IODINATION OF SOME DIAZINES AND DIAZINE N-OXIDES

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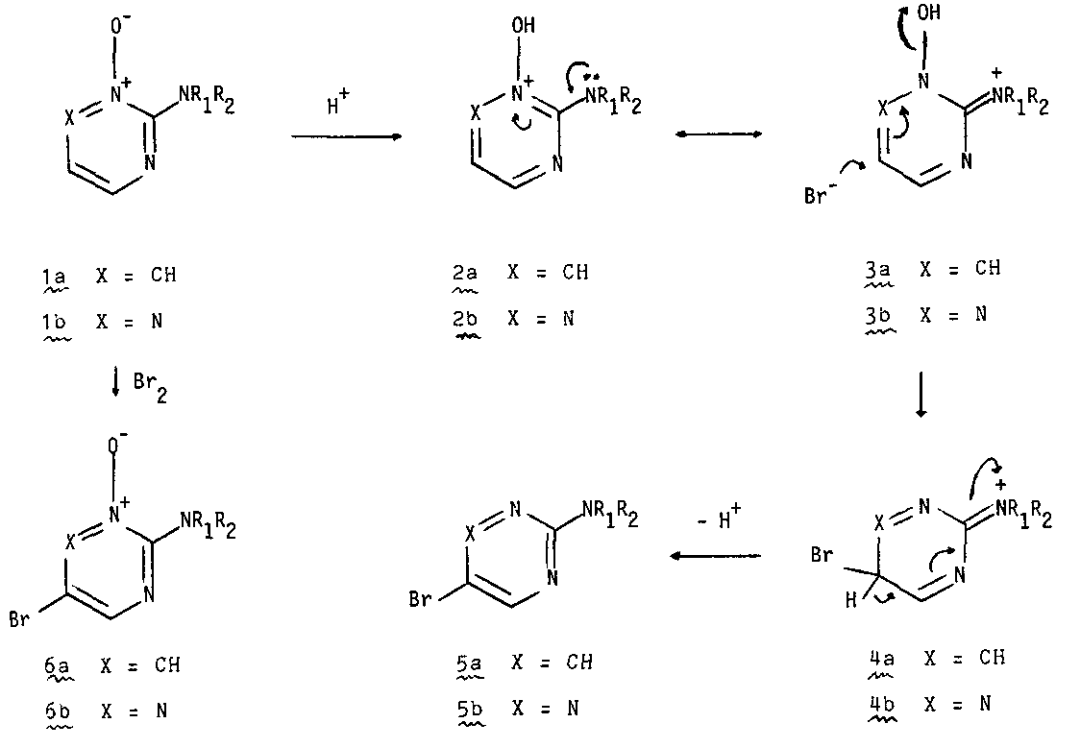
Abstract - A number of monosubstituted pyrazines, pyrimidines, and their N-oxides having the electron-donating amino groups were successfully iodinated. Depending on the reaction conditions, the 3-substituted pyrazine 1-oxides having a bulky dialkylamino group yielded the 6-iodo and 2,6-diiodopyrazine N-oxide derivatives together with some deoxygenated products. The mechanism with supportive evidence was presented to account for these chemical transformations.

Direct, low temperature halogenations of monocyclic π-deficient azines and polyazines occur with great difficulty, if at all. However, their corresponding N-oxides as well as the heterocycles with electron-donating substituents, such as amino groups, activate these systems toward electrophiles and facilitate aromatic substitution.[1]

We have already described the bromination of a number of pyridines, pyrazines, pyrimidines, 1,2,4-triazines and their N-oxides.[2-5] In general, the observations derived from those studies follow trends which are applicable to all the systems that were investigated. For instance, the N-oxide function itself is not sufficiently activating to cause electrophilic aromatic halogenation, but when its ortho/para directing influence was augmented with that of the moderately activating substituents (i.e. alkoxy groups), the bromination readily took place.[3,4] Similarly, we have demonstrated that deoxygenative bromination takes place only with 1,3-diazine N-oxides (pyrimidines, 1,2,4-triazines) congruently with direct bromination (6a, 6b).



1a X = CH
1b X = N

2a X = CH
2b X = N

3a X = CH
3b X = N

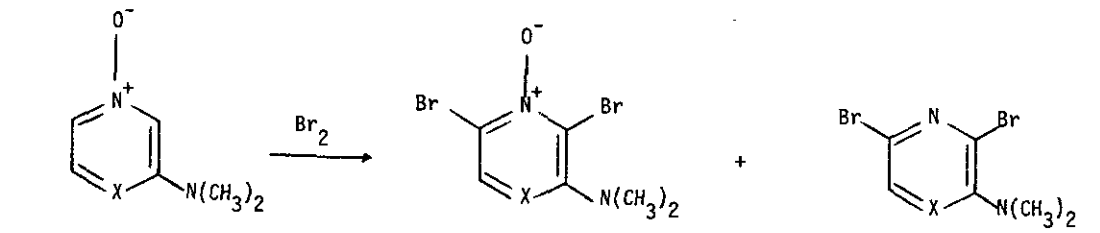
6a X = CH
6b X = N

5a X = CH
5b X = N

4a X = CH
4b X = N

The amount of deoxygenated products 5a and 5b was proportional to the nucleophilicity of the N-oxide oxygen atom. That is to say, the less π-deficient ring system,[6,7] (pyrimidine 1a) required less back-donation by the N-oxide group and was protonated faster in the rate determining step (2a vs 2b).[2-4]

