Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.05; H, 4.84; N, 13.39.

Acknowledgment.—We thank Mr. Marvin J. Olsen and Mr. Gerald Reiser for the nmr and uv spectra.

Registry No.—**4** (R = H), 13300-21-5; **4** (R = Ac), 40919-19-5; **4** (R = SO_2-*p*-tolyl), 40919-20-8; **4** (R = Et), 40919-21-9; **9**, 1640-60-4; **10** (R = *p*-tolyl), 40919-23-1; **10** (R = Me), 40919-24-2; **10** (R = *p*-nitrophenyl), 40919-25-3; **11**, 40919-26-4; **12**, 40919-27-5; phosphorus pentachloride, 10026-13-8; tosyl chloride, 98-59-9; 3-hydroxyanthranilic acid, 548-93-6.

Quinoxaline 1,4-Dioxides. Nucleophilic Displacement of Sulfinyl and Sulfonyl Groups in Acid Media. A Novel Method for the Preparation of 2-Haloquinoxaline 1,4-Dioxides

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The oxidation of the quinoxaline 1,4-dioxides **2a** and **2b** with *1* or *2* equiv of *m*-chloroperbenzoic acid furnished the corresponding sulfoxides (**3a** and **3b**) and sulfones (**4a** and **4b**), respectively, in high yields. Treatment of these compounds with aqueous halogen acids furnished the corresponding 2-haloquinoxaline 1,4-dioxides (**5**), almost in quantitative yields. The action of organic acids on these sulfoxides and sulfones produced, instead of the expected 2-acyloxy derivatives, esters of 1-hydroxyquinoxalin-2-one 4-oxide (**6**). The mechanism and the potential synthetic utility are discussed.

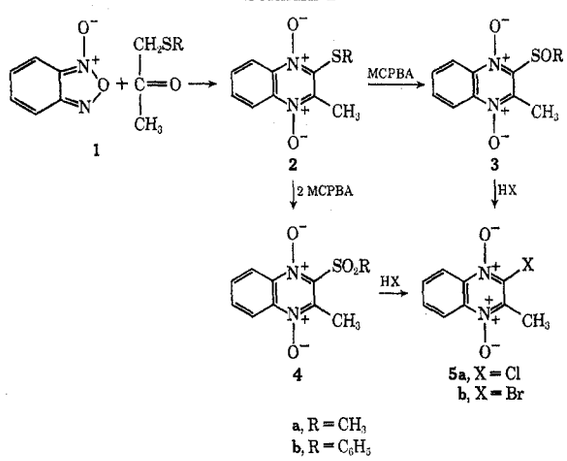
There are three general methods for the preparation of quinoxaline 1,4-dioxides: peracid oxidation of the parent amine,[2] the condensation of enamines and enolates with benzofurazan 1-oxide (BFO, **1**),[3] and the condensation of α diketones with *o*-benzoquinone dioxime.[4] However, none of these methods can be used for the synthesis of 2-haloquinoxaline 1,4-dioxides, owing to difficulties encountered in the oxidation of 2-halo aromatic amines, and the failure of 2-halo ketones to react successfully with BFO. The present work describes a novel nucleophilic displacement of sulfinyl and sulfonyl groups which provides a simple method for the synthesis of 2-haloquinoxaline 1,4-dioxides in high yield.

Preparation of the starting materials was accomplished according to earlier procedures.[3] Thus, condensation of BFO with acetonylmethyl sulfide and acetonylphenyl sulfide[5] furnished the corresponding quinoxaline 1,4-dioxides **2a** and **2b**, respectively (50–60%). These were in turn oxidized with either *1* or *2* equiv of *m*-chloroperbenzoic acid (MCPBA) to yield the corresponding sulfoxides (**3a** and **3b**) and sulfones (**4a** and **4b**), respectively, in 80–90% yields.

Treatment of **3** or **4** with aqueous hydrochloric or hydrobromic acid under mild conditions gave the quinoxaline 1,4-dioxides **5a** and **5b**, respectively, almost in quantitative yields. Scheme I summarizes the above reactions.

