orange residue (mp 90–95 °C) which was chromatographed on a silica gel column (30 × 1 cm i.d.) by eluting with methylene chloride/ethyl acetate (15:1 v/v). Compound-containing fractions (TLC, solvent system a) were evaporated, yielding white, crystalline **12**: 0.070 g (39%); mp 98–100 °C; R_f 0.53 (solvent system a); IR (KBr) 2120 cm^{-1} (NC); ^1H NMR ($CDCl_3$) δ 2.50 (3, s, 6-CH_3), 4.00 and 4.07 (6, 2 s, 4-OCH_3 and 2-OCH_3). Anal. Calcd for $C_8H_8N_3O_2$: C, 53.93; H, 4.53; N, 23.58. Found: C, 53.74; H, 4.73; N, 23.58.

Registry No. **1**, 84538-40-9; **2**, 30561-09-2; **3**, 84538-41-0; **4**, 84538-42-1; **5**, 84538-43-2; **6**, 84538-44-3; **7**, 83256-18-2; **10**, 84538-45-4; **11**, 84538-46-5; **12**, 84558-24-7; i, 1899-99-6; ii, 84538-47-6; 2,4-dichloro-6-methyl-5-nitropyrimidine, 13162-26-0.

Bromination of Some Pyridine and Diazine *N*-Oxides

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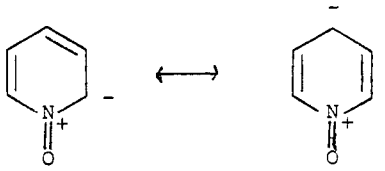
Selected monosubstituted pyridines, pyrazines, pyrimidines, and their *N*-oxides, having an electron-donating substituent, were successfully brominated under very mild conditions. The *N*-oxide function itself is not sufficient to cause these π-deficient systems to undergo electrophilic aromatic halogenation. Only strongly electron-donating substituents (amino groups) activate the heterocyclic nucleus toward bromination. These substituents direct the electrophilic substitution ortho/para to them with or without the *N*-oxide group present. Pyridine and diazines with moderately activating substituents such as alkoxy groups are brominated only when their ortho/para activation is augmented by the activation of the *N*-oxide function. Failure to brominate 5-methoxypyrimidine 1-oxide may well reflect the greater π deficiency of the pyrimidine ring.

It is a well-known axiom in heterocyclic chemistry that electrophilic substitution of the π-deficient azines and diazines occurs with great difficulty, if at all. If these compounds are converted to their *N*-oxides, electrophilic substitution occurs more readily. This increase in electrophilic reactivity has been attributed to resonance structures such as **1a** and **1b** contributing to the ground state of the *N*-oxides.[2a]



1a 1b

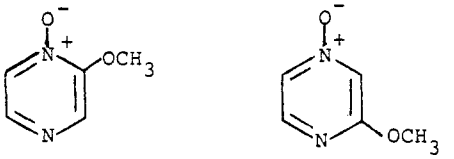
The presence of electron-donating groups on pyridine and the diazines, of course, also facilitates electrophilic substitution reactions.[2b]

We have recently described the bromination of a number of 1,2,4-triazine 1- and 2-oxides and have established that bromination occurs at the 6-position of these compounds. The 2-oxides also afford some of the corresponding deoxygenated compounds.[3,4]

In order to examine the relative activating influences of an *N*-oxide group and strongly electron-donating substituents and to gain some understanding of the bromination deoxygenation observed with 1,2,4-triazine 2-oxides, we studied the bromination of a number of substituted pyridines, diazines, and their *N*-oxides. The results of this bromination study, done under as identical conditions as possible, are the basis of this report.

Bromination of Pyrazines. The results of the bromination of a number of substituted pyrazines and their *N*-oxides are reported in Table I.

It is noteworthy that neither 2-methoxypyrazine (**2**) nor its 1-oxide (**6**) are brominated under these conditions, while



6 12

the isomeric 3-methoxy 1-oxide (**12**) affords the 6-bromo derivative (**26**). In this case, the methoxy group augments the ortho-activating behavior of the *N*-oxide. The other possible isomer (2-bromo-3-methoxypyrazine 1-oxide) is not obtained.