Only in two instances were the deoxygenative halogenation products isolated with meta substituted N-oxides. The 3-dimethylaminopyrazine 1-oxide, 7a, and 3-dimethylaminopyridine 1-oxide, 7b, yielded the deoxygenated 2,6-disubstituted bromo derivatives 9a, 9b, together with the expected oxides 8a, 8b, respectively. Since no deoxygenation was observed during the chlorination of these compounds,[8] the



7a X = N
7b X = CH

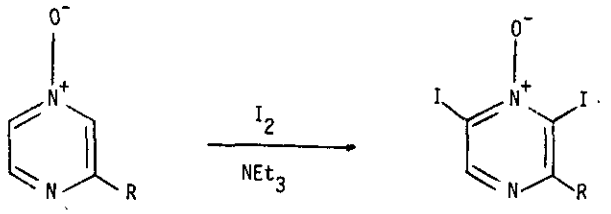
8a X = N
8b X = CH

9a X = N
9b X = CH

formation of 9a and 9b may be due to steric crowding. Therefore, it seemed appropriate to carry out iodination of these ring systems in order to assess the validity of this hypothesis and mechanistically reconcile those differences.

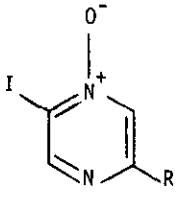
RESULTS AND DISCUSSION

When 3-substituted pyrazine 1-oxides (10, 11) were treated with iodine in carbon tetrachloride (or in methylene chloride) in the presence of triethylamine, 2,6-diiodo-3-substituted pyrazine 1-oxides (15, 16) were obtained in excellent yield. The question as to whether they were the 2,6-diiodo isomers and not the 2,5- or 5,6-diiodo compounds was readily established by a comparison of their ^1H nmr chemical shifts with the proton chemical shifts of the corresponding starting materials (Table 1).



10	R = NH_2	15	R = NH_2
11	R = $NHCH_3$	16	R = $NHCH_3$
12	R = $NHCOCH_3$		no reaction
13	R = CH_3		no reaction
14	R = Cl		no reaction

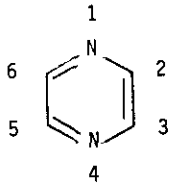
As expected, no ring substitution was observed when iodination was attempted with 3-methyl-, 13, 3-chloro-, 14, and 3-acetamidopyrazine 1-oxide, 12. However, when bulky 3-dimethylamino-, 17, and 3-morpholinopyrazine 1-oxide, 18, were treated with iodine and triethylamine, only mono-iodo derivatives (19, 20) were obtained. Two singlets in the aromatic region of the ^1H nmr spectrum (Table 1), coupled with their elemental analyses (Table 2) and mass spectra, single these compounds out



19 R = $N(CH_3)_2$

20 R = NC_4H_8O

TABLE 1. ^{1}H nmr Data for Some Pyrazines and Their N-Oxides



Cmpd No.	Molecular Formula	Substituents				Chemical Shifts[a,b]				Coupling Constants (Hz)
		R_2	R_3	R_5	R_6	R_2	R_3	R_5	R_6	
10[c]	$C_4H_5N_3O$	H	NH_2	H	H	7.92[d]	7.00	8.30	7.88	$J_{5,6}$=4.5
11[c]	$C_5H_7N_3O$	H	$NHCH_3$	H	H	7.60	2.90	7.84	7.38	$J_{5,6}$=4.0; $J_{2,6}$=1.5
15[c]	$C_4H_3I_2N_3O$	I	NH_2	H	I	-[d]	-	8.70	-	-
16[c]	$C_5H_5I_2N_3O$	I	$NHCH_3$	H	I	-	3.05	8.23	-	-
12[c]	$C_6H_7N_3O_2$	H	$NHCOCH_3$	H	H	9.38[d]	2.50	8.75	8.50	$J_{5,6}$=3.5; $J_{2,6}$=1.4
13[c]	$C_5H_6N_2O$	H	CH_3	H	H	8.36	2.54	8.02	7.98	$J_{5,6}$=4.0;
						9.05	2.91	8.92	8.79	$J_{2,6}$=1.5
14[c]	$C_4H_3ClN_2O$	H	Cl	H	H	8.12	-	8.22	7.96	$J_{5,6}$=4.0; $J_{2,6}$=1.5
						8.70[d]	-	8.44	8.38	$J_{5,6}$=4.1; $J_{2,6}$=1.3
17[c]	$C_6H_9N_3O$	H	$N(CH_3)_2$	H	H	7.61	3.09	7.95	7.47	$J_{5,6}$=4.0; $J_{2,6}$=1.5
18[c]	$C_8H_{11}N_3O_2$	H	NC_4H_8O	H	H	7.69	3.52(α) 3.76(β)	7.91	7.46	$J_{5,6}$=4.0; $J_{2,6}$=1.5
19[c]	$C_6H_8IN_3O$	H	$N(CH_3)_2$	H	I	7.88	3.08	8.37	-	-
20[c]	$C_8H_{10}IN_3O_2$	H	NC_4H_8O	H	I	7.96	3.50(α) 3.68(β)	8.34	-	-
21[c]	$C_8H_{10}BrN_3O_2$	NC_4H_8O	H	Br	H	3.46 (α) 3.97 (β)	8.44	-	8.08	-
22[c]	$C_9H_{12}BrN_3O$	NC_5H_{10}	H	Br	H	3.44 (α) 1.83 (β,γ)	8.36	-	8.08	-
23[c]	$C_6H_7I_2N_3O$	I	$N(CH_3)_2$	H	I	-	3.10	7.89	-	-
24	$C_6H_7I_2N_3$	$N(CH_3)_2$	I	I	H	3.14	-	-	8.19	-

