

Background counts,  $B_1$ ,  $B_2$ , were measured for half the scan time at each end of the scan range. The sample ( $0.20 \times 0.10 \times 0.05$  mm) was exposed to the atmosphere throughout data collection. The intensities ( $2\theta_{\max} = 110^\circ$ ) were corrected for absorption<sup>22</sup> ( $\mu = 52.0 \text{ cm}^{-1}$ ) and converted to  $F^2$ . No attempt was made to correct the data for the  $\sim 7\%$  crystal decomposition evident in the decay of two check reflection intensities. Standard deviations were assigned according to  $\sigma(I) = (C = B_1 + B_2)^{1/2}$  where  $C$  is the total integrated reflection count. The positions of all nonhydrogen atoms were obtained by Patterson and Fourier methods, and refined together with their anisotropic thermal parameters, by full-matrix least-squares methods in which the quantity minimized was  $\sum w(|F_o|^2 - |F_c|^2)^2$  with  $w = 1/\sigma^2$ . Atomic scattering factors, including the anomalous components for bromine, were taken from the International Tables for X-ray Crystallography.<sup>23</sup> Further refinement of the nonhydrogen atoms, after introduction of the aromatic hydrogens at calculated positions, resulted in  $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.07$ . At this stage, the hydrogen atoms bonded to oxygen were located in a difference map, and included, though not refined, in the final least-squares calculations. A final difference map showed no peaks above  $0.7 \text{ e } \text{Å}^{-3}$ ; parameter shifts during the final cycle of refinement were approximately one-third of the estimated errors. The final  $R$  factors are  $R_1 = 0.06$ ,  $(\sum w(|F_o|^2 - |F_c|^2)^2 / \sum w F_o^4)^{1/2} = 0.14$ . The final fractional atomic coordinates are given in Table II while Table III presents the calculated bond distances and angles.

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**Supplementary Material Available:** Tables of temperature factors, and the observed and calculated structure factors (13 pages). Ordering information is given on any current masthead page.

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- To increase further the stability of the salts, several of the structures were sealed in Pyrex capillary tubes, and examined at  $-10$  to  $-25^\circ \text{C}$ ; some instability to light and X-rays has been reported.<sup>3,10</sup> The zwitterionic sulfonates were examined at ambient temperatures and apparently are quite stable.<sup>5,6</sup>
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- Deviations from linearity of a similar magnitude have been observed in crystal structures of several covalent cyanides. See, for example, K. Emerson and D. Britton, *Acta Crystallogr.*, **17**, 1134 (1964).
- The shortest N-Br distance (3.65 Å) in  $\text{C}_6\text{H}_5\text{N}_2^+\text{Cu}_2\text{Br}_3^-$  involves the inner nitrogen atom.<sup>7</sup>
- The possibility that this close approach reflects an electrostatic attraction between the diazonium cation and *carboxylate anion* (several short intermolecular distances, in the range 2.73–3.06 Å were observed between oxygen and nitrogen atoms in the zwitterionic structure of *p*-benzenediazonium sulfonate<sup>5</sup>) seems unlikely in view of the IR spectrum of lb and the observed geometry of atoms C11, O12, O13. The (unrefined) coordinates of the hydrogen, H12, between O12 and O16 lead to the calculated distances O12-H12 = 1.1 Å and O16-H12 = 1.5 Å. The alternative formulation of lb in which H12 is covalently bonded to the water would consist of  $\text{H}_3\text{O}^+\text{Br}^-$  ions hydrogen bonded to the zwitterionic naphthalene-2-diazonium-3-carboxylate. The crystal structure of the zwitterion<sup>17</sup> ( $\nu_{\max} 1630 \text{ cm}^{-1}$ ) prepared from lb and  $\text{Ag}_2\text{O}$  is currently under investigation in this laboratory. lb and ld have the same infrared carbonyl absorption frequencies even though in ld no comparable interaction exists between the carbonyl oxygen and the diazonium group.
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## Ozonation of Nucleophiles. 10. Ethers<sup>1</sup>

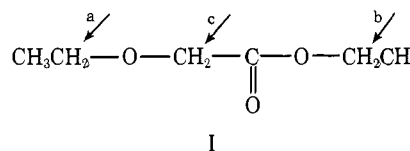
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**Abstract:** The ozonations of four ethers, ethyl isopropyl ether (VI), 4-oxa-2-heptanone (VII), 2-chloro-1-ethoxyethane (VIII), and ethyl ethoxyacetate (I), were studied in Freon 11 at  $0$ ,  $-30$ , and  $-78^\circ \text{C}$ , using ozone in a nitrogen stream. The ozone attack on VI was largely at the tertiary hydrogen, presumably by 1,3-dipolar insertion. The attack on VII occurred principally at the more acidic methylene group, as expected of internal oxidation, while the other two ethers were attacked, near equally, by both routes. Mechanisms of reactions leading from the initial attack to products are discussed.