In the 2-amino and 2-(methylamino)pyrazine 1-oxides, the amino substitutents *activate* C-6 and *deactivate* C-3 and C-5 toward electrophilic bromination. Consequently, it is not surprising that, while the nonoxides yield the 3,5-dibromo derivatives (**16–18**), the 1-oxides react less readily and afford the 3,5-dibromo (**20–22**) as well as some of the 3-bromo compounds (**19–21**). The 2-(dimethylamino)pyrazine 1-oxide (**9**) affords the 3,5-dibromo derivative (**23**) exclusively. The selective formation of the 5-bromo 1-oxides in the 2-morpholino (**10**) and 2-piperidino (**11**) instances is most probably caused by the steric bulk of the substituents, preventing bromination at C-3.

Bromination of 3-aminopyrazine 1-oxides **13–15**, where the oxide group increases the reactivity of the same positions as do the substituents (C-2 and C-6), affords the

(1) Present address: Department of Chemistry, Portland State University, Portland, OR 97207.

(2) (a) Katritzky, A. R.; Lagowski, J. M "Chemistry of the Heterocyclic N-Oxides"; Academic Press: London, 1971. (b) Barton, Derek; Ollis, W. D. "Comprehensive Organic Chemistry"; Vol. IV, Sammes, P. A., Ed.; Pergamon Press: New York, 1979; Vol. IV, Parts 16.1 and 16.2 and references therein.

(3) Keen, B. T.; Radel, R. J.; Paudler, W. W. *J. Org. Chem.* **1977**, *42*, 3498.

(4) Radel, R. J; Atwood, J. L.; Paudler, W. W. *J. Org. Chem.* **1978**, *43*, 2514.

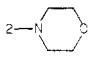
0022-3263/83/1948-1064$01.50/0

Table I. Brominations of Some Pyrazines and Their *N*-Oxides

substituents	compd no.	method	products[a] (mp,[b] °C)	compd no.	% yield	separation technique[e]	^{1}H NMR chemical shifts of products,[c,d] δ H-2	H-3	H-5	H-6	substituent(s)
2-OCH_3	2	A, B	no reaction								
2-NH_2	3	D[f]	3,5-dibromo[g] (109–110)	16	91	*h*				8.46	7.27 (NH_2)
2-$N(CH_3)_2$	4	A	3,5-dibromo (80–81)	17	88	*i*				8.16	3.09 ($N(CH_3)_2$)
	5	A, B	3,5-dibromo (28–30)	18	82, 95	*j*				8.25	3.87 (α), 3.46 (β)
2-OCH_3[r]	6	A, B	no reaction								
2-NH_2[r]	7	C, D	3-bromo[k] (169–170) + 3,5-dibromo 1-oxide[m] (135–136)	19	45, 65	*l*			8.05	7.62	6.15 (NH_2)
				20	8, 20	*l*				8.10	
2-$NHCH_3$[r]	8	B, C	3-bromo (128–129) + 3,5-dibromo 1-oxide (72–74)	21	3, 32	*n*			8.12	7.73	3.06 ($NHCH_3$)
				22	49, 36	*n*				8.17	3.09 ($NHCH_3$)
2-$N(CH_3)_2$[r]	9	A, C	3,5-dibromo 1-oxide (73–74.5)	23	90, 82	*n*				8.20	3.11 ($N(CH_3)_2$)
	10	B	5-bromo 1-oxide, 1.5 H_2O (138–140)	24	6[o]	*p*		8.44		8.08	3.46 (α-CH_2), 3.97 (β-CH_2)
	11	B	5-bromo 1-oxide, 1 H_2O (149–150)	25	4[o]	*p*		8.36	8.08		3.44 (α), 1.83 (m, β and γ)
3-OCH_3[r]	12	B	6-bromo 1-oxide (74–76)	26	45	*l*	7.94		8.23		4.09 (OCH_3)
3-NH_2[r]	13	C, D	2,6-dibromo 1-oxide[g] (215–216)	27	89, 95	*l*			8.70		
3-$NHCH_3$[r]	14	A, B	2,6-dibromo 1-oxide[g] (116–118)	28	76, 86	*n*			8.70		3.30 ($NHCH_3$) 7.52 (NH)
3-$N(CH_3)_2$[r]	15	A, B	2,6-dibromo 1-oxide (111–113) + **17**	29	80, 77	*n*				8.19	3.10 ($N(CH_3)_2$)
				17	11, 9	*n*					

[a] Elemental analyses (C, H, N) for all compounds were within +0.3% of the calculated values. [b] Melting points were taken on a Thomas-Hoover melting point apparatus. [c] All spectra were recorded as dilute solutions in $CDCl_3$ except where otherwise indicated. [d] Downfield from Me_4Si. [e] TLC, neutral alumina, unless other wise indicated. [f] Solvent for the reaction was acetic acid. [g] Me_2SO-d_6. [h] Vacuum sublimation. [i] 65:35 benzene/hexane. [j] 60:40 benzene/petroleum ether. [k] In Me_2SO-d_6: H-5, δ 8.69; H-6, δ 8.09; NH_2, δ 5.60. [l] Silica/acetonitrile. [m] In Me_2SO-d_6: H-6, δ 906; NH_2, δ 5.65. [n] 50:50 methylene chloride/benzene. [o] Other products not isolated. [p] Carbon tetrachloride. [q] Benzene. [r] 1-Oxide.