TABLE 1. continued

Cmpd No.	Molecular Formula	Substituents				Chemical Shifts[a,b]				Coupling Constants (Hz)
		R_2	R_3	R_5	R_6	R_2	R_3	R_5	R_6	
25[c]	$C_8H_9I_2N_3O_2$	I	NC_4H_8O	H	I	-	3.55(α) 3.73(β)	7.86	-	-
26	$C_8H_9I_2N_3O$	NC_4H_8O	I	I	H	3.54 (α) 3.82 (β)	-	-	8.28	-
27	$C_6H_9N_3$	$N(CH_3)_2$	H	H	H	3.12	8.07	7.83	8.06	$J_{5,6}$=2.5
28	$C_8H_{11}N_3O$	NC_4H_8O	H	H	H	3.57 (α) 3.86 (β)	8.17	7.92	8.12	$J_{5,6}$=3.0; $J_{3,6}$=1.0
29	$C_6H_8IN_3$	$N(CH_3)_2$	H	I	H	3.09	8.27	-	7.87	$J_{3,6}$=1.5
30	$C_8H_{10}IN_3O$	NC_4H_8O	H	I	H	3.57 (α) 3.85 (β)	8.33	-	7.99	$J_{3,6}$=1.5
31	$C_4H_3I_2N_3$	NH_2	I	I	H	7.37[d]	-	-	8.48	-
32	$C_5H_6IN_3$	NH_2	CH_3	I	H	7.27[e]	2.54	-	8.46	-
33	$C_6H_8IN_3$	NH_2	CH_3	I	CH_3	7.31[e]	2.59	-	2.41	-
53[c]	$C_6H_9N_3O$	$N(CH_3)_2$	H	H	H	3.09	8.15	8.00	8.00	-

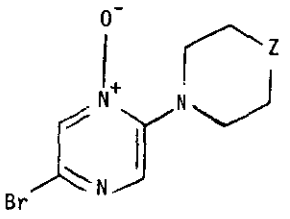
a. All spectra were recorded as dilute solutions in $CDCl_3$ unless indicated otherwise. b. δ (ppm) downfield from TMS. c. N_1-oxide. d. d_6-DMSO.
e. d_6-acetone/CH_3OD.

as 6-iodo-3-dialkylaminopyrazine 1-oxides. As an added proof, their ^1H chemical shifts are almost identical with those of other 3-substituted 6-bromo derivatives.[3] Steric factors may indeed be responsible for the absence of ring substitution at C_2 and parallel the results from our previous studies.[3] This was exemplified with 2-morpholino- and 2-piperidinopyrazine 1-oxides which afforded only the *para*-bromo compounds, 21 and 22, respectively. Similar pattern was also observed with 3-aminopyridine 1-oxides. The 3-dimethylamino group (7b) prevented the bromination at C_4 whereas the 3-amino and 3-monomethylamino compounds were substituted at both *ortho* carbon atoms (C_2 and C_4).[3]

TABLE 2. Analytical Data and Experimental Variables for Some Pyrazines and Their N-Oxides

