A Novel Class of Disulfides. The SS-2-Acetaminoethyl-O,O-dialkyl Thioperoxymonophosphorothionates[1]

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There is continuing interest in the chemistry of cysteamine, 2-aminoethanethiol, particularly in cysteamine derivatives in which the mercapto group has been transformed into a disulfide-type linkage.

$NH_2CH_2CH_2SX$

1a, X = $SCH_2CH_2NH_2$[2]
b, X = SO_3Na[3]
c, X = $S(=O)CH_2CH_2NH_2$[4]
d, X = SR[3,4]

Cysteamine and its derivatives are also among the most potent materials offering protection against ionizing radiation.[5]

It is believed that the SS-2-acetaminoethyl-O,O-dialkyl thioperoxymonophosphorothionates, where one-

$(RO)_2P(=S)SSCH_2CH_2NHC(=O)CH_3$
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half of the unsymmetrical disulfide is 2-acetaminoethyl and the other is the good leaving group, O,O-dialkylphosphorothioyl, would offer more protection against ionizing radiation than cystamine **1a** and would be less toxic than 2-aminoethanethiol.

The method of Field, *et al.*,[4] using mercaptans and 2-acetaminoethyl 2-acetaminoethanethiolsulfonate (**3**) was used to prepare **2** (eq 1). The crude product was

$$\underset{\mathbf{3}}{AcNHCH_2CH_2S(=O)_2SCH_2CH_2NHAc} + \underset{\mathbf{4}}{(RO)_2P(=S)SH} \longrightarrow \underset{\mathbf{2}}{AcNHCH_2CH_2SSP(=S)(OR)_2} + \underset{\mathbf{5}}{AcNHCH_2CH_2SO_2H} \quad (1)$$

R = C_3H_7, *i*-C_3H_7, or C_4H_9

purified by column chromatography using 200 mesh Florisil and the method of Patchett and Batchelder.[6]

For yield data, see Table I. The products had absorption bands in the infrared spectrum for NH (3300 cm^{-1}), —C(=O)NH— (1655 cm^{-1}, 1550 cm^{-1}), and phosphate (980 cm^{-1}). All preparations also yielded some tetraalkyl thioperoxydiphosphorothionate (**6**) which arises from the disproportionation of **2**. The infrared spectra of **6** had bands for phosphate at 980 cm^{-1} but no bands for —NH— or —C(=O)NH—. The **6** where R = *i*-C_3H_7 is solid and was further identified by its melting point.

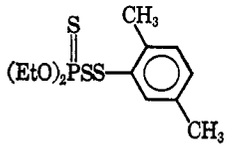
When 2-aminoethyl 2-aminoethanethiolsulfonate dihydrochloride was used in place of the acetamino compound, only the two symmetrical disulfides, cystamine dihydrochloride (**7**) and **6**, were obtained.

$(RO)_2P(=S)SSP(=S)(OR)_2$ **6**

$NH_2CH_2CH_2SSCH_2CH_2NH_2 \cdot 2HCl$ **7**

No reaction was obtained when the Bunte salt of cysteamine (**1b**) was allowed to react with **4**, even when heated at reflux with methanol as the solvent.[7]

Almasi and Paskucz[8] reported the preparation of SS-2,5-dimethylphenyl-O,O-diethyl thioperoxymonophosphorothionate (**8**) from diethoxyphosphinothioylsulfenyl chloride (**9**) and 2,5-dimethylbenzenethiol, and Michalski, *et al.*,[9] reported the preparation of SS-butyl-O,O-diethyl thioperoxymonophosphorate (**10**) from butanethiol and diethoxyphosphinylsulfenyl chloride (**11**). Similar reactions of dialkoxyphosphinyl-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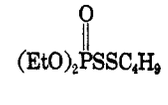
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$(EtO)_2P(=S)Cl$ **9**

$(EtO)_2P(=O)Cl$ **11**

sulfenyl chlorides or dialkoxyphosphinothioylsulfenyl chlorides with cysteamine, cysteamine hydrochloride, or sodium 2-aminoethylmercaptide gave only the symmetrical disulfides. The unsymmetrical disulfides formed but disproportionated under the conditions of the reaction. Such disproportionations are well known in the chemistry of disulfides.[10]

Experimental Section[11]

SS-2-Acetaminoethyl-O,O-dialkylmercapto Phosphorodithioates (2).—A mixture of 13.5 g (0.05 mol) of 2-acetaminoethyl 2-acetaminoethanethiolsulfonate,[4] 0.05 mol of O,O-dialkylphosphorodithioic acid, and 100 ml of acetone was allowed to stand at room temperature for 5 days. Some 2-acetaminoethanesulfinic acid had crystallized from the reaction mixture as a white solid. The solvent was removed on a rotary evaporator at reduced

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(11) All melting points were uncorrected and were taken with a Mel-Temp apparatus.