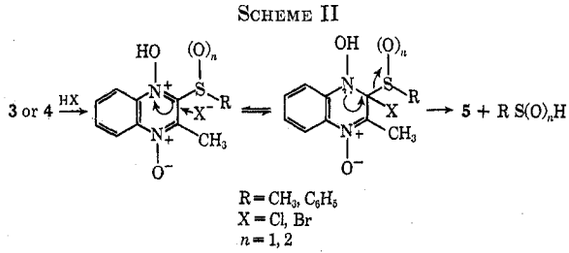
The structures of **5a** and **5b** were based on mass spectral data, which showed the expected molecular ion doublets indicating the presence of chlorine and bromine. The nmr spectra of **5a** and **5b** were consistent with the proposed structures and each consisted of a three-hydrogen methyl singlet at δ 2.76 (**5a**) and 2.88 (**5b**). The typical aromatic A_2B_2 pattern observed for other quinoxaline 1,4-dioxides was preserved in **5a** and **5b** and appeared at δ 7.78 and 8.6.

SCHEME I



A plausible mechanism for these reactions is depicted in Scheme II.

SCHEME II



Initial protonation of the *N*-oxide group is probably involved followed by halide attack at C-2, with subsequent elimination of a sulfinic or sulfenic acid. Support for this mechanism came from the reaction of hydrochloric acid with the phenyl sulfoxide **3b**. In addition to the chloro compound **5a**, there were isolated two additional compounds, namely diphenyl disulfide[6] and *S*-phenyl benzenethiosulfonate[7] in 84

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(2) E. Ochiai, "Aromatic Amine Oxides," Elsevier, New York, N. Y., 1967, pp 31, 35, 44.

(3) (a) M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 3253 (1965); (b) *J. Org. Chem.*, **31**, 4067 (1966).

(4) E. Abushanab, *J. Org. Chem.*, **35**, 4279 (1970).

(5) C. K. Bradsher, R. C. Brown, and R. J. Grantham, *J. Amer. Chem. Soc.*, **76**, 114 (1954).

(6) F. Krafft and W. Vorster, *Chem. Ber.*, **26**, 2815 (1893).

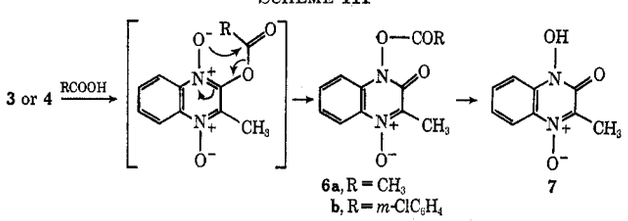
(7) H. J. Backer, *Recl. Trav. Chim., Pays-Bas*, **71**, 409 (1952).

and 90% yields, respectively. These compounds are known to originate, by disproportionation,[8] from the unstable benzenesulfenic acid initially formed.

When the sulfone **4a** was dissolved in glacial acetic acid at room temperature, a new compound was formed in 40% yield which was not the expected 2-acetoxy product but rather 1-acetoxy-3-methylquinoxalin-2-one 4-oxide (**6a**). The characterization of **6a** was based upon its ir spectrum, which showed two carbonyl absorptions at 5.5 and 5.8 μ. The nmr spectrum had signals for two methyl singlets at δ 2.5 and 2.58 but did not have the usual aromatic A_2B_2 multiplet. Instead it had two separate one-proton quartets (J = 7.5, 2.0 Hz) at δ 7.7 and 8.3 assigned to protons at C-8 and C-5, respectively, and a multiplet for the two remaining protons (δ 7.15–7.5). Upon heating the sulfoxide **3a** with acetic acid, two products were obtained, namely the acetate **6a** and its hydrolysis product **7**, in 13 and 44% yields, respectively. Similar results were obtained during the preparation of the sulfone **4b**. Heating the sulfide **2b** with MCPBA in chloroform resulted in the formation of **6b**, presumably from the reaction of the sulfone with *m*-chlorobenzoic acid. The use of pH 7.5 phosphate buffer as part of a two-phase system allowed the successful isolation of **4b**.

Similar arguments can be used to explain the action of organic acids on these compounds. Initial formation of the 2-acyloxy derivative followed by acyl migration to the *N*-oxide oxygen results in **6**, whose hydrolysis affords **7** (Scheme III). Transacylation

SCHEME III



involving other forms of *N*-oxides have recently appeared. Shemyakin and coworkers reported acetyl migrations to aldonitrones[9] and transtosylation in the thermal rearrangement of β-phenyl azoxytosylates.[10] Skramstad proposed a similar mechanism to explain the migration of an acetyl group to the oxygen of a nitro group.[11]

Several analogies for the reactions of sulfones with aqueous acid are known.[12] In the case of sulfoxides, however, only one such reaction has been found, which involves the acid hydrolysis of 2-methylsulfinyladenine 1-oxide to isoguanine 1-oxide.[13]

The above reactions, therefore, provide an attractive method for the preparation of 2-haloquinoxaline 1,4-dioxides, which can be used as intermediates for the synthesis of other classes of quinoxaline 1,4-dioxides, *e.g.*, 2-amino-, 2-alkoxy-, etc., not easily accessible by existing methods.