Table II. Brominations of Some Pyrimidines and Their N-Oxides

substituents	compd no.	method	products[a] (mp,[b] °C)	compd no.	% yield	separation technique[e]	^{1}H NMR chemical shifts of products, c,d δ H-2	H-3	H-5	H-6	substituent(s)
2-OCH_3	30	A, B	no reaction								
2-NH_2	31	D[f]	5-bromo[g] (242-244)	44	75	*i*		8.75		8.75	8.40 (NH_2)
2-$NHCH_3$	32	C, D	5-bromo[g] (171-173)	45	81, 90	*i*		8.85		8.85	3.16 ($NHCH_3$)
	33	C, D	5-bromo (113-114.5)	46	80, 94	*j*		8.62		8.62	3.43 (α-CH_2), 3.95 (β-CH_2)
2-OCH_3[o]	34	A, B	no reaction								
2-NH_2[o]	35	C[h]	5-bromo 1-oxide[g] (234-236)	47	88	*h*		9.13		8.36	8.24 (NH_2)
2-$NHCH_3$[o]	36	C, D	5-bromo 1-oxide[g] (175-177)	48	92, 93	*i*		9.10		8.31	3.10 ($NHCH_3$)
4-NH_2	37	D[f]	5-bromo[g] (209-211)	49	83	*l*	8.33			8.35	
4-$HNCH_3$	38	A, C	5-bromo (88-89)	50	66, 78	*m*	8.55			8.30	3.10 ($NHCH_3$)
4-$N(CH_3)_2$	39	B, C	5-bromo (46-48)	51	85, 91	*n*	8.54			8.39	$N(CH_3)$
4-OCH_3[o]	40	A, B	no reaction								
4-NH_2[o]	41	C[h]	5-bromo 1-oxide[g] (246-247)	52	96	*h*	8.93			7.85	8.60 (NH_2)
4-$NHCH_3$[o]	42	C, D	5-bromo 1-oxide[g] (203-205)	53	75, 89	*i*	8.80			7.88	3.11 ($NHCH_3$)
5-OCH_3[o]	43	A, B	no reaction								

[a] Elemental analyses (C, H, N) for all compounds were within ±0.3% of the calculated values. [b] Melting points were taken on a Thomas-Hoover melting point apparatus. [c] All spectra were recorded as dilute solutions in $CDCl_3$ except where otherwise indicated. [d] Downfield from Me_4Si. [e] TLC (neutral alumina) unless otherwise indicated. [f] Solvent for the reaction was acetic acid. [g] Me_2SO-d_6. [h] 50:50 acetonitrile/methanol. [i] Silica, acetonitrile. [j] Benzene. [k] Solvent for the reaction was acetonitrile. [l] Vacuum sublimation. [m] Methylene chloride. [n] 50:50 methylene chloride/benzene. [o] 1-Oxide.

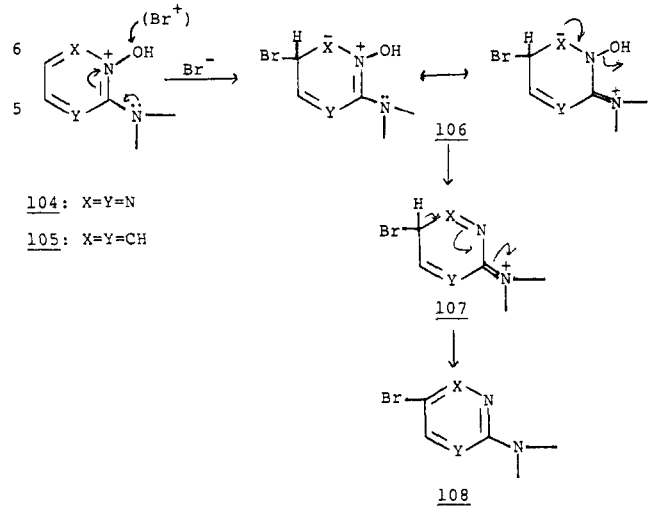
dibromo compounds as the exclusive products (**27–29**). The formation of the 3,5-dibromo nonoxide **17**, in the 3-(dimethylamino)pyrazine 1-oxide instance, will be commented on later.

