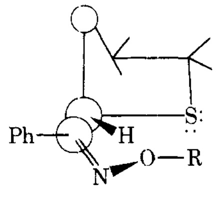
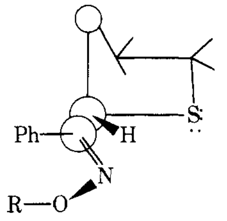


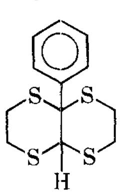
4a



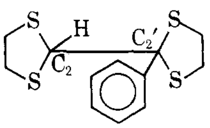
4b

oxathiolane ring. Heating in polar solvents results in predomination of the cis (**4a**) isomer.

Reaction of **1** with ethanedithiol (**2**, X = Y = S) produced a yellow, crystalline product in which the alkoxyimino moiety was no longer present, as determined from an examination of the infrared spectrum. However, characteristic bands for C–S vibration (ν 655 cm^{-1}) were apparent. Low-resolution mass spectral data (obtained at 10 eV) indicated that the compound had a molecular weight of 286, which, with the elemental analysis, was shown to correspond to the molecular formula $C_{12}H_{14}S_4$. It was concluded that 2 mol of 1,2-ethanedithiol had combined with 2-alkoxyiminophenylacetaldehyde, forming either of two structural isomers: a *cis*-naphthodithiane, **5**, or 2-phenyl-2-[2-(1,3-dithiolano)]-1,3-dithiolane (**6**).



5



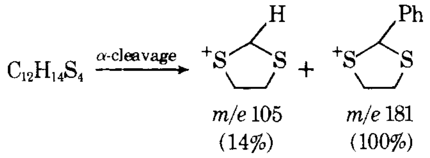
6

Elucidation of the structure of the $C_{12}H_{14}S_4$ compound was made by a mass spectrometric technique capable of distinguishing the pendant from the alternative fused ring system in the determination of the structure of glyoxal bisthioacetals.[5,6,7]

The major fragmentation pathway of the 2,2′-bis(1,3-dithiolanyl) derivative, **6**, involves α-cleavage of the molecular ion resulting in the loss of a 1,3-dithiolane ring fragment by homolysis of the C_2–$C_{2'}$ bond.

$C_{12}H_{14}S_4$ undergoes fission under electron impact at 10 eV[3] to generate the fragments shown in Scheme II. This mode of fragmentation, giving rise to α-cleavage products (*m/e* 181, 105), clearly excludes the fused bicyclic structure, **5**. It must be concluded, then, that the reaction of 2-alkoxyiminophenylacetaldehydes, **1**, with 1,2-ethanedithiol yields 2-phenyl-2-[2-(1,3-dithiolano)]-1,3-dithiolane (**6**).

Scheme II



In conclusion, whereas both sulfur and oxygen nucleophiles react at the carbonyl carbon, only the thiol reacts at the imino carbon. The high nucleophilicity of the soft mercaptan base permits reaction at both the harder Lewis acid (i.e., carbonyl carbon) and softer acid (i.e., imino carbon). Hydroxyl groups are less nucleophilic, harder bases and tend to react at the harder electrophilic (carbonyl) center, rather than the imino carbon, a less reactive, softer acid.[8] Reaction at the imino carbon occurs exclusively with the more nucleophilic, softer sulfur-containing bases. The isomerization of the oxime observed during reaction of **1** with 2-mercaptoethanol may reflect reaction of the thiol moiety at the imino carbon to yield a transient thiocarbinolamine. The free hydroxyl group in this intermediate lacks the reactivity to cause cyclization (with loss of alkoxyamine) but rather eliminates the reactant to re-form the oxime with concomitant loss of stereochemical purity. These results are consistent with the fact that the aldehydic carbonyl group is more polar and generally more reactive toward nucleophilic attack than the corresponding imino function.

The dioxolane and oxathiolane derivatives were submitted for pharmacological testing, and all showed moderate antibacterial activity toward *S. aureus* (Smith strain) and *K. pneumoniae* (AD strain) in an in vivo test.

Experimental Section

Preparation of 2-alkoxyiminophenylacetaldehydes was carried out as previously described and products had physical properties identical with reported values.[1]

General Procedure for Preparation of Heterocyclic Derivatives. The optimum conditions varied from compound to compound, but a general procedure involved heating a benzene solution containing the aldehyde and a 10% molar excess of ethylene glycol, 2-mercaptoethanol, or ethanedithiol in a round-bottom flask equipped with a Dean-Stark trap and a condenser fitted with a calcium chloride for 20 min. Five milligrams of *p*-toluenesulfonic acid or 1 ml of boron trifluoride etherate was added and heating at reflux continued for 24–48 h. The cooled benzene solution was washed with ice-cold saturated $NaHCO_3$ solution, then water and dried over anhydrous magnesium sulfate. The dried solution was decanted and the benzene removed by distillation to yield either a solid which could be recrystallized or an oil which was then purified by distillation.

Registry No.—1 (R = CH_3), 32349-36-3; 1 (R = C_2H_5), 32349-37-4; 2 (X = Y = O), 107-21-1; 2 (X = O; Y = S), 60-24-2; 2 (X = Y = S), 540-63-6.

Supplementary Material Available. Full NMR data for oxime isomerization studies (3 pages). Ordering information is given on any current masthead page.