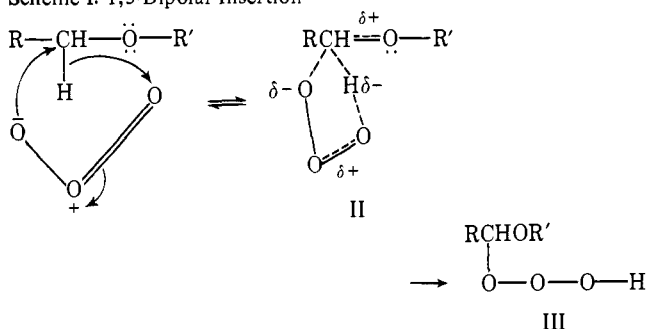
Diethyl ether appears to be the first organic substance ever ozonized, by Schönbein in 1855.<sup>2</sup> Other early studies with ethers were made by von Babo,<sup>3</sup> Berthelot,<sup>4</sup> Harries,<sup>5</sup> and Fischer.<sup>6</sup> More recently, the mechanism of ether ozonation has been investigated by Price and Tumulo<sup>7</sup> and by Erickson, Hansen, and Harkins.<sup>8</sup>

Price and Tumulo<sup>7</sup> showed that only carbon-hydrogen bonds  $\alpha$  to the ether oxygen were attacked and that the less acidic these were, the faster the ozonation. For example, the tertiary hydrogen of propyl isopropyl ether was found to be, on a statistical basis, 1.7 times more reactive than an  $\alpha$  secondary hydrogen. Likewise, for ethyl ethoxyacetate (I) the overall ozone attack was slow, but occurred at positions a, b,



and c, in the proportions 72:21:6.<sup>7</sup> The ozonations were carried out at room temperature with ozone in an oxygen stream. The fact that a maximum of 1.18 mol of ether reacted per mol of ozone consumed indicated that ozone was the major oxidant and that very little autoxidation was involved. Price and Tumulo<sup>7</sup> proposed an ozone insertion mechanism similar to the 1,3-dipolar insertion suggested by White and Bailey<sup>9</sup> and

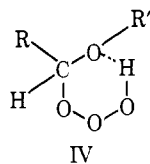
Scheme I. 1,3-Dipolar Insertion



Batterbee and Bailey<sup>10</sup> for ozonations of carbon-hydrogen bonds of aldehydes and hydrocarbons. The transition state (II, Scheme I) for such a process has carbonium ion character and is stabilized by electron donation from the ether oxygen, in contrast to the diradical-type transition state proposed by Hamilton et al.<sup>11</sup> and by Whiting et al.<sup>12</sup> for similar insertion reactions of ozone. Such a transition state (II) has also been proposed by Deslongchamps et al.<sup>13</sup> for similar ozonations of acetals. They showed that the only reactive conformations were those in which each oxygen of the acetal had an electron pair orbital oriented antiperiplanar to the C-H bond.<sup>13</sup>

Erickson et al.<sup>8</sup> also proposed 1,3-dipolar insertion of ozone to give a hydrotrioxide (III) in their studies with several different ethers. They ozonized not only with ozone-oxygen, but also with ozone-nitrogen, both at  $-78$  and  $0$  °C, and found that the presence of oxygen definitely affected product distribution, deuterium isotope effects, and the relative rates of ozonation of various ethers. They appear to accept the 1,3-dipolar insertion reaction (Scheme I) as being major at  $-78$  °C, but believe that competing radical chain reactions are also occurring, involving both oxygen and ozone, and suggest that these become predominant at higher temperatures, especially in the presence of oxygen.

Strong chemical and physical evidence for the hydrotrioxide intermediate (e.g., III) in ether ozonations has been obtained by Murray et al.,<sup>14</sup> who presented NMR evidence that the hydrotrioxides were stabilized by hydrogen bonding,<sup>14c</sup> e.g., as shown in IV.

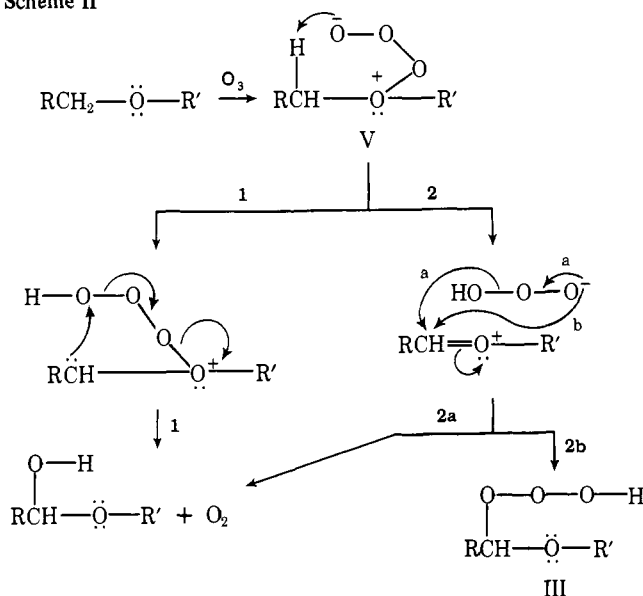


Earlier studies in the present series of papers have dealt with the ozonations of various primary,<sup>15-17</sup> secondary,<sup>18,19</sup> and tertiary amines.<sup>1,15,20</sup> These investigations furnished evidence for an initial electrophilic ozone attack upon the nucleophilic nitrogen to afford an amine-ozone adduct for which four fates were found. One of these fates involved an internal oxidation to yield side-chain oxidation products similar to those afforded by ethers. Evidence was obtained that this is the major route to side-chain oxidation products for amines possessing primary alkyl groups,<sup>1,15,17,19,20</sup> whereas 1,3-dipolar insertion appears to be the major route for ozone attack at secondary alkyl groups.<sup>1,17,19</sup>