Bromination of Pyrimidines. As is the case with the methoxypyrazine 1-oxides, the 2-, 4-, and 5-methoxypyrimidine *N*-oxides (**34, 40, 43**) as well as 2-methoxypyrimidine (**30**) are not brominated under the conditions employed in this study. Thus, a methoxy group is not activating enough to cause facile bromination ortho or para to it in pyrimidine *N*-oxides (electrophilic substitution in pyrimidines under more drastic conditions occurs at C-5).[2] Amino groups, on the other hand, either at C-2 (**31–33**) or at C-4 (**37–39**) sufficiently activate C-5 for bromination to take place (formation of **44–46** and **49–51**, respectively). The same reactivity at C-5 is observed with the corresponding pyrimidine *N*-oxides (**34–36** and **41–43**). The absence of any C-4- or C-6-brominated products in the *N*-oxide brominations again points to the lesser activating effect of an *N*-oxide group vs. an amino group (Table II).

Bromination of Pyridines. Table III lists the bromination results of a number of pyridines and their *N*-oxides. A 2-methoxy substituent (**54**) is not sufficiently activating to allow bromination. The presence of an *N*-oxide group, as in 4-methoxypyridine *N*-oxide (**63**), simply facilitates, as is well-known, hydrolysis of the alkoxy function, and the resulting *N*-hydroxy-4-pyridinone (**103**) is then brominated. In the 2- and 4-aminopyridine *N*-oxides **58–60** and **64–66** bromination occurs as in the nonoxides. Thus, amino groups in the pyridines also activate positions ortho and para to them more effectively than does the *N*-oxide function. In 2-(dimethylamino)pyridine 1-oxide (**60**) for instance, substantial amounts of the 5-bromo nonoxide **74** are also obtained.

In the 3-substituted pyridine 1-oxides, both of the substituents activate C-2, C-4, and C-6, and all of these products, along with some brominated nonoxides (**89–102**; See Table III), are formed. 3-Methoxypyridine *N*-oxide

Scheme I



(**67**) is the only one of the methoxypyridine *N*-oxides which is brominated; it forms the 2,6- and 4,6-dibrom-3-methoxypyrazine 1-oxides (**89** and **90**, respectively). A small amount of the 4,6-dibromo nonoxide **97** is also obtained (these results are contrary to literature reports[5] which state that 3-methoxypyridine 1-oxide cannot be brominated).

Results and Discussion

(1) The fact that in the 2- and 3-substituted pyridine *N*-oxides, as well as in the 3-substituted pyridazine 1-oxides,[6,7] electrophilic substitution occurs first at the

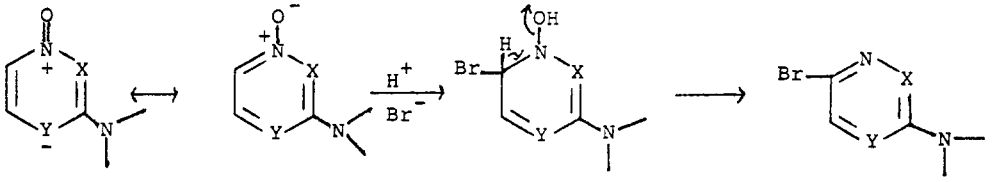
(5) Hoogzand, C.; den Hertog, H. J. *Recl. Trav. Chim. Pays-Bas* **1957**, *76*, 261.
(6) (a) Okusa, G.; Kamiya, S.; Itai, T. *Chem. Pharm. Bull.* **1967**, *15*, 1172. (b) Kamiya, S.; Okusa, G.; Hirakawa, H. *Ibid.* **1970**, *18*, 632.
(7) Nakagome, T. *Yakugaku Zasshi* **1960**, *80*, 712.