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(12) See, for example (a) C. W. Noell and R. K. Robins, *J. Amer. Chem. Soc.*, **81**, 5997 (1959); (b) M. Saneyoshi and M. Ikehara, *Chem. Pharm. Bull.*, **16**, 1390 (1968).

(13) R. M. Cresswell and G. B. Brown, *J. Org. Chem.*, **28**, 2560 (1963).

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover capillary apparatus. Nmr spectra were obtained on a Varian A-60 instrument. Mass spectral data were recorded on a Perkin Elmer RMV-65 mass spectrometer. The commercially available MCPBA is 88% pure, and was used as such without purification. All evaporations were conducted *in vacuo* using a water aspirator.

2-Methyl-3-methylthioquinoxaline 1,4-Dioxide (2a).—Acetonylmethyl sulfide (30 g, 0.3 mol) and BFO (40 g, 0.3 mol) were dissolved in methanol (200 ml) and ammonia gas was bubbled in for 10 min. The reaction mixture was allowed to stand at room temperature overnight. The crystalline precipitate was filtered off and washed with methanol. The dried residue weighed 30 g. Crystallization from methanol gave the analytical sample, mp 146–148°, nmr ($CDCl_3$) δ 2.85 (s, 3), 2.95 (s, 3).

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.01; H, 4.50; N, 12.61. Found: C, 53.80; H, 4.52; N, 12.49.

2-Methylthio-3-phenylquinoxaline 1,4-Dioxide (2b).—Acetonylphenyl sulfide (8.3 g, 0.05 mol) and BFO (6.8 g, 0.05 mol) were dissolved in methanol (75 ml) and ammonia gas was bubbled in for 5 min. The product (7.0 g) was isolated and crystallized from methanol–chloroform, mp 153–154°, nmr ($CDCl_3$) δ 2.85 (s, 3).

Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.37; H, 4.23; N, 9.86. Found: C, 63.26; H, 4.11; N, 10.12.

2-Methyl-3-methylsulfinylquinoxaline 1,4-Dioxide (3a).—A solution of MCPBA (2.0 g, 5 mmol) in chloroform (15 ml) was added to an ice-cold solution of the sulfide **2a** (1.1 g, 5 mmol) in chloroform (10 ml) and the reaction mixture was stirred at room temperature overnight. The chloroform solution was washed with aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and evaporated to the finished product (1.2 g). Crystallization from methanol–chloroform furnished the analytical sample, mp 201–202°, nmr ($CDCl_3$) δ 2.92 (s, 3), 3.25 (s, 3).

Anal. Calcd for $C_{10}H_{10}N_2O_3S$: C, 50,42; H, 4.20; N, 11.76. Found: C, 50.27; H, 4.25; N, 11.83.

2-Methyl-3-phenylsulfinylquinoxaline 1,4-Dioxide (3b).—An identical procedure with that used in the preparation of **3a** was followed using the sulfide **2b** (7.0 g, 24 mmol) and MCPBA (5.1 g, 24 mmol). The product obtained weighed 8.6 g, and was crystallized from methanol–chloroform, mp 164–165°, nmr ($CDCl_3$) δ 2.9 (s, 3).

Anal. Calcd for $C_{15}H_{12}N_2O_3S$: C, 60.00; H, 4.00; N, 9.33. Found: C, 60.11; H, 4.25; N, 9.30.

2-Methyl-3-methylsulfonylquinoxaline 1,4-Dioxide (4a).—A solution of MCPBA (4.0 g, 10 mmol) in chloroform (30 ml) was added dropwise to an ice-cold solution of the sulfide **2a** (1.1 g, 5 mmol) in chloroform (15 ml), and the reaction mixture was stirred at room temperature overnight. Similar work-up to that used for the preparation of **3a** furnished the product (1.22 g). The analytical sample was obtained by crystallization from methanol–chloroform, mp 153–154°, nmr ($CDCl_3$) δ 2.92 (s, 3), 3.6 (s, 3).

Anal. Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.94; N, 11.02. Found: C, 47.05; H, 3.90; N, 10.97.