TABLE I

$(RO)_2\overset{S}{\overset{\|}{P}}SSCH_2CH_2NHAc$

R	Yield, %	$n^{25}D$	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	P, % Calcd	P, % Found	S, % Calcd	S, % Found
C_3H_7	22	1.5420	36.24	36.11	6.69	6.77	4.23	4.16	9.34	9.13	29.02	28.83
i-C_3H_7	27	1.5375[a]	36.24	35.95	6.69	6.67	4.23	4.47	9.34	9.16	29.02	29.06
C_4H_9	39	1.5345	40.09	39.84	7.28	7.39	3.89	3.73	8.61	8.09	26.55	26.55

[a] Solidified upon standing, recrystallized from benzene–petroleum ether (mp 40–42°).

pressure to give a pasty solid. This crude product was mixed with 25 ml of cyclohexane–benzene 1:1 mixture, filtered, and washed with more solvent to separate out the remaining sulfinic acid. The solvent was removed from the combined filtrates to give an amber oil. This oil was chromatographed on an 18 in. × 1 in. column filled with 125 g of 200 mesh Florisil. The sample was put on and then developed with 400 ml of cyclohexane–benzene 1:1, 200 ml of benzene, and then 400 ml of chloroform. The cyclohexane–benzene fraction contained the alkylthioperoxyphosphorothionates.[12]

The benzene and chloroform fractions were rechromatographed as before. The benzene and chloroform fractions were combined, and the solvents were removed under high vacuum on a rotary evaporator to give the SS-2-acetaminoethyl-O,O-dialkyl thioperoxymonophosphorothionates.

Registry No.—2 (R = propyl), 15790-97-3; 2 (R = isopropyl), 15790-98-4; 2 (R = butyl), 15790-99-5.

(12) In cases where R = i-C_3H_7, the thioperoxy compound was a solid, mp 90–91° [lit. 90–91°, N. I. Zimbyanksii, O. A. Prib, and B. S. Dreck, *Zh. Obshch. Khim.*, **31**, 880 (1961)]. *Anal.* Calcd for $C_{12}H_{28}O_4P_2S_4$: C, 33.79; H, 6.62. Found: C, 33.79; H, 6.58.

Kinetics of Hydrolysis of the Tetramethyl Ketal of *p*-Benzoquinone[1]

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One of the more interesting features of the kinetics of hydrolysis of ortho esters is the lack of parallelism between substrate reactivity and stability of the corresponding carbonium ions which are evidently formed as the products of the rate-determining step.[3] Thus, ethyl orthocarbonate is less reactive than ethyl orthobenzoate which is less reactive than ethyl orthoformate.[4] In fact, ortho esters are generally less reactive than ketals. Thus, reactivities are inversely related to the expected carbonium ion stabilities within this series. This behavior has been suggested to result from considerations regarding substrate basicity,[4,5] substrate stabilization through double-bond–no-bond resonance,[6] and saturation effects.[7] In contrast, the rates of hydrolysis of acetals and ketals appear to be correlated well, for the most part, with stabilities of the derived carbonium ions.[8,9] However, Kreevoy and Taft have observed that the rates of hydrolysis of diethyl ketals derived from benzophenone and fluorenone are substantially less than would have been predicted on the basis of expected resonance stabilization of the corresponding carbonium ions.[10,11] This behavior was rationalized on the basis that as the transition state became increasingly stable relative to starting material it would be reached progressively earlier and, hence, would possess less carbonium ion character and be less susceptible to stabilization by resonance.[12] A related argument has been applied to the kinetics of hydrolysis of ortho esters.[13] While such arguments certainly will have validity in some cases, there seems to be a reasonable limitation to their applicability. *Thus, a change in substrate structure which would impart additional stabilization to the transition state relative to the ground state will not alter the transition state structure to such an extent that the structural change actually results in a less reactive substrate.*

We now wish to report an additional apparent lack of correlation between carbonium-ion stability and substrate reactivity for ketal hydrolysis.

Acid-catalyzed hydrolysis of the tetramethyl ketal of *p*-benzoquinone(3,3,6,6-tetramethoxy-1,4-cyclohexadiene) proceeds in two distinct steps, the first reaction being about 300 times more rapid than the second. The intermediate exhibits a shoulder in the ultraviolet spectrum near 235 mμ and is almost certainly the monoketal (6,6-dimethoxy-1,4-cyclohexadien-3-one). The product is *p*-benzoquinone as evidenced by its absorption spectrum and by direct isolation.[14] First-order rate constants for both the hydrolysis and decomposition of the intermediate in aqueous solution at 25° and ionic strength 0.50 are collected as a function of pH in Table I. Both reactions are seen to be first order in hydrogen ion activity: formation of the monoketal has a second-order rate constant of 650 M^{-1} sec^{-1} and the hydrolysis of this species a corresponding value of 2.1 M^{-1} sec^{-1}. The greater reactivity of the diketal is certainly expected since the electron-withdrawing properties of the carbonyl function present in the monoketal should destabilize the carbonium ion formed from the latter species with respect to that derived from the former. What is surprising is that the diketal is about an order of magnitude less reactive than 2,2-dimethoxy-

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(3) For a discussion of this and related points, see E. H. Cordes, *Progr. Phys. Org. Chem.*, **4**, 1 (1967).

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