Registry No.—**3a,** 61788-10-1; **3b,** 61788-11-2; **4a,** 61788-12-3; **4b,** 61788-13-4; **9a,** 21383-22-2; **9b,** 38736-23-1; **9c,** 61788-14-5; **10a,** 61788-15-6; **10c,** 61788-16-7; **11a,** 61788-17-8; **11b,** 61788-18-9; **11c,** 61788-19-0; **12a,** 874-40-8; **12b,** 19542-10-0; **13a,** 57351-74-3; **13b,** 57250-39-2; **14,** 25623-69-2; **15a,** 61788-20-3; **15b,** 61788-21-4; **15c,** 61788-22-5; 2,5-dihydro-2-methyl-3-hydrazino-5-oxo-1,2,4-triazine, 39214-97-6.

References and Notes

(1) A. Dornow, H. Menzel, and P. Marx, *Chem. Ber.*, **97,** 2185 (1964).
(2) A. Dornow, H. Menzel, and P. Marx, *Chem. Ber.*, **97,** 2647 (1964).
(3) M. M. Goodman, J. L. Atwood, R. Carlin, W. Hunter, and W. W. Paudler, *J. Org. Chem.*, **41,** 2860 (1976).
(4) J. Daunis, R. Jacquir, and F. Viallefont, *Bull. Soc. Chim. Fr.*, 2492 (1969).
(5) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972.
(6) Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6M instrument on all new compounds. Their molecular ions and fragmentation patterns are consistent with the indicated structures. A Varian HA-100 instrument was used to record the ^{1}H NMR spectra. Melting points are corrected. Elemental analyses on all new compounds were performed by Atlantic Microlab. Inc., Atlanta, Ga., and the Analytical Services Laboratory, Department of Chemistry, The University of Alabama, and are within the accepted standards for C, H, and N analyses.

Selective N-Oxidations of Chlorinated Pyrazines and Quinoxalines

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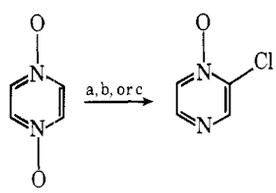
Chlorinated pyrazines and quinoxalines are specifically oxidized on the nitrogen adjacent to the halogen-bearing carbon by means of Caro's acid (peroxysulfuric acid) in concentrated sulfuric acid. This procedure affords the first simple, direct, and high-yield synthesis of 2-chloropyrazine 1-oxides. The use of lanthanide induced shift (LIS) reagents to unambiguously identify isomers was complicated by the presence of two nonequivalent coordination sites. The role of the strong-acid reaction medium in determining the steric course of oxidation is discussed.

Aromatic diazines in which the basicity of the ring nitrogens is severely reduced by electron-withdrawing substituents such as halogens are often resistant to N-oxidation by the usual peroxycarboxylic acid reagents.[2-4] The peracetic acid oxidations of chloropyrazines and chloroquinoxalines occur in such a manner that the most basic and least hindered nitrogen atom is oxidized exclusively.[2-5] In other words, N-oxidation of a pyrazine bearing a halogen substituent takes place on the nitrogen farthest removed from that substituent, e.g., 2-chloropyrazine → 2-chloropyrazine 4-oxide. Several 2-chloro 1-oxide isomers of pyrazine and quinoxaline have been prepared, but generally in low yield and indirectly from the bis *N*-oxide (eq 1).[6-11] Furthermore, dihalogenated py-



(1)

a, $POCl_3$
b, aq HCl, $h\nu$
c, $C_6H_5SO_2Cl$ or $SOCl_2$

razines are notoriously difficult to oxidize; 2,6-dichloropyrazine 4-oxide is obtained in only 4% yield by direct oxidation.[12]

Quite recently, several new oxidizing systems (peroxydichloromaleic acid,[13] CF_3CO_2H–H_2SO_4–90% H_2O_2,[14] and H_2SO_4–60% H_2O_2[15]) have been found to effect the oxidation of polyhalogenated diazines. The success of these novel reagents prompted us to extend the application of one of them to mono- and dichlorinated pyrazines and quinoxalines.

In terms of simplicity, cost, and availability of reagents, the oxidation procedure of Kyriacou appeared to be the method of choice for large-scale applications.[15] The handling of 60–90% hydrogen peroxide, however, presented serious safety implications. The conditions employed in such strong-acid oxidations, viz., sulfuric acid and hydrogen peroxide, suggest that the actual oxidizing agent is Caro's acid (peroxysulfuric acid). This being the case, this same intermediate could be generated from potassium persulfate and sulfuric acid, thus avoiding the use of potentially hazardous concentrated peroxide. Duplication of the previously reported oxidations of tetrachloropyrazine, substituting persulfate for peroxide, verified this hypothesis.