2-Methyl-3-phenylsulfonylquinoxaline 1,4-Dioxide (4b).—The sulfide **2b** (2.0 g, 7 mmol) was dissolved in chloroform (100 ml) and was added to phosphate buffer (pH 7.5, 100 ml). A solution of MCPBA (4.25 g, 21 mmol) in chloroform (50 ml) was added to the cooled two-phase system dropwise with vigorous stirring overnight. Thin layer chromotography on silica gel (1:1 EtOAc–benzene) indicated the presence of the desired product with small amounts of **6b**. Similar work-up to that of **4a** furnished the product (1.5 g), which is very sensitive to light. Crystallization from methanol–chloroform furnished the analytical sample, mp 180–181°.

Anal. Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.96; H, 3.79; N, 8.86. Found: C, 56.74; H, 3.70; N, 8.58.

2-Chloro-3-methylquinoxaline 1,4-Dioxide (5a).—The procedure described here for the conversion of **3b** to **5a** applies to all other sulfoxides and sulfones. The sulfoxide **3b** (2.0 g, 8.4 mmol) was dissolved in concentrated hydrochloric acid (10 ml). The solution was warmed up on the steam bath for few minutes. An

oily layer separated at the bottom of the reaction flask which was taken up in ether. Drying and evaporation gave an oil (0.7 g). The aqueous acidic layer was diluted with water (75 ml), precipitating the product (1.5 g). The analytical sample was obtained from methanol, mp 166–168°, nmr ($CDCl_3$) δ 2.80 (s, 3), M^+ 212 and 210.

Anal. Calcd for $C_9H_7N_2O_2Cl$: C, 51.30; H, 3.32; N, 13.25. Found: C, 51.32; H, 3.35; N, 13.38.

Thin layer chromotographc analysis of the above oil on silica gel (benzene) showed it to be a mixture of two compounds. Column chromotography (silica gel, 20 g) was used for their separation. Elution with hexane (300 ml) furnished diphenyl disulfide, mp 59–60° (0.28 g). Further elution with a 1:1 mixture of benzene–hexane (700 ml) gave *S*-phenyl benzenethiosulfonate (0.38 g) as a low-melting solid, mp 41–42°.

2-Bromo-3-methylquinoxaline 1,4-Dioxide (5b).—This compound was obtained using 48% HBr solution following the same procedure described for the preparation of **5a**. Crystallization from methanol–chloroform furnished the analytical sample, mp 163–164°, nmr ($CDCl_3$) δ 2.87 (s, 3), M^+ 256 and 254.

Anal. Calcd for $C_9H_7N_2O_2Br$: C, 42.35; H, 2.74; N, 10.98. Found: C, 42.12; H, 2.83; N, 11.03.

1-Acetoxy-3-methylquinoxaline-2-one 4-Oxide (6a). A.—The sulfone **4a** (1.0 g, 4 mmol) was dissolved in acetic acid (25 ml) and was allowed to stand at room temperature for 18 hr. Dilution with water (250 ml) was followed by extraction with chloroform. The chloroform layer was backwashed with water, dried over magnesium sulfate, filtered, and evaporated to dryness to give a gum (0.37 g). The analytical sample was obtained by crystallization from ether–chloroform without the use of heat, mp 142–143°, nmr ($CDCl_3$) δ 2.5 (s, 3), 2.57 (s, 3).

Anal. Calcd for $C_{11}H_{10}O_4N_2$: C, 56.41; H, 4.27; N, 11.96. Found: C, 56.38; H, 4.49; N, 11.77.

B.—The sulfoxide **3a** (2.5 g, 10 mmol) was dissolved in acetic acid (25 ml) by heating for 0.5 hr. Dilution with water (250 ml) was followed by extraction with chloroform. A similar work-up to that above gave a gum (1.9 g). This was chromatographed on Florisil eluting first with chloroform (400 ml) to give **6a** (0.32 g), followed by a 1:1 mixture of methanol–chloroform (500 ml) to furnish the hydroxamic acid **7** (1.0 g), mp 224–225°, identical with an authentic sample.[4]

1-*m*-Chlorobenzoxy-3-methylquinoxalin-2-one 4-Oxide(6b).—The sulfide **2b** (2.0 g, 7 mmol) was dissolved in chloroform (100 ml). To this solution MCPBA (2.83 g, 14 mmol) in chloroform (50 ml) was added and the resulting mixture was refluxed for 1 hr. One more equivalent of MCPBA (1.4 g) was added and the reaction mixture was refluxed for an additional 1 hr. The chloroform solution was first washed with a saturated solution of sodium bicarbonate (3 × 50 ml), and then with water, dried, filtered, and evaporated to dryness to yield a solid. The solid residue (0.6 g) was crystallized from methylene chloride–ether, mp 161–162°, nmr ($CDCl_3$) δ 2.6 (s, 3), M^+ 332 and 330.