Table III. Brominations of Some Pyridines and Their *N*-Oxides

substituents	compd no.	method	products[a] (mp,[b] °C)	no.	% yield	separation technique[e]	^{1}H NMR chemical shifts of products,[c,d] δ H-2	H-3	H-4	H-5	H-6	substituent(s)
2-OCH_3	54	A, B	no reaction									
2-NH_2	55	D	5-bromo[f] (136–138)	71	68	*g*		6.82	7.88		8.34	6.52 (NH_2)
			3,5-dibromo[f] (104–105)	72	23	*g*			8.34		8.41	6.85 (NH_2)
2-$N(CH_3)_2$	56	A, B	3,5-dibromo (41–43)	73	69, 77	*h*			7.88		8.24	2.9 ($N(CH_3)_2$)
			5-bromo (69–71)	74	13, 19	*h*		6.43	7.38		8.22	2.9 ($N(CH_3)_2$)
2-OCH_3[r]	57	A, B	no reaction									
2-NH_2[r]	58	D	5-bromo[f] 1-oxide (180–181)	75	76	*i*		7.20	7.70		8.70	7.42 (NH_2)
			3,5-dibromo 1-oxide[f] (93–95)	76	15	*i*			8.15		8.90	7.62 (NH_2)
2-$NHCH_3$[r]	59	A, B	5-bromo (98–100/0.05 torr)	77	68, 81	*j*		6.49	7.33		8.29	3.01 ($NHCH_3$), 8.03 (NH)
			3,5-dibromo 1-oxide[f] (135–136/0.05 torr)	78	11, 14	*j*			7.72		8.14	3.35 ($NHCH_3$), 8.03 (NH)
2-$N(CH_3)_2$[r]	60	A, B	5-bromo 1-oxide (78–81/0.05 torr)	79	48, 57	*j*		6.69	7.25		8.24	2.99 ($N(CH_3)_2$)
			3,5-dibromo 1-oxide[f] (105–109/0.05 torr)	80	8, 9	*j*			7.66		8.08	3.30 ($N(CH_3)_2$)
			74	74	35, 26	*j*						
4-NH_2	61	D	3-bromo[k] (181–182.5)	81	45	*i*	8.42			6.64	8.15	
			3,5-dibromo[l] (156–158)	82	48	*i*	8.35				8.35	
4-$N(CH_3)_2$	62	B	3-bromo (83–85)	83	93	*m*	8.52			6.83	8.39	3.00 ($N(CH_3)_2$)
4-OCH_3[r]	63	B	hydrolysis									
4-NH_2[r]	64	B, D	3-bromo[f] 1-oxide (195.5–197)	84	46, 61	*i*	8.73			6.68	8.66	7.40 (NH_2)
			3,5-dibromo 1-oxide[f] (171–173)	85	45, 34	*i*	8.85			6.68	8.55	8.35 (NH_2)
4-$NHCH_3$[r]	65	B	3-bromo (96–99/0.05 torr)	86	39	*j*	8.32			6.50	8.38	3.32 ($NHCH_3$), 4.90 (NH)
			3,5-dibromo 1-oxide (127–129/0.05 torr)	87	47	*j*	8.34				8.34	3.32 ($NHCH_3$), (NH)
			3-bromo deox (96)[n]	96	5	*j*						
4-$N(CH_3)_2$[r]	66	B	3-bromo 1-oxide (103–105/0.05 torr)	88	77	*j*	8.28			6.55	8.20	3.15 ($N(CH_3)_2$)
			83	83	8	*j*						
3-OCH_3[r]	67	B	2,6-dibromo 1-oxide (203–205)	89	37	*o*			7.60	6.70		3.94 (OCH_3)
			4,6-dibromo 1-oxide (189–190.5)	90	33	*o*	8.17			7.81		3.99 (OCH_3)
			4,6-dibromo deox (97)[n]	97	3	*o*						
3-NH_2[r]	68	D	2,6-dibromo[p] 1-oxide (156–157)	91	31	*g*			8.22	7.31		6.71 (NH_2)
			2,4,6-tribromo 1-oxide[f] (231–234)	92	46	*g*				8.52		5.42 (NH_2)
			2,6-dibromo deox (98)[n]	98	3	*g*						
			2,4,6-tribromo deox (99)[n]	99	7	*g*						
3-$NHCH_3$[r]	69	B	2,6-dibromo[p] 1-oxide (126–128.5/0.05 torr)	93	22	*j*			8.10	7.73		3.20 ($NHCH_3$)
			2,4,6-tribromo 1-oxide[p] (141–144/0.05 torr)	94	35	*j*				8.27		3.31 ($NHCH_3$)
			2,6-dibromo[p] 1-oxide (126–128.5/0.05 torr)	100	8	*j*						
			2,4,6-tribromo deox (100)[n]	101	6	*j*						
3-$N(CH_3)_2$[r]	70	B	2,6-dibromo 1-oxide (68–70/0.05 torr)	95	66	*j*			8.13	7.75		3.28 ($N(CH_3)_2$)
			2,6-dibromo deox (102)[n]	102	13	*j*						