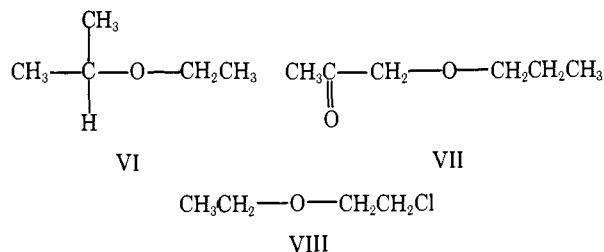
Although ethers are not as nucleophilic as amines, it seemed worthwhile to investigate the possibility that an internal oxidation mechanism occurs in the ozonation of ethers. The possible variations, by analogy to amines,<sup>20</sup> are shown in Scheme II. This type of attack, leading to V, also has analogy in the proposed attacks of ozone<sup>21</sup> and singlet oxygen<sup>22</sup> on sulfides, and a suggested mechanism for the photooxidation of ethers with oxygen.<sup>23</sup>

The ethers chosen for our study were ethyl isopropyl ether

Scheme II



(VI), 4-oxa-2-heptanone (VII), and 2-chloro-1-ethoxyethane (VIII). The ozonation of ethyl ethoxyacetate (I) was also studied, less thoroughly, for comparison with the results of Price and Tumulo.<sup>7</sup> 2,2,2-Trifluoroethyl and 2,2,2-trichloroethyl ethers were ozonized, but were too unreactive for study. Of the three principal ethers studied, the order of reactivity with ozone was, qualitatively, VI > VII > VIII. Ethyl



ethoxyacetate (I), also, was of medium reactivity. The reactivity of each of the ethers decreased as the reaction temperature decreased. At  $-78$  °C a special procedure was necessary for ethyl ethoxyacetate (I), 4-oxa-2-heptanone (VII), and 2-chloro-1-ethoxyethane (VIII), in which the Freon solution of the ether was saturated with ozone and allowed to stand (12-24 h) until all of the ozone had reacted, after which the procedure was repeated two more times. The results of the ozonations are shown in Tables I-IV.

The products shown in Tables I-IV can all be accounted for via reactions involving two hydrotrioxy and/or two hydroxy intermediates for each ether, as illustrated in Scheme III. The hydrotrioxide intermediates, products of pathways IA and IIA of Scheme III, could arise mechanistically either by 1,3-dipolar insertion (Scheme I) or by internal oxidation (Scheme II, route 2b). Pathways IB and IIB of Scheme III are included in order to accommodate the alternative internal oxidation routes (1 and 2a of Scheme II).

The only products obtained in identifiable yields from ozonation of ethyl isopropyl ether (VI, Table I) were acetone (1), ethanol, ethyl acetate (2), isopropyl formate (3), and isopropyl acetate (4). Ethanol was not included in Table I because it is produced in the same reaction which yields acetone (1). Of the reaction routes shown in Scheme III, acetone could arise from IA1a, IBa, or IA3c. It is also conceivable that it could arise from reaction routes IIA1a or IIBa, followed by ozonation of isopropyl alcohol. This is not thought to be a source of acetone, however, since no trace of isopropyl alcohol was found among the products even at  $-78$  °C. In contrast, ethanol (from routes

Table I. Ozonation of Ethyl Isopropyl Ether (VI)<sup>a</sup>

temp, °C	product distribution <sup>b</sup> at		
	0	-30	-78
O <sub>3</sub> /VI <sup>c</sup>	1.9	1.7	1.9
O <sub>2</sub> /O <sub>3</sub> <sup>d</sup>	0.51	0.50	<i>e</i>
products			
1 Me <sub>2</sub> C=O	49	38	42
2 MeCO <sub>2</sub> Et	25	33	36
3 <i>i</i> -PrOCHO	13	12	6
4 <i>i</i> -PrOCOMe	13	17	16
total yield <sup>f</sup>	91	89	91
O <sub>3</sub> attack: <i>i</i> -Pr/Et <sup>g</sup>	2.8	2.4	3.5

<sup>a</sup> The solvent was Freon 11. Ozone in a nitrogen stream was employed (see Experimental Section). <sup>b</sup> The products yields represent the percentages (or relative amounts) of each product in the total yield of products isolated, and are averages of two or more runs. <sup>c</sup> This is the molar ratio of ozone actually consumed to starting material actually consumed. Neither reactant originally employed (2-3 mol of the ether in 10 mL of solvent treated with 1.5 times the amount of ozone) was totally consumed. <sup>d</sup> This is the molar ratio of molecular oxygen evolved to ozone consumed (see Experimental Section). <sup>e</sup> Not determined, owing to low reactivity of ozone at -78 °C. <sup>f</sup> This is the total percentage yield of products shown (1-4) based on the amount of starting material actually consumed. Ethanol also was a product, but was not included since it was produced in the same reaction that yielded acetone. <sup>g</sup> This is the ratio of the ozone attack at the isopropyl group (products 1 and 2) to that at the ethyl group (products 3 and 4). The actual reactivity ratios of these groups would be twice these values, since isopropyl has one reactive hydrogen to two for ethyl.