Anal. Calcd for $C_{16}H_{11}N_2O_4Cl$: C, 58.09; H, 3.32; N, 8.47. Found: C, 57.98; H, 3.23; N, 8.40.

Acknowledgment.—The author wishes to thank Mr. Leo B. Keith, Jr., for his technical assistance.

Registry No.—**2a**, 39576-50-6; **2b**, 39576-56-2; **3a**, 39576-76-6; **3b**, 40735-40-8; **4a**, 39576-77-7; **4b**, 40735-42-0; **5a**, 39576-78-8; **5b**, 39576-79-9; **6a**, 40735-45-3; **6b**, 40735-46-4.

O-Nitrene and *O*-Nitrenium Cation Intermediates in Reactions of O-Substituted Hydroxylamines[1]

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Two methods were investigated for the generation of *O*-nitrenes (**3**) and/or *O*-nitrenium cations (**4**): lead tetraacetate oxidation of *O*-alkylhydroxylamines (**5**) and thermal base-catalyzed decomposition of *N*-*p*-toluenesulfonyl-*O*-alkylhydroxylamines (**6**). Lead tetraacetate oxidation of *O*-diphenylmethylhydroxylamine (**5a**) was solvent dependent and afforded mixtures of products containing *O*-diphenylmethylbenzophenone oxime, benzophenone, benzhydrol, and products corresponding to net O to N migration of Ph_2CH–, *N*-diphenylmethoxy-*N'*-diphenylmethyldiazine *N'*-oxide (**9**), and benzophenone oxime. *p*-Nitrobenzyl alcohol was the only product formed on oxidation of *O*-*p*-nitrobenzylhydroxylamine (**5b**) with lead tetraacetate. The stereochemical course of formation of *N*-alkoxyaziridines from lead tetraacetate oxidation of *O*-*n*-butylhydroxylamine in the presence of *cis*- and *trans*-2-butene was examined and found to be nonstereospecific. *trans*-2-Butene afforded *N*-*n*-butoxy-*trans*-2,3-dimethylaziridine (**12**) and *N*-*n*-butoxy-*cis*-2,3-dimethylaziridine (**13**) in an 82:18 ratio while the **12**:**13** ratio from *cis*-2-butene was 38:62. The dominant thermal reaction from **6** and sodium hydride involved O–N bond cleavage. Thus **6a** and excess sodium hydride gave benzhydrol as the major product which was shown to arise *via* cleavage of the carbanion of **6a** to benzophenone and *p*-toluenesulfonamide anion followed by reduction of benzophenone to benzhydrol. O to N migration was observed when either *n*-butyllithium or only small excesses of sodium hydride were used to yield benzophenone oxime (quantitative from *n*-butyllithium). No O to N migration was observed using **6c** or **6d** and NaH with the products being *p*-bromobenzoic acid and *p*-methoxybenzoic acid, respectively, probably arising *via* oxidation of the corresponding aldehydes. The suggestion is made that there is, as yet, no conclusive evidence for the intermediacy of **3** in any reactions of O-substituted hydroxylamines or its derivatives. Mechanisms not involving *O*-nitrenes are suggested including the possibility of organolead intermediates being the species undergoing O to N migration and addition to olefins in the lead tetraacetate oxidations, and fragmentation–recombination pathways for the base-catalyzed reactions of **6a**.

Species possessing an electron-deficient nitrogen have been proposed and, in some instances, detected as reactive intermediates in a great many organic reactions.[2] Even-electron intermediates of this type may be either nitrenes ($R\ddot{N}$:) or nitrenium ions (R^+-$\ddot{N}R'$), and each of these may exist either in a singlet or triplet electronic state with the triplet usually being lower in energy.[2c,3] If substituents are chosen so as to be able to interact electronically with the unfilled 2p orbital on nitrogen, the energy levels of the singlet and triplet states will be perturbed so that the singlet could become the ground state, *e.g.*, when R or R' is nitrogen, oxygen, or fluorine. With

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