With a modified procedure which consisted of dissolving the halogenated diazine in sulfuric acid and of slowly adding potassium persulfate at 10 °C, a series of chlorinated pyrazines and quinoxalines were successfully converted to their *N*-oxides in high yield (see Experimental Section). Somewhat unexpectedly, however, the monochloropyrazines afforded the 2-chloro 1-oxide isomers in high purity. To verify the structural assignments of these derivatives, the 2-chloro 4-oxide isomers were prepared by known routes for comparison of physical and spectral properties. With the exception of the *N*-oxide isomers of 2,6-dichloropyrazine, all isomers could be distinguished by well-separated melting points. 2,6-Dichloropyrazine 1-oxide (mp 122–123.5 °C) and 2,6-dichloropyrazine 4-oxide (mp 119–121 °C) gave a typical mixture melting point depression (mp 85–90 °C).

The IR and NMR spectra of each pair of isomers are substantially different. All of the *N*-oxides display an N–O stretching frequency in the region of 1350–1260 cm^{-1}, but isomer identification by this method (1-oxides exhibit a deviation to lower frequencies than the corresponding 4-oxides)[8,9] was deemed tenuous because more than one substituent was present in most cases. The NMR spectra, however, are more informative (see Table I). Based on an examination of these data and on the shielding effects of the *N*-oxide function,[9] the following corollary can be formulated: *a given ring proton will generally resonate at higher field in 2-chloropyrazine 4-oxides than in the corresponding 1-oxide isomers.* While this criterion is useful in distinguishing between a pair of isomers, its utility is limited in that both isomers should be available for direct comparison.

In an attempt to develop a method to unambiguously identify a single isomer, the effects of lanthanide induced

Table I. Chemical Shift Data for Heteroaromatic Protons of Chloropyrazines and Chloroquinoxalines and Their *N*-Oxides

Registry no.	Compd		δ, ppm	Registry no.	Compd		δ, ppm
14508-49-7	I	a	8.70	5227-59-8	XIII	a	8.38
		b	8.46				
		c	8.63				
6863-76-9	II	a	8.12	5227-57-6	XIV	a	8.75
		b	7.96				
		c	8.22				
16025-16-4	III	a	8.62	4858-85-9	VII	a	8.40
		b	8.36				
		c	8.22				
95-58-9	IV	a	8.20	61689-43-8	VIII	a + b	8.15
61689-41-6	V	a	8.20	4774-14-5	IX	a	8.60
61689-42-7	VI	a	8.48	14399-36-1	X	a	8.02
1448-87-9	XII	a	8.75	61655-70-7	XI	a	8.50

Table II. Direct Oxidation of Halogenated Pyrazines and Quinoxalines

Substrate	Registry no.	Method	Product[25]	Registry no.	% yield	Mp, °C
		a	1-Oxide		55	131–132 (lit.[9] 133–134)
		b	4-Oxide		22	94–95 (lit.[5] 95–96)
		a	1-Oxide		40	105–109 (lit.[7] 106–109)
		b	4-Oxide		42	110–112 (lit.[7] 116–117)
		a	1-Oxide		62	122–123
		b	4-Oxide		1.2	119–121 (lit.[12] 123–125)
		a	1-Oxide		85	104–106
		b			0	
	13484-50-9	a	1-Oxide	27338-53-0	65	216–218 (lit.[26] 216–218)
		c	1,4-Dioxide	32051-15-3	70	315 (lit.[15] 310)
		a	1-Oxide		52	110–112 (lit.[10,11] 114)
		b	4-Oxide		6	150–152 (lit.[10] 152–153)
	32601-86-8	a	1-Oxide	61689-44-9	32	105–106
		b	4-Oxide	61689-45-0	31	89–91
	2213-63-0	a	1-Oxide	53870-24-9	80	138–139 (lit.[11] 138–139)
		b			0	