Table II. Ozonation of 4-Oxa-2-heptanone (VII)<sup>a</sup>

temp, °C	product distribution <sup>b</sup> at		
	0	-30	-78
O <sub>3</sub> /VII <sup>c</sup>	2.2	1.9	<i>e</i>
O <sub>2</sub> /O <sub>3</sub> <sup>d</sup>	0.54	0.46	<i>e</i>
products			
5 PrOCHO	64	59	26
6 PrOH	10	13	14
7 PrOCOCOCH <sub>3</sub>	8	14	50
8 MeCOCH <sub>2</sub> OCHO	7	5	trace
9 MeCOCH <sub>2</sub> OCOEt	11	9	10
total yield <sup>f</sup>	87	93	87
O <sub>3</sub> attack: acetomethyl/propyl <sup>g</sup>	4.6	6.1	9.0

<sup>a</sup> The solvent was Freon 11. At 0 and -30 °C, ozone in a nitrogen stream was employed by the usual procedure. A special procedure was employed at -78 °C; see Experimental Section. <sup>b-e</sup> Same as for Table I, except that 2-3 mol of ozone per mol of VII was employed initially. <sup>f</sup> This is the total percentage yield of the products shown (5-9), based on the amount of starting material actually consumed. <sup>g</sup> This is the ratio of the ozone attack at the acetomethyl group (products 5-7) to that at the propyl group (products 8 and 9).

IA1a or IBa) was a product in amounts varying from about one-tenth (0 °C) to one-half (-78 °C) the amount of acetone obtained. Further, it is logical that the hemiketal from routes IA1 and/or IB would decompose to an alcohol and a ketone whereas the hemiacetal from routes IIA1 and/or IIB would be more stable and would, therefore, be oxidized further (route IIBb or IIA1b). Thus, we identify acetone as a product of ozone attack at the isopropyl group rather than at the ethyl group, probably via route IA1a or IBa rather than IA3c, since ethanol is produced along with it. It is also conceivable that acetone and ethanol arose by direct decomposition of the hydrotrioxy intermediate, as shown in eq 1, which makes use of a decomposition transition state such as suggested by Murray and co-workers.<sup>14c</sup>

Concerning the other products of ozonation of ethyl isopropyl ether, ethyl acetate (2) must have arisen via pathway IA3a, isopropyl formate (3) via route IIA3b, and isopropyl

Table III. Ozonation of Ethyl Ethoxyacetate (I)<sup>a</sup>

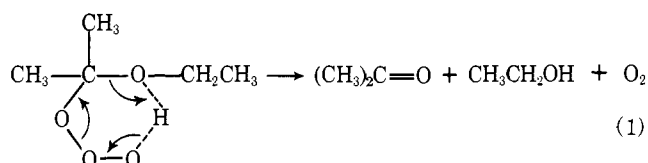
products	product distribution <sup>b</sup> at	
	0 °C	-78 °C
10	18	21
11	21	33
12	17	trace
13	23	39
total yield <sup>c</sup>	79	93
O <sub>3</sub> attack at positions a/c in structure I <sup>d</sup>	1.0	1.4

<sup>a</sup> Same as for Table II. <sup>b</sup> These values represent actual yields. <sup>c</sup> This is the sum of the above yields. <sup>d</sup> This is the ratio of the ozone attack at the ethyl (ether) group (products 10 and 11) to that at the acetate methylene group (products 12 and 13).

Table IV. Ozonation of 2-Chloro-1-ethoxyethane (VIII)<sup>a</sup>

temp, °C	product distribution <sup>b</sup> at		
	0	-30	-78
O <sub>3</sub> /VIII <sup>c,d</sup>	2.4	2.1	<i>e</i>
products			
14 ClCH <sub>2</sub> CH <sub>2</sub> OCHO	32	25	11
15 ClCH <sub>2</sub> CH <sub>2</sub> OCOMe	25	31	50
16 EtOCHO	27	22	15
17 EtOCOCH <sub>2</sub> Cl	16	22	24
total yield <sup>f</sup>	77	73	<i>e</i>
O <sub>3</sub> attack: Et/ClEt <sup>g</sup>	1.3	1.3	1.6