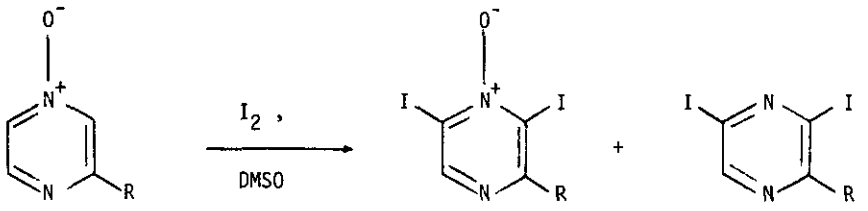
Cmpd No.	mp[a], °C (bp, °C/Torr)	Reactant	Reaction Time (h)	Yield %	Analysis C Calcd (Found)	H Calcd (Found)	N Calcd (Found)
15	150-152	$I_2/N(CH_2CH_3)_3/CH_3CN$	2, refl.	18[b]	13.24 (13.25)	0.83 (0.79)	11.58 (11.33)
		I_2/DMSO	0.5, 80°C	97			
16	119-120	$I_2/N(CH_2CH_3)_3/CCl_4$	5, refl.	56	15.93 (15.89)	1.34 (1.64)	11.15 (10.69)
19	169-170.5	$I_2/N(CH_2CH_3)_3/CCl_4$	3.5, ref.	87	27.18 (27.03)	3.05 (3.14)	15.86 (15.77)
		$I_2/K_2CO_3/CH_2Cl_2$	48, 25°C	31[c]			
20	85-87/0.5	$I_2/N(CH_2CH_3)_3/CCl_4$	3, refl.	91	31.28 (31.40)	3.29 (3.05)	13.69 (13.56)
		$I_2/K_2CO_3/CH_2Cl_2$	48, 25°C	73			
23	72-73	I_2/DMSO	0.3, 100°C	95	18.43 (18.77)	1.81 (1.98)	10.75 (9.98)
24	86.5-87	$I_2/N(CH_2CH_3)_3/CH_2Cl_2$	72, 40°C (18, 29)	75	19.22 (19.10)	1.88 (1.74)	11.21 (11.22)
		I_2/DMSO	4, 100°C	21			
		I_2/DMSO	48, 100°C (58, 23)	89			
25	71-72	I_2/DMSO	0.3, 100°C	97	22.19 (21.92)	2.10 (1.88)	9.71 (9.50)
26	93-95/0.5	$I_2/N(CH_2CH_3)_3/CH_2Cl_2$	72, 40°C (13, 30)	78	23.04 (23.17)	2.18 (2.05)	10.08 (9.78)
		I_2/DMSO	4, 100°C	36			
		I_2/DMSO	48, 100°C (45, 25)	94			
29	118-119	$I_2/N(CH_2CH_3)_3/CH_2Cl_2$	72, 40°C (75, 24)	18	28.93 (28.76)	3.24 (3.17)	16.87 (16.95)
		I_2/DMSO	0.5, 60°C (53, 24)	37			
30	159-160	$I_2/N(CH_2CH_3)_3/CH_2Cl_2$	72, 40°C (78, 26)	13	33.00 (32.89)	3.47 (3.51)	14.44 (14.21)
		I_2/DMSO	0.5, 60°C (42, 26)	45			
31	168-169.5	I_2/DMSO	0.5, 80°C	92[d]	13.85 (14.01)	0.87 (0.90)	12.12 (11.86)
32	94-96	I_2/DMSO	0.5, 80°C	100	lit.[9] 95-96°C		
33	130-131.5	I_2/DMSO	1.5, 80°C	98	lit.[9] 129-130°C		

a. Melting points are not corrected. b. Lower yield is probably due to the low solubility of the starting material in the designated solvent. c. Some starting material was recovered. d. Some 2-amino-3,5-diiodopyrazine was also isolated in trace amounts.



21 Z = O
22 Z = CH

Under forcing reaction conditions the desired diiodo derivatives were prepared. Accordingly, when 17 and 18 were heated for 4 h at 100°C in a polar solvent (such as dimethylsulfoxide) containing I_2, some deoxygenated products were obtained together with diiodopyrazine N-oxides. Furthermore, when the same reaction was



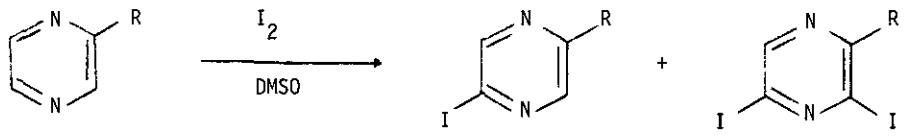
17 R = $N(CH_3)_2$
18 R = NC_4H_8O

23 R = $N(CH_3)_2$
25 R = NC_4H_8O

24 R = $N(CH_3)_2$
26 R = NC_4H_8O

carried out over a longer period (two days), starting materials (17,18) were almost quantitatively converted to 24 and 26. Consequently, the deoxygenation of meta substituted N-oxides seems to occur only when steric requirements demand it; i.e., when three bulky groups are adjacent to each other.

The identity of structures 24 and 26 were readily established by a comparison of their ^1H nmr spectra (Table 1) with those of the non-halogenated compounds (27,28). Also, 24 and 26 were identical in all respects to the authentic samples prepared by direct iodination of the corresponding non-oxides 27 and 28. Here, too, steric factors played an important role in determining the extent of halogenation (isolation of monoiodo derivatives 29 and 30).



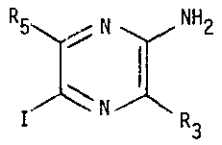
27 R = $N(CH_3)_2$
28 R = NC_4H_8O

29 R = $N(CH_3)_2$
30 R = NC_4H_8O

24 R = $N(CH_3)_2$
26 R = NC_4H_8O

The structural assignments of compounds 23 and 25 were based on the following considerations: a) their mass spectra indicated that the N-oxide moiety had been retained; b) the ^1H chemical shift comparison with the analogous dibromo compounds (8a)[3] clearly showed that the two iodine atoms were substituted at positions 2 and 6 (also see Table 1).