[a] Elemental analyses (C, H, N) for all compounds were within ±0.3% of the calculated values. [b] Melting points were taken on a Thomas-Hoover melting point apparatus. [c] All spectra were recorded as dilute solutions in $CDCl_3$ except where otherwise indicated. [d] Downfield from Me_4Si. [e] TLC (neutral alumina) unless otherwise indicated. [f] Me_2SO-d_6. [g] 85:15 methylene chloride/acetonitrile. [h] Petroleum ether. [i] Silica, methylene chloride. [k] In Me_2SO-d_6: H-2, δ 8.68; H-5, δ 7.15; H-6, δ 8.43; NH_2, δ 6.71. [l] In Me_2SO-d_6: H-2, δ 8.71; H-6, δ 8.71. [m] 80:20 hexane/ether. [n] Not isolated; identification was accomplished by ^{1}H spectral comparison with the literature data. [o] Benzene. [p] Acetone-d_6 and $CDCl_3$ were employed since the isolated hydrate gave a nonhomogeneous solution in $CDCl_3$ only. [q] 50:50 methylene chloride/benzene. [r] 1-Oxide.

Scheme II



109: X=N, Y=CH

110: X=CH, Y=N

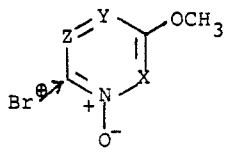
111: X=Y=CH

112

113

position para to the substituent followed by substitution at the ortho position is noteworthy, since this is *not* the case with 2-substituted pyrazine 1-oxides, where the first position that undergoes electrophilic substitution is the ortho one.

(2) Among the methoxy *N*-oxides, bromination always takes place as long as the *N*-oxide as well as the substituent activates the same positions (3-methoxypyridine *N*-oxide, 3-methoxypyrazine 1-oxide, 3-methoxy-1,2,4-triazine 1-oxide) toward electrophilic substitution. In 5-methoxypyrimidine 1-oxide the activated sites, located ortho to the nonoxidized nitrogen, are deactivated by it. Thus, this compound is *not* brominated. This argument predicts that 3-methoxypyridazine 1-oxide should be halogenated preferentially at C-6, followed by C-4.



(a) When Z = N, bromination does not take place

(b) When either X or Y, both, or neither are N, bromination occurs

(3) In order to account for the formation of the brominated non-*N*-oxides obtained from 3-amino-1,2,4-triazine 2-oxides,[4] 2-, 3-, and 4-aminopyridine 1-oxides, 3-aminopyrazine 1-oxides, and 3-aminopyridazine 1-oxide, we need to consider the nucleophilic deoxygenative bromination mechanisms we proposed in the 1,2,4-triazine *N*-oxide series[3,4] (see Scheme I). In the 1,2,4-triazine 2-oxide instance, **104**: X = Y = N), the intermediate resulting from nucleophilic attack at C-6 is stabilized by the presence of the nitrogen at X. The formation of the deoxygenated product follows the indicated paths (**106** → **107** → **108**). In the 2-aminopyrimidine *N*-oxide **104** (X = CH, Y = N) instance **106** (X = CH, Y = N) cannot be stabilized by formation of a comparable anion (since X = CH and not N), and consequently no deoxygenated bromo derivatives are obtained. However, when Y = CH and X = N, as in 3-aminopyridazine 2-oxide, the intermediate **106** (X = N, Y = CH) and deoxygenated products are, in fact, obtained.

In the 3-amino 1-oxide instances **109–111**, the deoxygenative bromination mechanism shown in Scheme II can be considered.

The initial step involves protonation (or reaction with Br^+) of the N–O oxygen. Thus, the more nucleophilic this oxygen is, i.e., the less back-bonding that is occurring, the more likely becomes the nucleophilic substitution–deoxygenation path **112** → **113**. We have already shown[4] that when X = Y = N (1,2,3-triazine 1-oxides), the amount of back-bonding is so strong as to prevent facile protonation of the oxygen, and no brominated deoxygenated products are obtained from these compounds. When either Y or X is N (X or Y is CH), as in pyrazines or pyridazines, respectively, the nucleophilicity of the oxygen is sufficient to allow this path to take place, and, consequently, some deoxygenated products are obtained. Finally, in the pyridine series (Table III) where X and Y are CH, the amount of back-donation is minimal, and some deoxygenated products are obtained.

(4) Since sublimation of 2-amino-5-bromopyridine *N*-oxide (**75**) causes some deoxygenated product to be formed, it is conceivable that the small amounts of 3-bromo-4-(methylamino)- and 3-bromo-4-(dimethylamino)pyridines obtained may, as well, have been formed through a thermal process. Mechanistic studies to account for these thermal deoxygenations are in progress.