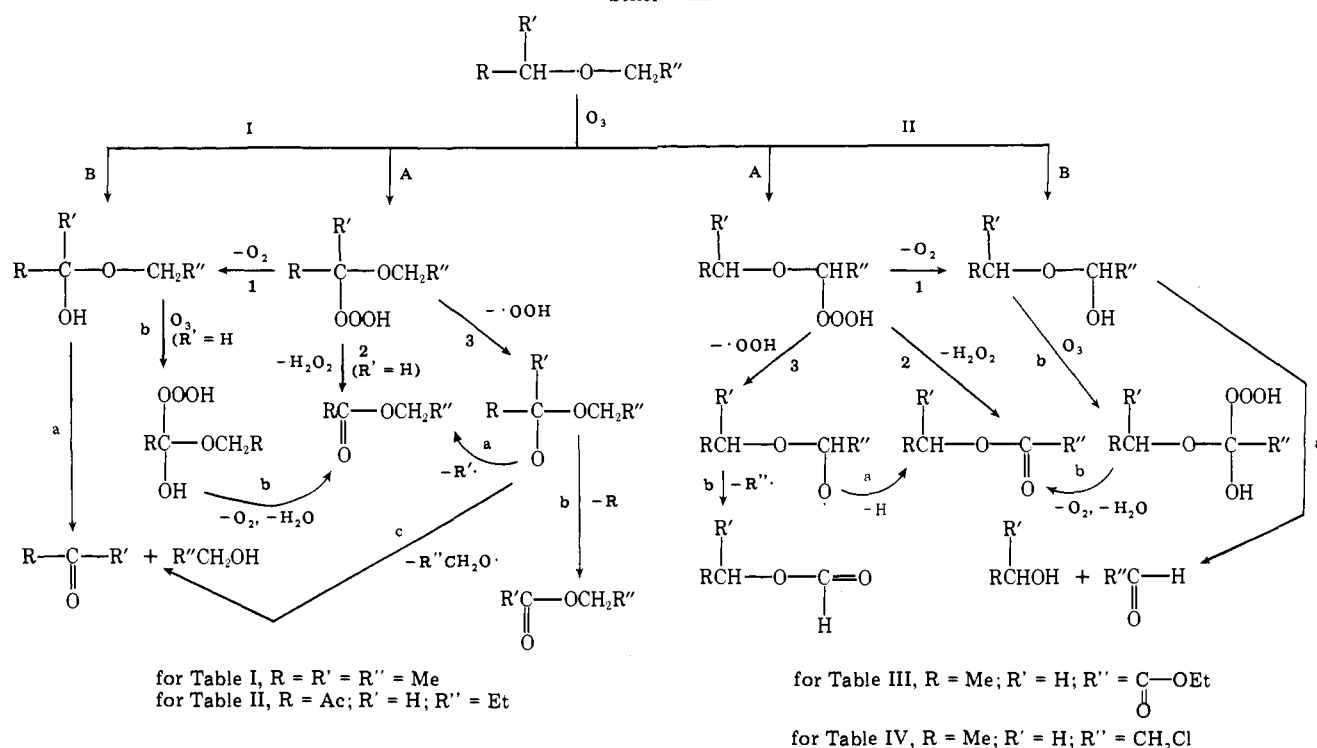
<sup>a-c</sup> Same as for Table II. <sup>d</sup> The molecular oxygen yield was not determined because of the low reactivity of the ether. <sup>e</sup> Same as for Table I. <sup>f</sup> This is the total percentage yield of the products shown (14-17) based on the amount of starting material actually consumed. <sup>g</sup> This is the ratio of ozone attack at the ethyl group (products 14 and 15) to that at the chloroethyl group (products 16 and 17).



acetate (4) via one or more of routes IIA2, IIA3a, IIA1b, or IIBb. Of the four possibilities for products 4, IIA1b or IIBb appear to be the most likely sources, since nearly 2 mol of ozone per mol of ethyl isopropyl ether reacted. The extra ozone required could also come from ozonation of some of the ethanol produced and from destruction of the methyl and hydroperoxy radicals obtained via routes IA3a and IIA3b. It is difficult to account exactly for the 50% yield of molecular oxygen (based upon ozone reacting). Most of it, undoubtedly, came from the reaction or reactions leading to acetone (1).

As a result of the above reasoning, it appears that the major ozone attack occurred at the isopropyl rather than the ethyl group of VI. The ratio of attack at the two groups is shown in Table I. Since there is only one isopropyl hydrogen to two ethyl hydrogens to be attacked, the actual reactivity ratio for these groups is twice these values, i.e., 5.6 at 0 °C and 7.0 at -78 °C. These results, certainly, are much more in agreement with the 1,3-dipolar insertion mechanism (Scheme I) than with the internal oxidation mechanisms of Scheme II, as also found by

Scheme III



Price and Tumulo.<sup>7</sup> It is interesting to note that in the  $-78\text{ }^{\circ}\text{C}$  reaction a gas (assumed to be oxygen) was evolved as the reaction mixture temperature was allowed to arise above  $-78\text{ }^{\circ}\text{C}$ . Oxygen evolution under similar circumstances has also been reported by Erickson et al.<sup>8</sup> and Murray and co-workers.<sup>14</sup> This indicates the presence, and stability, of the hydrotrioxide intermediate and further lends support to Scheme I. Certainly, it tends to discredit routes B of Scheme III, which are based on pathways 1 and 2a of Scheme II.

The activity ratios determined above are greater than the one determined by Price and Tumulo<sup>7</sup> for a similar ether (1.7). The difference could be due to several factors. We used ozone in a nitrogen stream, whereas Price and Tumulo<sup>7</sup> used ozone-oxygen. As suggested by Erickson et al.,<sup>8</sup> perhaps more competing radical-type reactions were involved under Price and Tumulo's conditions. Further, Price and Tumulo<sup>7</sup> ozonized their ether neat at room temperature, whereas we used a polar solvent at 0,  $-30$ , and  $-78\text{ }^{\circ}\text{C}$ . It is noteworthy that under our conditions, the ozone attack was more selective at  $-78\text{ }^{\circ}\text{C}$  than at  $0\text{ }^{\circ}\text{C}$ .

