₃(N-O)] is negative implying that doubly charged pyrazine N-oxides are not the best representations for these compounds. It is more likely that structures such as 20 are more appropriate.

TABLE 4. Comparison of N-CH₃ Chemical Shifts of Some N-Methylpyrazinium and N-Methylpyrazinium N-Oxide Salts in D₂O (δ ppm).

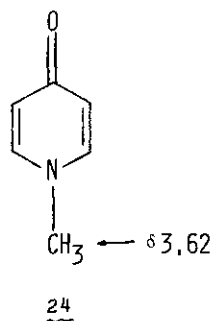
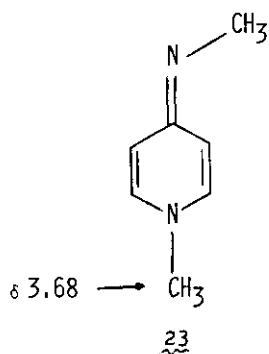
Substituent	Methiodides	N-Oxide Salts	⁺ Δ N-CH ₃ (NO)
parent	4.53	4.30	-0.23
2-methyl	4.45	4.30	-0.15
3-methyl	4.37	4.20	-0.17
2,6-dimethyl	-	4.02	-
3,5-dimethyl	4.45	4.27	-0.18
2,5-dimethyl	4.40	4.16	-0.24

⁺Δ N-CH₃(N-O) = ⁺δ N-CH₃(N-oxide salt) - ⁺δ N-CH₃ (pyrazinium salt).

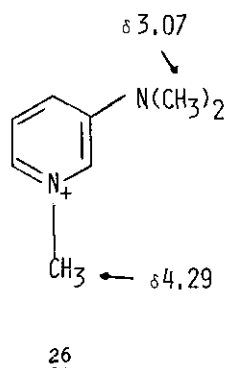
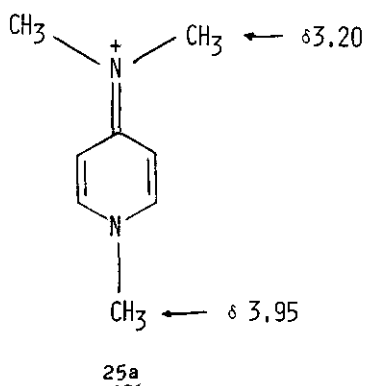


Even though 20 is only one of many of the resonance forms for these derivatives, it is still safe to infer from the proton nmr data that structures such as 20 contribute significantly to the overall ground state of these compounds. The slight upfield shift of the N-methyl group in 6c and 6e may be due to the "through space" shielding or the electron releasing ability of the adjacent methyl groups or may be due to some other steric factors. The same structures may be important for 1-methylquinoxalinium (21) and 4-methylquinoxalinium 1-oxide iodide salts (22) with N-methyl chemical shifts at δ 4.62 and 4.40 ppm, respectively.³

More difficult task is to try and estimate quantitatively how much does the "quinoidal" resonance form 20 contribute to the ground state of the methylated pyrazine N-oxides. We are currently doing the MO calculations on compounds 6a-f which should show the electron density sites in these molecules. In the meantime, we would like to consider some interesting observations. Both, N₁-methyl-(4-N-methylimino)-1,4-dihydropyridine (23) and N₁-methyl-1,4-dihydropyridin-4-one (24) are isoelectronic with structure 20. The N₁-methyl proton chemical shifts for 23 and 24 are at δ 3.68 and 3.62 ppm, respectively.^{22,23}