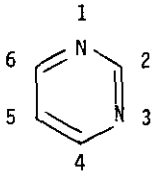
Iodination of various aminopyrazines was accomplished in greater than 90% yield (compounds 31-33), illustrating that in these instances there was no inhibition to halogenation. Physical properties of known 31-33 matched those of reported compounds, prepared by other methods.[9]



31 R_3 = I, R_5 = H
32 R_3 = CH_3, R_5 = H
33 R_3 = R_5 = CH_3

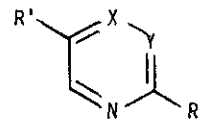
Various 2- and 4-substituted pyrimidine 1-oxides (34-37) were also rapidly iodinated in high yields (Table 4). Contrary to bromination, no deoxygenative halogenation products (such as 5a and 5b) were detected. In both instances, iodination occurred at C_5, the site of most electron density. The disappearance of the most shielded proton in the ^1H nmr spectrum of starting materials (34-37) unquestionably determined the halogenation site (Table 3).

TABLE 3a. ^{1}H nmr Data for Some Pyrimidines and Their N-Oxides



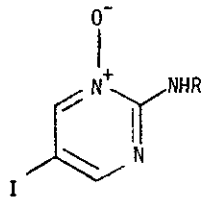
Cmpd No.	Molecular Formula	Substituents				Chemical Shifts[a,b]				Coupling Constants (Hz)
		R_2	R_4	R_5	R_6	R_2	R_4	R_5	R_6	
34[c]	$C_4H_5N_3O$	NH_2	H	H	H	8.07[d]	8.79	7.12	8.27	$J_{4,5}$=6.0; $J_{4,6}$=2.0; $J_{5,6}$=5.0
35[c]	$C_5H_7N_3O$	$NHCH_3$	H	H	H	3.12 7.40 (NH)	8.29	6.59	7.99	$J_{4,5}$=5.0; $J_{4,6}$=2.0; $J_{5,6}$=6.5
38[c]	$C_4H_4IN_3O$	NH_2	H	I	H	8.16[d]	9.10	-	8.39	$J_{4,6}$=2.0
39[c]	$C_5H_6IN_3O$	$NHCH_3$	H	I	H	3.11[d]	8.95	-	8.40	$J_{4,6}$=2.0
36[c]	$C_4H_5N_3O$	H	NH_2	H	H	8.65[d]	8.40	7.64	7.25	$J_{2,6}$=2.5; $J_{5,6}$=8.0
37[c]	$C_5H_7N_3O$	H	$NHCH_3$	H	H	8.10	3.08	6.53	7.42	$J_{2,6}$=2.0; $J_{5,6}$=6.0
40[c]	$C_4H_4IN_3O$	H	NH_2	I	H	8.88[d]	8.45	-	7.90	$J_{2,6}$=2.0
41[c]	$C_5H_6IN_3O$	H	$NHCH_3$	I	H	8.91[d]	3.11	-	7.95	$J_{2,6}$=2.0
42	$C_4H_5N_3$	NH_2	H	H	H	6.97[d]	8.57	6.68	8.57	$J_{4,5}$=4.5 (5,6)
43	$C_5H_7N_3$	$NHCH_3$	H	H	H	3.11 5.80 (NH)	8.41	6.63	8.41	$J_{4,5}$=5.0 (5,6)
46	$C_4H_4IN_3$	NH_2	H	I	H	7.25[d]	8.90	-	8.90	-
47	$C_5H_6IN_3$	$NHCH_3$	H	I	H	3.17[d]	8.96	-	8.96	-
44	$C_4H_5N_3$	H	NH_2	H	H	9.12[d]	-	7.26	8.60	$J_{2,5}$=1.3; $J_{2,6}$=0.4; $J_{5,6}$=5.8
45	$C_5H_7N_3$	H	$NHCH_3$	H	H	8.55	2.93 7.35 (NH)	6.38	8.16	$J_{2,5}$=1.4; $J_{2,6}$=0.4; $J_{5,6}$=6.0
48	$C_4H_4IN_3$	H	NH_2	I	H	8.98[d]	8.20	-	8.90	-
49	$C_5H_6IN_3$	H	$NHCH_3$	I	H	8.63	3.15	-	8.37	-

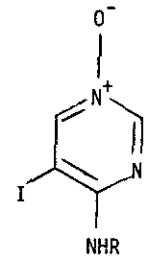
TABLE 3b. ^{1}H nmr Data for Other Iodinated Azines and Polyazines



Cmpd No.	Molecular Formula	Substituents R	R'	X	Y	Chemical Shifts[a,b] R	Other	Coupling Constants (Hz)
50a	$C_3H_4N_4$	NH_2	H	N	N	8.28[d]	8.53(H_5) 8.88(H_6)	$J_{5,6}$=2.5
51a	$C_4H_6N_4$	$NHCH_3$	H	N	N	3.80	8.12(H_5) 8.56(H_6)	$J_{5,6}$=2.5
50b	$C_3H_3IN_4$	NH_2	I	N	N	7.74[d]	8.63(H_5)	-
51b	$C_4H_5IN_4$	$NHCH_3$	I	N	N	3.06 3.10	8.19(H_5)	-
52a	$C_5H_6N_2$	NH_2	H	CH	CH	5.88	6.54(H_3) 7.41(H_4) 6.56(H_5) 8.17(H_6)	$J_{3,4}$=9.0; $J_{4,6}$=2.5
52b	$C_5H_5IN_2$	NH_2	I	CH	CH	6.52[d]	6.82(H_3) 7.88(H_4) 8.34(H_6)	-
52c	$C_5H_4I_2N_2$	NH_2	I	CH	C-I	7.12[d]	8.34(H_4) 8.41(H_6)	$J_{4,6}$=2.0

a. All spectra were recorded as dilute solutions in $CDCl_3$ unless indicated otherwise. b. δ(ppm) downfield from TMS. c. N_1-oxide. d. d_6-DMSO.