The results with 4-oxa-2-heptanone (VII, Table II) were just the opposite of those obtained with ethyl isopropyl ether. The products identified were propyl formate (5) from route IA3b (Scheme III); 1-propanol (6) from route IA1a or IA1b; propyl pyruvate (7) from route IA2, IA1b, IBb or IA3a; acetomethyl formate (8) from route IIA3b; and acetomethyl propionate (9) from route IIA2, IIA1b, IIBb, or IIA3a. It is obvious, as shown in Table II, that the ozone attack occurred more strongly at the acetomethyl group than at the propyl group, analogous to the results obtained from an earlier study with 1-di-*n*-butylamino-2-butanone.<sup>20</sup> This attack at the more acidic  $\alpha$ -methylene group is indicative of one of the internal oxidation mechanistic routes of Scheme II.

Since, however, the major product of ozonation of 4-oxa-2-heptanone (VII) at 0 and  $-30\text{ }^{\circ}\text{C}$  was propyl formate (5), it was necessary to determine whether or not this could have arisen from ozonolysis of the enol of VII rather than from ozonation of VII itself. This involved a study of the rate of reaction of VII with a bromine solution. At room temperature the bromine disappearance was fairly rapid (0.05 molar equiv in

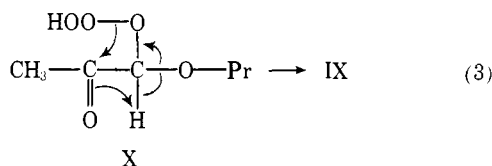
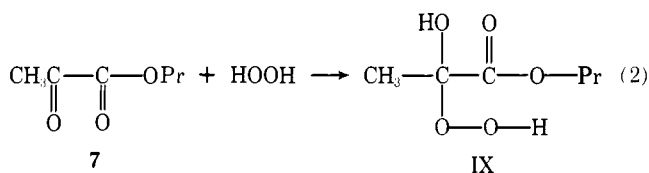
1 min), but not as rapid as ozonation occurred at  $0\text{ }^{\circ}\text{C}$ . At  $-30\text{ }^{\circ}\text{C}$ , the bromine color had not completely disappeared after 24 h. Thus, at  $-30\text{ }^{\circ}\text{C}$ , at which temperature propyl formate was the major product, enolization was extremely slow and the products shown in Table II could not have arisen from ozonation of the enol of VII. This conclusion is supported by the fact that preference for ozone attack at the more acidic methylene group increased strongly as the ozonation temperature decreased.

A novel aspect of the 4-oxa-2-heptanone (VII) ozonation was the observation of a major product from the ozonation at  $-78\text{ }^{\circ}\text{C}$ , which, however, decomposed to propyl pyruvate (7) on the gas chromatograph. The material gave a strong hydroperoxide test with lead tetraacetate.<sup>24</sup> It was identified as propyl 2-hydroperoxy-2-hydroxypropanoate (IX) by comparison of its IR and NMR spectra with those of an authentic sample prepared by reaction of hydrogen peroxide with propyl pyruvate (7). These results indicate that the major intermediate in the ozonation of 4-oxa-2-heptanone (VII) is a hydrotrioxide (X, see also route IA, Scheme III), produced by pathway 2b of Scheme II. This finding further tends to eliminate the need for the B routes of Scheme III.

The major ozonation course for VII at 0 and  $-30\text{ }^{\circ}\text{C}$ , as shown in Scheme III, was IA3b, whereas at  $-78\text{ }^{\circ}\text{C}$  it was IA2. This is logical since the higher the temperature, the more readily homolytic cleavage of the hydrotrioxy group should occur. Compound IX could have arisen either by addition of hydrogen peroxide to 7, as shown in eq 2, or by rearrangement of hydrotrioxide X (eq 3).

The approximately 2:1 ratio of ozone reacting to VII reacting, obtained in the 0 and  $-30\text{ }^{\circ}\text{C}$  ozonations, must reflect pathways IA1b and IIA1b (Scheme III) as the major routes to 7 and 9 at these temperatures, as well as some use of ozone through oxidation of 1-propanol and methylglyoxal, which should have been produced along with 1-propanol (route IA1a, Scheme III). Routes analogous to eq 1 could also be involved. The molecular oxygen yields also support these conclusions.

The great difference in the position of ozone attack observed by us with 4-oxa-2-heptanone (VII) in Freon 11 at 0,  $-30$ , and  $-78\text{ }^{\circ}\text{C}$  and by Price and Tumulo<sup>7</sup> with neat ethyl ethoxy-