Experimental Section[8]

General Procedure A. Reaction of 2-(Dimethylamino)-pyrazine 1-Oxide in the Presence of Et_3N. To a solution of 139 mg (1 mmol) of 2-(dimethylamino)pyrazine 1-oxide dissolved in 30 mL of CCl_4 was added 320 mg (2 mmol) of Br_2. The solution was stirred at room temperature for 30 min, and 151 mg (115 mmol) of triethylamine was added. Stirring was continued until TLC showed that all of the starting material had been consumed (2 h). The solvent was then removed in vacuo, and the residue was chromatographed on neutral alumina (grade III) with CH_2Cl_2 as the eluent. The resulting component mixture was separated by thin-layer chromatography with 50:50 $CHCl_3/C_6H_6$ as the eluent to give 196 mg (90%) of 3,5-dibromo-2-(dimethylamino)pyrazine 1-oxide (**23**).

General Procedure B. Reaction of 3-Methoxypyrazine 1-Oxide in the Presence of K_2CO_3. To a solution of 126 mg (1 mmol) of 3-methoxypyrazine 1-oxide in 20 mL of dry CCl_4 were added 1.94 mmol of Br_2 and 1.94 mmol (278 mg) of K_2CO_3. The resulting suspension was stirred for 6 h, and the solvent was removed in vacuo. The residue was passed through 15 mL of neutral alumina (grade III) with CH_2Cl_2. The main component was separated as above to give 92 mg (45%) of 6-bromo-3-methoxypyrazine 1-oxide (**26**).

General Procedure C. Reaction of 2-(Dimethylamino)-pyrazine 1-Oxide with NBS. To a solution of 139 mg (1 mmol) of 2-(dimethylamino)pyrazine 1-oxide dissolved in 40 mL of CH_2Cl_2 was added 354 mg (2 mmol) of *N*-bromosuccinimide (NBS). The solution was stirred for 48 h, after which time the solvent was removed under reduced pressure. The residue was passed through 15 mL of neutral alumina (grade III) with CH_2Cl_2. The resulting material was further purified as above to give 179 mg (82%) of 3,5-dibromo-2-(dimethylamino)pyrazine 1-oxide (**23**).

General Procedure D (for Slightly Soluble Amine Oxides). Reaction of 3-Aminopyrazine 1-Oxide with Bromine. To a solution of 211 mg (1.9 mmol) of 3-aminopyrazine 1-oxide dissolved in 100 mL of CH_2Cl_2 and 40 mL of CH_3CN was added 4.4 mmol (704 mg) of Br_2, and the solution was stirred for 2 h.

(8) Starting materials were prepared by the procedures described in: Humphrey, S. Ph.D. Dissertation, Ohio University, Athens, OH, 1968 and references given therein.

$NaHCO_3$ (420 mg, 49 mmol) was then added, and stirring was continued for 1 h. The progress of the reaction was monitored by TLC (CH_3CN, silica gel). The resulting mixture was filtered and the solvent evaporated. The residue was purified by thick-layer chromatography with silica gel (grade III) and CH_3CN as the eluent to give 255 mg (95%) of 2,6-dibromo-3-aminopyrazine 1-oxide (**27**).

General Comments. The experimental variables applicable to other compounds are listed in Tables I–III.

It is of some importance to note that bromination conditions were kept constant. Minor alterations were sometimes necessary in order to compensate for the physical properties of the reagents. For instance, acetonitrile was added to the methylene chloride in order to dissolve the amino compounds.