38 R = H

39 R = CH_3

40 R = H

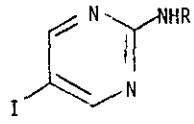
41 R = CH_3

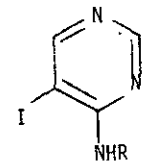
The N-oxide seems to have no effect on these reactions since the parent 2- and 4-substituted pyrimidine non-oxides (42-45) were iodinated with ease to yield the 2-amino-5-iodo- (46, 47) and 4-amino-5-iodopyrimidines (48, 49). Compound 46 has previously been prepared via the 5-mercurioacetate derivatives.[10]

TABLE 4. Analytical Data and Experimental Variables for Some pyrimidines, Other Azines, and Their N-Oxides

Cmpd No.	mp[a], °C (bp, °C/Torr)	Reactant	Reaction Time (h)	Yield %	Analysis C Calcd (Found)	H Calcd (Found)	N Calcd (Found)
38	226-228	$I_2/N(CH_3CH_3)_3/CH_3CN$	10, 72°C	42[b]	20.27 (20.27)	1.70 (1.53)	17.73 (17.58)
		I_2/DMSO	0.3, 100°C	100			
39	196-197	I_2/DMSO	0.3, 100°C	96	23.92 (23.87)	2.41 (2.42)	16.74 (16.70)
40	241-243.5	I_2/DMSO	0.2, 80°C	91	20.27 (20.48)	1.70 (1.62)	17.73 (17.77)
41	200-201	$I_2/N(CH_2CH_3)_3/CH_2Cl_2$	72, 40°C	77	23.92 (23.77)	2.41 (2.49)	16.74 (16.59)
		$I_2/K_2CO_3/CHCl_3$	4, refl.	63			
		I_2/DMSO	0.3, 80°C	95			
46	224-226	I_2/DMSO	0.6, 100°C	93	lit.[10] 224-225°C		
47	136-137	$I_2/K_2CO_3/CHCl_3$	5, refl.	81	25.55 (25.47)	2.58 (2.32)	17.88 (17.94)
		I_2/DMSO	0.5, 100°C	90			
48	188-189	I_2/DMSO	0.2, 80°C	100	21.74 (21.70)	1.83 (1.69)	19.02 (18.84)
49	55-56/0.5	$I_2/N(CH_2CH_3)_3/CH_2Cl_2$	72, 40°C	64	25.55 (25.51)	2.58 (2.60)	17.88 (17.68)
		I_2/DMSO	0.2, 80°C	90			
50b	71-72/0.5	I_2/DMSO	1.5, 100°C	87	16.23 (16.17)	1.36 (1.18)	25.24 (24.97)
51b	66-67.5/0.5	I_2/DMSO	1, 100°C	82[c]	20.35 (20.46)	2.14 (2.03)	23.74 (23.56)
52b	126-128	I_2/DMSO	0.5, 100°C	71 (12, 52c)	lit.[11] 129-130°C		
52c	147-149	I_2/DMSO	0.5, 100°C	12 (71, 52b)	lit.[10] 147-148°C		

a. Melting points are not corrected. b. Lower yield is probably due to the low solubility of the starting material in the designated solvent. c. Slight decomposition of the product was observed.





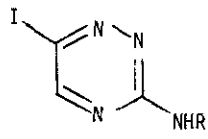
46 R = H

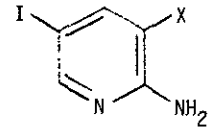
47 R = CH_3

48 R = H

49 R = CH_3

The same I_2/DMSO medium was also used to prepare the novel 6-iodo-3-amino-1,2,4-triazines (50b, 51b) and the known 5-iodo (52b)[11] and 3,5-diiodo-2-aminopyridine (52c) from the corresponding amino compounds (50a, 51a, 52a).