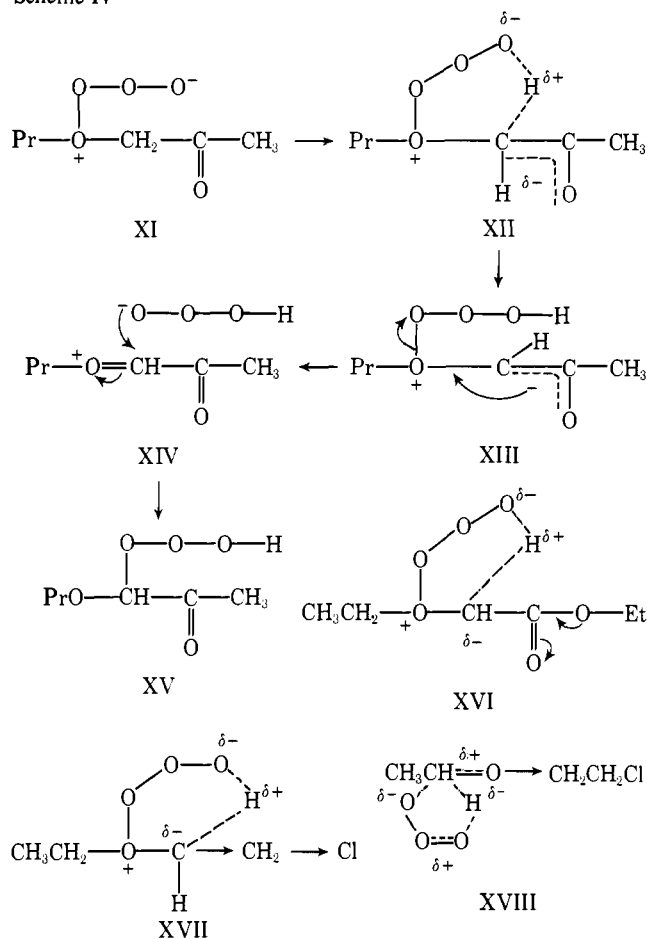
acetate (I) at room temperature led us to reinvestigate the ozonation of I, in Freon 11 at 0 and  $-78^\circ\text{C}$ . The products (Table III) were ethyl hydroxyacetate (10), from route IA1a (Scheme III), or a route analogous to eq 1; ethyl acetoxyacetate (11), from route IA2, IA1b, or IA3a; ethyl formate (12), from route IIA3b; and ethyl oxalate (13), from route IIA2, IIA1b, or IIA3a. This constitutes no preference in ozone attack at positions "a" and "c" of I at  $0^\circ\text{C}$ , and a slight preference for position "a" (1.4) at  $-78^\circ\text{C}$ . These results are not as strikingly different from those with VII (Table II) as were the results of Price and Tumulo,<sup>7</sup> but nevertheless are in the same direction as their results. A rationale for this will be given later in the discussion.

The products identified from ozonation of 2-chloro-1-ethoxyethane (VIII, Table IV) were 2-chloroethyl formate (14), from route IA3b (Scheme III); 2-chloroethyl acetate (15), from route IA2, IA3a, or IA1b; ethyl formate (16), from route IIA3b; and ethyl chloroacetate (17), from route IIA2, IA3a, or IIA1b. The ozone to VIII reacting ratios indicate the importance of routes such as IA1b and IIA1b. Again, it is noteworthy that products definitely derived from oxygen-oxygen bond cleavage (14 and 16) decreased in yield and those derived from other routes (15 and 17) increased in importance as the ozonation temperature was lowered. As shown in Table IV, the proportions of the products obtained at all three temperatures reflect a slight preference for ozone attack at the least acidic methylene group of VIII.

Of the four ethers studied, only one, 4-oxa-2-heptanone (VII), showed a strong preference for ozone attack at the more acidic methylene group; ethyl isopropyl ether (VI) showed a strong preference for ozone attack at the least acidic methylene group  $\alpha$  to the ether oxygen, and the other two ethers were in between, with a slight preference for ozone attack at the least acidic methylene group  $\alpha$  to the ether oxygen. As stated earlier, we interpret these results as reflecting a 1,3-dipolar insertion (Scheme I) mechanism for ozonation of VI, analogous to the ozonation of amines with secondary alkyl groups,<sup>1,17,19</sup> the internal oxidation mechanism (pathway 2b, Scheme II) for VII, and probably a near-equal competition between the two mechanisms for the other two ethers. These differences in regioselectivity, as well as differences in rates of ozonation, can be rationalized in terms of competing stabilizing and destabilizing effects for the transition states of Schemes I and II. The latter is illustrated in greater detail in Scheme IV.

Although the nucleophilicity of the ether oxygen of 4-oxa-2-heptanone (VII) has been depressed, in comparison to dialkyl ethers, by the acetyl group, thereby slowing down the rate of formation of adduct XI and, consequently, of the oxidation itself, once the adduct (XI) is formed, it is ideally structured to stabilize the transition state (XII) for proton abstraction. The reaction then proceeds through intermediate XIII and/or XIV to hydrotrioxide XV. In contrast, the carboethoxy group of ethyl ethoxyacetate (I) is less able to stabilize an analogous transition state (XVI) because of the carboethoxy resonance. Thus, ozonation occurs equally well, or better, at the other

Scheme IV



$\alpha$ -methylene group, via 1,3-dipolar insertion, in which the transition state is stabilized by the ether oxygen.

Similar principles apply to ozonation of 2-chloro-1-ethoxyethane (VIII). Formation of an ether-ozone adduct is retarded by the electron-attracting chloroethyl group, which also deactivates the transition state (XVIII) for 1,3-dipolar insertion. The latter occurs at the farthest removed  $\alpha$ -methylene group. These effects were so powerful with 2,2,2-trifluoroethyl and 2,2,2-trichloroethyl ethyl ethers that they scarcely reacted with ozone at all. The only stabilizing effect for the transition state for proton abstraction (XVII) in the case of 2-chloro-1-ethoxyethane (VIII) is the inductive effect of the chloromethyl group. This is not as efficient as the resonance stabilization of transition state XII for 4-oxa-2-heptanone (VII). Thus, neither ozonation mechanism is particularly favored in the case of VIII.