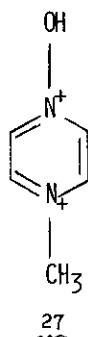


The closest model compound to 20 with the charge on nitrogen would be that of N_1 -methyl-(4-dimethylamino)pyridinium iodide (25). Assuming that the *meta*-substituent in the pyridine ring is remote enough from the cationic center (N_1) so that the electron density can only be effectively transmitted through the π -system and not through the σ bonds (the classical inductive effects through σ bonds of substituents directly attached to one of the principal charge bearing atoms are real only over one or two bond lengths)²¹ and disregard any other effects (i.e. field, etc), we can roughly estimate the percent contribution of the quinoidal resonance forms, such as 20, to the overall mesomeric interactions in the given molecule. For instance, 4-dimethylamino group in 25 is capable of mesomeric electronic contribution to N_1 (as in 25a) unlike the 3-dimethylamino group in N_1 -methyl-(3-dimethylamino)pyridinium iodide (26).²⁴ The difference between 23 and 26 represent 100 and 0% of this contribution with 25 inbetween the two models. (¹H nmr data from Table 3).



The N_1 -methyl chemical shift of 25 is about halfway inbetween δ 3.68 and 4.29 ppm so that 25a may contribute up to 50% to the overall mesomeric interactions in 25. In a similar manner, we can estimate that structure 20 contributes about 75% (\pm 10% to account for solvent effect) to the overall stabilization of 6a provided

that the N-methyl chemical shifts of the protonated 6a (27) are roughly equivalent to the N-alkyl chemical shifts of diquat 17 and using 25a as the other reference.



EXPERIMENTAL

Starting Materials - All pyrazine mono- and di-N-oxides were prepared from commercially available compounds by methods described in ref. 1 and references cited therein. Their identities were established by correct melting points, mass spectroscopy and proton nmr spectra (Table 2a).

General Procedure for the Reaction of Pyrazine N-Oxides with Methyl Iodide. In a typical experiment, 1.0 mmol of a given pyrazine N-oxide was dissolved in 5 ml of spectroscopic grade acetone. To this solution was added four fold excess (4.0 mmol) of methyl iodide and the resulting mixture heated in a sealed tube for 4h over a steam bath. On cooling, orange-brown needles precipitated out. They were filtered and recrystallized from absolute ethanol to give bright yellow needles in quantitative yields (> 90%). (See Table 1a for analytical data, physical properties and experimental variables. Table 2b contains ¹H nmr data).

Reaction of Pyrazine Dioxides with Methyl Iodide. 1.0 mmol of a given pyrazine 1,4-dioxide was dissolved in 5 ml of absolute ethanol. To this solution was added four to five fold excess of methyl iodide and the whole mixture heated as described for pyrazine mono-N-oxides. Upon workup, the isolated solid material contained a mixture of N₁-methylpyrazinium (8) and N₄-methylpyrazinium N₁-oxide (6) iodide salts, identified by their proton nmr (Table 2a-c). No further attempts were made to isolate and purify 6 and 8. Evaporation of mother liquor yielded, in addition to 6 and 8, some starting material. When the same reaction was repeated and run for 10 h, no starting material was recovered and only 6 and 8 were isolated in nearly equal amounts.

Preparation of N-Methylpyrazinium Iodides. In a typical experiment, 1.0 mmol of a selected pyrazine was dissolved in 5 ml of spectroscopic grade acetone and to this solution was added 2.1 mmol of methyl iodide. This mixture was refluxed for 2-4 h, the orange-brown precipitate was collected and recrystallized from 50:50 ethanol-acetone solvent mixture. The methiodide salts were then characterized by matching their physical properties with those of the known compounds or were identified on the basis of their elemental analysis, mass spectrum and ^1H nmr. (Tables 1b and 2c).

N-Methylpyridinium Salts. A number of N-methylpyridinium salts were prepared as reference compounds by the following procedure. Given pyridine was dissolved in minimal volume of methylene chloride, acetone, acetonitrile or a mixture of these three solvents. To this solution was added a three fold excess of methyl iodide, whole stirred for 2 h at room temperature and left standing for 2-48 h within which time, the methiodide salt precipitated out. In most cases, the product was of high purity and was rinsed with additional solvent or was recrystallized from benzene-ethanol or absolute ethanol prior to the ^1H nmr runs (Table 3).

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