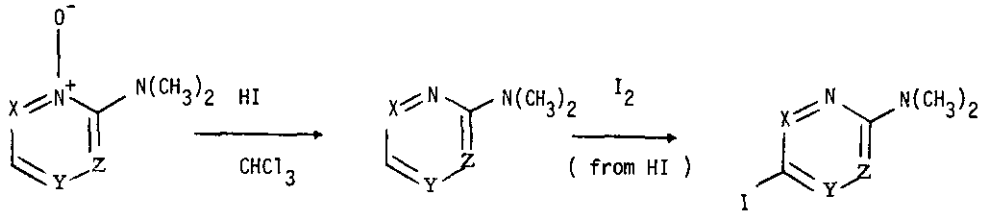
50b R = H

51b R = CH_3

52b X = H

52c X = I

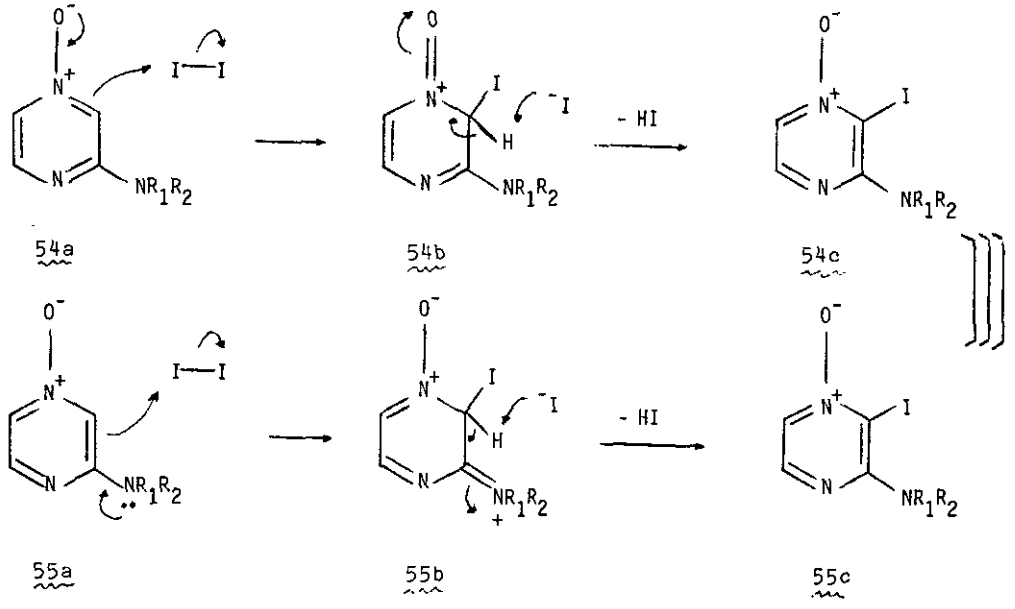
In view of these findings, it seemed appropriate to mechanistically account for the deoxygenation of compounds 17 and 18 since the deoxygenation products were absent with other amino derivatives. The hydrohalic acids were shown to be the effective reducing agents[2] and the fact that no deoxygenation took place in the presence of the base (NEt_3) we elected to examine the role of HI and its effect on iodination. When diiodo derivatives 23 and 25 were refluxed in acetonitrile having a trace amount of HI, they were converted quantitatively to their non-oxides, 24 and 26, respectively. The generality of this reaction was further exemplified by treating the 2-dimethylaminopyrazine 1-oxide, 53, with catalytic amount of hydriodic acid in chloroform at room temperature. Within 15 min, 53 was reduced to 2-dimethylaminopyrazine, 27, (tlc) and the light yellow solution turned the characteristic brown color of elemental iodine. After 0.5 h this reaction mixture was worked up and contained some 5-iodo-2-dimethylaminopyrazine, 29, in addition to 27. It seemed unquestionable that hydriodic acid was



53 X = Z = CH, Y = N 27 X = Z = CH, Y = N 29 X = Z = CH, Y = N

responsible for this acid-induced reduction of the N-oxides studied. The fact that 3-dimethylamino-1,2,4-triazine 2-oxide (53; X=Z=N; Y=CH) was only reduced with hydrogen iodide[5] to 3-dimethylamino-1,2,4-triazine (27; X=Z=N; Y=CH) but not iodinated may simply be due to greater π-deficiency of 1,2,4-triazine vs that of pyrazine ring.[12]

On the basis of the experimental evidence presented so far, the following mechanistic pathways should be considered. The mechanism for electrophilic iodination is straightforward. This ring substitution can proceed either by the N-oxide activation, 54a, or by substituent mesomeric electron-donation, 55a, or both. Proton abstraction from intermediates 54b and 55b yields the iodinated heterocycles.