An interesting extreme example of the regioselectivity in an insertion reaction of ozone, caused by a powerful electron-withdrawing group, is found in the ozonations of alcohols in superacidic media.<sup>25</sup> The ozone attack occurred at the methylene groups farthest away from the oxonium ion center.

Previous to these studies it was uncertain whether the internal oxidation route occurred by a mechanism analogous to the Polanovsky reaction (pathway 2, Scheme II) or by one similar to the Stevens rearrangement (pathway 1, Scheme II).<sup>20</sup> At least with ethers it now appears that the mechanism is more closely related to that of the Polanovsky reaction.

Finally, under our conditions, there is little evidence for radical initiation of the ozonation process, as found by Erickson et al.<sup>8</sup> It would appear that such reactions are of importance primarily in oxygen media or at higher temperatures. This is the most reasonable explanation for the differences observed in our results and those of Price and Tumulo,<sup>7</sup> in regard to both

the isopropyl ethyl (or propyl) ethers and ethyl ethoxyacetate.

### Experimental Section

**Materials.** Ethyl isopropyl ether was prepared from isopropyl alcohol and diethyl sulfate and distilled from the reaction mixture (bp 54 °C).<sup>26</sup> 4-Oxa-2-heptanone was prepared by the general oxidation method of Mariella and Leech<sup>27</sup> from 4-oxa-2-heptanol, which was synthesized from propylene oxide and 1-propanol by the procedure of Chitwood and Freure.<sup>28</sup> The keto ether boiled (spinning band column) at 150–151 °C;<sup>29</sup> NMR  $\delta$  3.9 (2 H, s), 3.4 (2 H, t), 2.1 (3 H, s), 1.6 (2 H, m), and 1.0 (3 H, t). 2-Chloro-1-ethoxyethane was prepared according to the procedure of Dutta,<sup>30</sup> bp 108–110 °C. 2,2,2-Trichloroethyl ethyl ether (bp 138 °C) and 2,2,2-trifluoroethyl ethyl ether (bp 50–51 °C) were prepared as described by Scherer and Hahn.<sup>31</sup> All other materials were either obtained from commercial sources or were prepared by standard procedures.

**General Ozonation Procedures.** Most ozonations were performed with ozone in a nitrogen stream. The general procedure, including the determination of molecular oxygen, was as described previously.<sup>32</sup> Owing to the low reactivities of 4-oxa-2-heptanone, ethyl ethoxyacetate, and 2-chloro-1-ethoxyethane toward ozone at –78 °C, a special procedure had to be used in which a solution of 3–4 mmol of the reactant in 30–40 mL of Freon 11 was saturated with ozone at –78 °C, after which the reaction mixture was kept at –78 °C until the blue color of ozone disappeared (12–24 h). The process was repeated one to two more times with 24–48 h being required for the ozone color to disappear.

**General Product Determination Procedures.** Product determination was done with a Varian Aerograph 1520B gas chromatograph using an internal standard. The columns employed were (1) 10% Carbowax 20M on Chromosorb G (AW), 1/8 in.  $\times$  10 ft; (2) 30% Silicone Gum Rubber SE-30 on Chromosorb P, 1/8 in.  $\times$  15 ft; (3) same as column 2, except 10 ft.

**Ozonation of Ethyl Isopropyl Ether (VI).** The conditions and results are shown in Table I. Owing to the volatility of the products, columns 3 and 1 were employed together, in that order, at 70 °C. Benzene was the internal standard.

For ethyl ethoxyacetate (Table III), column 1 was utilized at 118 °C, with 3,6,9-trioxaundecane as internal standard for ethyl formate and ethyl ethoxyacetate; the latter was then used as an internal standard for the other products. For 2-chloro-1-ethoxyethane (Table IV), column 2 was used at 125 °C, with benzene as the internal standard.

**Ozonation of 4-Oxa-2-heptanone (VII).** The conditions and results are shown in Table II. Column 1 at 125 °C was used, with diethyl malonate as the internal standard. Although GLC afforded only the products shown in Table II for the –78 °C ozonation, NMR gave evidence for another product with a large singlet at  $\delta$  1.5 ppm. This product was left behind when the reaction mixture was stripped at room temperature and 3 mm pressure. It gave strong peroxide and hydroperoxide tests with iodide and lead tetraacetate,<sup>24</sup> respectively, and decomposed with heat (and on the gas chromatograph), or upon reduction, to propyl pyruvate. A substance obtained by treating propyl pyruvate with 90% hydrogen peroxide afforded the same IR and NMR spectra as did the unknown. The substance is, therefore, tentatively

identified as propyl 2-hydroperoxy-2-hydroxypropanoate (IX).

In order to determine the rate of enolization of 4-oxa-2-heptanone (VII) under ozonolysis conditions, a solution of 5 mmol of VII in 20 mL of Freon 11 containing ca. 5 mmol of acetic acid (for possible acid catalysis) was cooled to –30 °C, after which 0.2 mmol of bromine was added. Even after 24 h considerable bromine color remained, indicating a very slow rate of enolization.

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