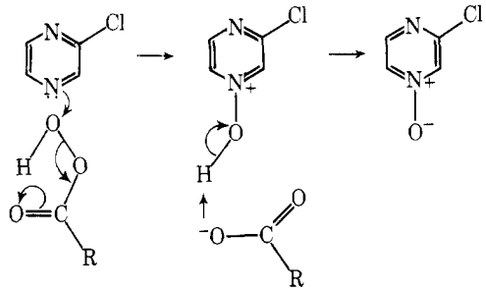
[a] H_2SO_4–$K_2S_2O_8$. [b] HOAc–30% H_2O_2. [c] 2 equiv of $K_2S_2O_8$–H_2SO_4.

shifts (LIS) on the NMR spectra of chlorinated pyrazine *N*-oxides were qualitatively examined. The site of coordination between such difunctional substrates and a shift reagent depends upon the basicity of the individual groups.[16–18] Both the oxygen of the *N*-oxide and heterocyclic nitrogen can effectively coordinate with lanthanide shift reagents,[17,18] and only one example of both functionalities in the same molecule has been reported.[19] From Rondeau's work,[19] one might expect the *N*-oxide to be the preferential site of coordination. However, steric conditions in the vicinity of the basic center are an equally important factor.[16] The LIS for a series of isomeric pyrazine and quinoxaline *N*-oxides with europium(III) tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dione) indicate that coordination at only one site is inconsistent with

the observed behavior.[20] Although positive isomer identification is unfeasible, LIS proved most useful for resolving the accidental degeneracy of the ring protons in 2,3-dichloropyrazine 1-oxide.

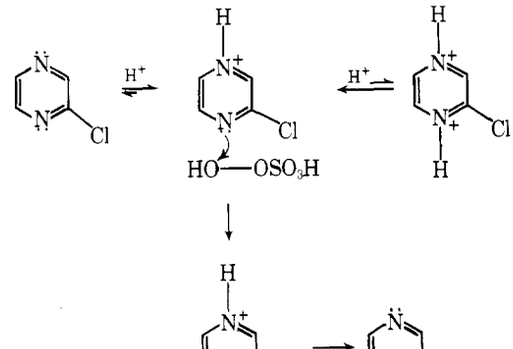
With the course of the reaction verified, the scope of the persulfate oxidation was investigated. In general, the oxidation terminates at the mono *N*-oxide stage regardless of the amount of oxidizing agent employed. The attempted oxidation of 2-chloropyrazine 4-oxide under similar conditions also fails to give any bis *N*-oxide. Only in the case of tetrachloropyrazine is the bis *N*-oxide obtained. Furthermore, the persulfate oxidation method is apparently limited to 1,4-diazines, as polyhalogenated pyridines and pyrimidines are recovered unchanged and pyridazines are hydrolyzed or oxidatively cleaved.[21] Although the yields are generally lower, 30% H_2O_2 can replace $K_2S_2O_8$ as the precursor to the actual oxidizing agent (Caro's acid). Therefore, the orientation of this oxidation is solely dependent on the strong acid medium.

The generally accepted mechanism of N-oxidation involves the nucleophilic attack of the lone pair of electrons on nitrogen on the outermost oxygen of the peracid (eq 2).[2-4] The progress



(2)

of the reaction depends primarily on the basicity (nucleophilicity) of the nitrogen atom and on the ability of the oxidizing agent to form a positively polarized (electrophilic) outermost oxygen. The orientation of the peracetic acid oxidation of chlorinated pyrazines (the exclusive formation of 2-chloro 4-oxide isomers) is governed by the relative basicities of the ring nitrogens.[2-5] In sulfuric acid at low pH, the equilibrium strongly favors the protonation of the most basic nitrogen, effectively eliminating it as a reaction center (eq 3).



(3)

Although the nucleophilicity of the remaining nitrogen is reduced by both the electron-withdrawing chlorine and protonated nitrogen, the electrophilicity of persulfuric acid is sufficient to effect oxidation. As with the peracetic acid case, the regiospecificity of the oxidation is controlled by the relative basicities of the pyrazine nitrogens.

Recent work has established that protonation of pyrazine and quinoxaline monooxides occurs preferentially on the unoxidized nitrogen atom.[22,23] This observation explains the inability to form bis *N*-oxides with any substrate except tetrachloropyrazine where perhalogen substitution sufficiently reduces the basicity of the unoxidized nitrogen to allow oxidation to compete with protonation.

Experimental Section

Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were run on a T-60 spectrometer in $CDCl_3$ with a Me_4Si internal standard at a probe temperature of 39 °C. Elemental analyses were performed by Dow Analytical Services, Midland, Mich. The experimental data are summarized in Table II.[24,25] The following example is illustrative of the general synthetic procedure.