Registry No. **3**, 5049-61-6; **4**, 5214-29-9; **5**, 5625-94-5; **7**, 21720-40-1; **8**, 84539-02-6; **9**, 84539-03-7; **10**, 84539-04-8; **11**, 84539-05-9; **12**, 23902-69-4; **13**, 6863-77-0; **14**, 84539-06-0; **15**, 13134-49-1; **16**, 24241-18-7; **17**, 84539-07-1; **18**, 84539-08-2; **19**, 21943-12-4; **20**, 84539-09-3; **21**, 84539-10-6; **22**, 84539-11-7; **23**, 84539-12-8; **24**, 84539-13-9; **25**, 84539-14-0; **26**, 84539-15-1; **27**, 84539-16-2; **28**, 84539-17-3; **29**, 84539-18-4; **31**, 109-12-6; **32**, 931-61-3; **33**, 57356-66-8; **35**, 35034-15-2; **36**, 84539-19-5; **37**, 591-54-8; **38**, 22632-10-6; **39**, 31401-45-3; **41**, 84539-20-8; **42**, 84539-21-9; **44**, 7752-82-1; **45**, 31402-54-7; **46**, 84539-22-0; **47**, 84539-23-1; **48**, 84539-24-2; **49**, 1439-10-7; **50**, 56181-38-5; **51**, 84539-25-3; **52**, 84539-26-4; **53**, 84539-27-5; **55**, 504-29-0; **56**, 5683-33-0; **58**, 14150-95-9; **59**, 54818-70-1; **60**, 3618-79-9; **61**, 504-24-5; **62**, 1122-58-3; **63**, 1122-96-9; **64**, 3535-75-9; **65**, 1122-92-5; **66**, 1005-31-8; **67**, 14906-61-7; **68**, 1657-32-5; **69**, 54818-71-2; **70**, 36100-40-0; **71**, 1072-97-5; **72**, 35486-42-1; **73**, 84539-28-6; **74**, 26163-07-5; **75**, 696-15-1; **76**, 84539-29-7; **77**, 84539-30-0; **78**, 84539-31-1; **79**, 84539-32-2; **80**, 84539-33-3; **81**, 13534-98-0; **82**, 84539-34-4; **83**, 84539-35-5; **84**, 84539-36-6; **85**, 84539-37-7; **86**, 84539-38-8; **87**, 84539-39-9; **88**, 84539-40-2; **89**, 84539-41-3; **90**, 84539-42-4; **91**, 84539-43-5; **92**, 84539-44-6; **93**, 84539-45-7; **94**, 84539-46-8; **95**, 84539-47-9; **97**, 84539-48-0; **98**, 39856-57-0; **99**, 84539-49-1; **100**, 84539-50-4; **101**, 84539-51-5; **102**, 84539-52-6.

1,3-Dipolar Cycloaddition Reactions of Diazopyrazolinones with Electron-Deficient Dipolarophiles

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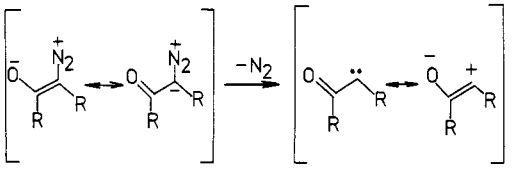
A study of the reactivity of a series of 4-diazopyrazolin-5-ones toward dipolar cycloaddition with electron-deficient olefinic and acetylenic dipolarophiles has been carried out. Reactions with dimethyl acetylenedicarboxylate afford pyrazolo[1,5-*d*][1,2,4]triazin-7-ones which result from dipolar cycloaddition followed by a van Alphen–Huttel rearrangement of the initially produced spiro 3*H*-pyrazole adducts. Reaction with unsymmetrical acetylenic esters afforded variable mixtures of regioisomeric pyrazolotriazinones and 1*H*-furo[2,3-*c*]pyrazoles. Product formation has been rationalized in terms of a substituent-dependent partitioning between spiro 3*H*-pyrazole adducts and ring-opened diazoalkenes. Spiro[pyrazoline-4,1′-cyclopropane]carboxylate esters were the only products isolated from reactions with acrylate ester.

Apart from the significance of diazoalkanes for the generation of carbenes,[1,2] these compounds also play a dominant role in dipolar cycloaddition chemistry.[3–5] Recent advances in the synthesis of diazoalkanes have frequently led to new application in cycloaddition chemistry.[6] α-Diazo ketones represent an interesting subclass of this family of dipoles since several discrete modes of intermolecular cycloaddition are possible.[7] Among these are those involving reaction as a 1,3-dipole, either through the diazoalkane moiety or through a reactive intermediate possessing the stoichiometry of a keto carbene species derived from an initial loss of nitrogen (see below). Much



less common modes of addition involving the extended 6-π-electron 1,5-dipolar system are also observed with certain quinonoid α-diazo ketones.[8] The use of extended diazoalkanes with six or more electrons has received little attention despite the obvious synthetic and theoretical interest in such processes.[9,10] When the diazo ketone moiety is incorporated into a heterocyclic ring, dipolar cycloaddition processes can provide ready access to more elaborate and rare heterocyclic ring systems. As part of a general program designed to study profiles of reactivity of diazoalkanes as 1,3-dipolar and/or extended dipolar systems,[11–13] we initiated a study dealing with representatives of the 4-diazopyrazolinone ring system. We now report on the mechanistic and regiochemical features as-

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