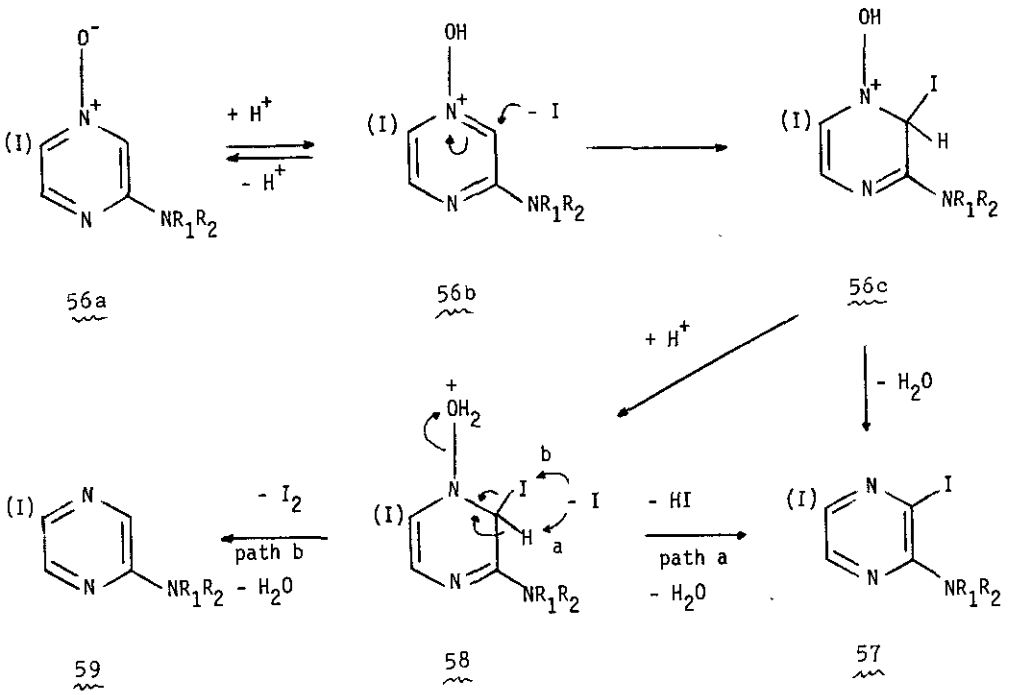


54a 54b 54c

55a 55b 55c

However, as this reaction takes place, concentration of hydriodic acid builds up and the N-oxide function may become protonated, 56b, followed by the addition of

iodide, 56c. This intermediate can then either eliminate water, 57, or protonate



again and lose HI (path a) or elemental iodine (path b). This mechanism accounts for the deoxygenative iodination (57) as well as N-oxide reduction (59). It also explains the formation of compound 27 (X=Z=CH; Y=N). Path b is only favored when steric interactions exist (i.e., three relatively large groups are next to each other) and justifies why no deoxygenation was observed with pyrimidine N-oxides. It is also noteworthy to point out that the halogen abstraction by the halide ion (path b) is proportional to the polarizability of that halogen. For instance, chloride ion does not reduce the N-oxide group,[8] bromide ion does, yielding both the brominated products as well as deoxygenated bromo derivatives,[2,3] and iodide anion gives all three products: deoxygenated, iodinated, and deoxygenated iodo compounds. (For reactions and attempted deoxygenation of diazine N-oxides with HF, see ref. 13).

Careful search for deoxygenated pyrimidines 46 and 47 arising from their respective N-oxides 34 and 35 via nucleophilic halogenation/deoxygenation mechanism failed (as in 3a and 3b). Further studies are in progress.

EXPERIMENTAL PROCEDURE

General Procedure for Iodination with I_2/DMSO. The desired amine (5.0 mmol) was dissolved in 10 ml of freshly-distilled dimethyl sulfoxide containing twice the amount of elemental iodine (2.54 g; 10.0 mmol). The mixture was either heated or left standing at room temperature as specified in Tables 2 and 4, after which time it was worked up. The amines having the $-NH_2$ or -NHR groups precipitated from solution by cooling or by standing at room temperature for extended periods of time. More product was collected by dilution of the remaining mother-liquor with equal volume of water (10 ml). The combined solids were shaken in aqueous sodium thiosulfate solution (5 ml) for 3-5 min, aqueous layer decanted, and the remaining solid rinsed with 5 ml of sodium bicarbonate. The residual solid was air-dried, recrystallized, and sublimed at 60-100°C/0.05 Torr to yield the pure iodo derivative, generally in high yields. In many instances, the isolated product was better than 95% pure after the first filtration and did not require further purification.

The dialkylamines were extracted from the DMSO/water mixture with methylene chloride (5 x 30 ml). The combined extracts were dried over anhydrous Na_2CO_3, evaporated to dryness, and the remaining orange or yellow oil chromatographed on a short column of neutral alumina (5 ml, 1 cm o.d.) preceded by a short charcoal plug (2 ml). The separated iodo compound(s) was sublimed at 60-80°C/0.05 Torr to yield the analytically pure sample for elemental analysis.

General Procedure for Iodination of Azines and Polyazines in the presence of $N(Et)_3$. To a solution of 1.0 mmol of the given amine dissolved in 30 ml of CCl_4 was added 2.0 mmol (508 mg) of elemental iodine. The mixture was stirred for 20 min, 111 mg (1.1 mmol) of triethylamine was added, and whole stirred and/or heated as specified in Tables 2 and 4. After the reaction went to completion (tlc indicated that all of the starting material had been consumed), the solvent was removed under reduced pressure (80 Torr) and the residue chromatographed on neutral alumina as described above to yield the pure iodination product(s). Similar procedure was employed with K_2CO_3. However, solid bases were less efficient in neutralization of HI and did not form complexes with iodine which resulted in lower yields of iodinated products and recovery of some starting material. (For further detail, see Tables 3 and 4.)

Reduction of 2-Dimethylaminopyrazine 1-Oxide with HI. To 50 ml of chloroform at 35°C was added 139 mg (1.0 mmol) of 2-dimethylaminopyrazine 1-oxide, 53 (X=Z=CH; Y=N). After the amine N-oxide dissolved, 0.5 ml of 47% HI was added and the whole mixture stirred vigorously. Within 15 min the pale yellow solution turned dark brown and 53 was reduced to 2-dimethylaminopyrazine, 27 (tlc with an authentic sample). After additional 30 min the reaction mixture was worked up to yield 27 in 78% yield (96 mg) and some 5-iodo-2-dimethylaminopyrazine, 29, (19%, 48 mg), which was identical in all respects with the sample prepared by direct iodination of 27 (see Table 2).

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