2,3-Dichloropyrazine 1-Oxide. To a stirred solution of 150 g (~1 mol) of 2,3-dichloropyrazine in 1 L of sulfuric acid at 10 °C is gradually added 300 g (~1.1 mol) of potassium persulfate. The reaction mixture is stirred for 24 h at room temperature and carefully poured into 3 L of ice water. The aqueous solution is extracted with chloroform and the extract is washed with bicarbonate solution and brine and then dried over magnesium sulfate. Evaporation of the solvent affords a white solid which is recrystallized from alcohol to give 140 g (85%) of white needles.

For lower halogenated pyrazines and quinoxalines, 30% hydrogen peroxide can be substituted for potassium persulfate with only small decreases in yield.

Note: Halogenated pyrazine N-oxides have been found to be severe skin and eye irritants and necessary precautions are required to prevent contact.

Supplementary Material Available. A table of the LIS shifts (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) Address correspondence to Organic Chemicals Research, 1710 Building, Dow Chemical USA, Midland, Mich. 48640.
(2) E. Ochiai, "Aromatic Amine Oxides", Elsevier, Amsterdam, 1967.
(3) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides", Academic Press, New York, N.Y., 1971, Chapter 2.
(4) G. W. H. Cheeseman and E. S. G. Werstiuk, *Adv. Heterocycl. Chem.*, **14**, 99 (1972).
(5) B. Klein, N. E. Hetman, and M. E. O'Donnell, *J. Org. Chem.*, **28**, 1682 (1963).
(6) L. Bernardi, G. Palamidessi, A. Leone, and G. Larini, *Gazz. Chim. Ital.*, **91**, 1431 (1961).
(7) K. W. Blake and P. G. Sammes, *J. Chem. Soc. C*, 1070 (1970).
(8) H. Shindo, *Chem. Pharm. Bull.*, **8**, 33 (1960).
(9) S. Okada, A. Kosasayama, T. Konno, and F. Uchimara, *Chem. Pharm. Bull.*, **19**, 1344 (1971).
(10) G. W. H. Cheeseman and E. S. G. Torzs, *J. Chem. Soc. C*, 157 (1966).
(11) J. M. Cox, R. T. V. Fox, and R. A. Burrell, U.S. Patent 3 903 281 (1975).
(12) G. Palamidessi, L. Bernardi, and A. Leone, *Farmaco, Ed. Sci.*, **21**, 805 (1966).
(13) A. Pollak, M. Zupan, and B. Sket, *Synthesis*, 495 (1973).
(14) G. E. Chivers and H. Suschitzky, *Chem. Commun.*, 28 (1971).
(15) D. Kyriacou, *J. Heterocycl. Chem.*, **8**, 697 (1971).
(16) R. von Ammon and R. D. Fischer, *Angew. Chem., Int. Ed. Engl.*, **11**, 675 (1972).
(17) A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, **73**, 553 (1973).
(18) B. C. Mayo, *Chem. Soc. Rev.*, **2**, 49 (1973).
(19) R. E. Rondeau, R. E. Steppel, H. M. Rosenberg, and L. E. Knaak, *J. Heterocycl. Chem.*, **10**, 495 (1973).
(20) See paragraph at end of paper regarding supplementary material.
(21) Hexachloroquinoxaline is hydrolyzed to tetrachloro-1,4-dihydro-2,3-quinoxalinedione under the reaction conditions.
(22) B. Klein, J. Berkowitz, and N. E. Hetman, Abstracts, 138th National Meeting of the American Chemical Society, New York, N.Y., 1960, p 89P.
(23) G. G. Dvoryantseva, M. M. Kaganskii, I. S. Musatova, and A. S. Elina, *Khim. Geterotsikl. Soedin.*, 1554 (1974).
(24) Reported yields refer to recrystallized products following the prescribed workup. In general the aqueous solution of the reaction mixture is extracted with 1-2 volumes of chloroform. The organic layer contains the product and traces of unoxidized substrate. Because of the appreciable water solubility of the *N*-oxides, often significant quantities of product remain in the aqueous layer along with unknown water-soluble oxidation products. Continuous or repeated extraction significantly improves the isolated yields of all but the methyl derivatives.
(25) Satisfactory analytical data were reported for all new compounds listed in the table.
(26) H. Johnston, U.S. Patent 3 509 144 (1970).