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Thermodynamic pK_a's for the Second Ionization of Some Alkylphosphonic Acids[1]

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There is considerable current interest in determining the curvature of Brønsted plots.[2] A structurally homogeneous set of acid–base catalysts covering a wide pK_a range is required for this purpose, and it is useful also if these catalysts are reasonably transparent to ultraviolet and visible light, for then rate measurements may be made by the very convenient spectroscopic method now in widespread use. Unfortunately, many of the acids and bases commonly employed as catalysts fail to meet these requirements, and it is of interest therefore to develop new catalyst sets.

Simple aliphatic phosphonic acids show considerable promise in this respect. They are readily available, highly stable substances with no strongly chromophoric groups, and in their second dissociation

Table I. Summary of pK_a Determinations

Registry no.	Acid	$[RPO_3H^-]/[RPO_3^{2-}]$	Ionic strength, M	pK_a[a]
993-13-5	$CH_3PO_3H^-$	0.80	0.24–0.081	7.996 ± 0.002
		1.79	0.20–0.068	8.006 ± 0.002
		4.43	0.18–0.062	7.998 ± 0.003
				Av 8.000 ± 0.003
4923-84-6	$(CH_3)_3CPO_3H^-$	0.74	0.22–0.073	8.710 ± 0.003
		1.86	0.20–0.067	8.714 ± 0.003
		4.53	0.18–0.062	8.714 ± 0.003
				Av 8.713 ± 0.001
2617-47-2	$HOCH_2PO_3H^-$	0.60	0.25–0.083	7.369 ± 0.002
		1.25	0.21–0.070	7.363 ± 0.001
		3.20	0.19–0.064	7.362 ± 0.001
				Av 7.364 ± 0.002
2565-58-4	$CH_2ClPO_3H^-$	1.13	0.079–0.0079	6.579 ± 0.003
		2.22	0.16–0.016	6.588 ± 0.001
		3.41	0.15–0.017	6.596 ± 0.002
				Av 6.588 ± 0.005
13113-88-7	$CHCl_2PO_3H^-$	1.28	0.23–0.078	5.606 ± 0.002
		2.58	0.19–0.065	5.606 ± 0.003
		5.63	0.20–0.068	5.601 ± 0.002
				Av 5.604 ± 0.002
5994-41-2	$CCl_3PO_3H^-$	0.99	0.21–0.071	4.930 ± 0.003
		2.94	0.19–0.064	4.934 ± 0.003
		3.79	0.21–0.071	4.926 ± 0.003
				Av 4.930 ± 0.002

[a] Error limits are standard deviations of mean values.

$$RPO_3H^- \rightleftarrows RPO_3^{2-} + H^+ \qquad (1)$$

they span a pK_a range which extends from 4 ($CF_3PO_3H^-$) to 9 (t-$BuPO_3H^-$). These monohydrogen phosphonate ions, moreover, because of their negative charge, are likely to be especially effective proton donors toward neutral substrates.[3]

The pK_a's for both the first and the second dissociation of a fair number of phosphonic acids have been determined, and several useful compilations are available.[4] Unfortunately, most of the values reported are apparent rather than thermodynamic ionization constants, i.e., they refer to some finite (and usually unspecified) ionic strength. Since thermodynamic values are needed for the accurate analysis of kinetic data and since thermodynamic values are also preferred for the construction of Brønsted plots, we have determined these for a series of six phosphonate monoanions. The results obtained differ significantly from the apparent pK_a's available in the literature.

Experimental Section

Materials. Methylphosphonic acid was prepared by hydrolyzing dimethyl methylphosphonate (Aldrich Chemical Co.) in refluxing 6 M HCl overnight.[5] *tert*-Butylphosphonic, chloromethylphosphonic, and dichloromethylphosphonic acids were made from the corresponding phosphonyl dichlorides which were themselves prepared by the reaction of phosphorus trichloride and aluminum chloride with either *tert*-butyl chloride, methylene dichloride, or chloroform.[6] Trichlorophosphonic acid was synthesized by the Arbuzov reaction between triethyl phosphite (J. T. Baker Co.) and carbon tetrachloride[7] followed by hydrolysis of the diethyl ester so obtained.[6b] Hydroxymethylphosphonic acid was prepared by treating paraformaldehyde with phosphorus trichloride.[8]

All other reagents were best available commercial grades. Solutions were prepared from distilled, CO_2-free water.

pK_a Determinations. Ionization constants were determined by measuring the pH of successively diluted buffer solutions of the acid and its conjugate base. Buffer ratios, $[RPO_3H^-]/[RPO_3^{2-}]$, were in the range 1–5, and initial concentrations were arranged so that the starting ionic strength was ca. 0.2 M. Measurements were made using a Beckman Research pH meter (Model 1019) operating with a Beckman G.P. glass electrode (Model 39000) and a Beckman calomel reference electrode (Model 39071).

In a typical experiment, the buffer was prepared by combining stock solutions of phosphonic acid and sodium hydroxide of known concentrations. A 10-ml aliquot of this solution contained in a beaker was then placed in a constant temperature bath operating at 25.0 ± 0.02 °C, and, after it had come to thermal equilibrium, its pH was measured. To this solution, 2 ml of pure water was then added, an interval of 2–3 min was allowed for further equilibration, and the pH was measured again. Generally, ten such dilutions were made (total volume of water added 20 ml), which provided pH readings at 11 different buffer concentrations.

Results and Discussion

Since thermodynamic ionization constants refer to infinitely dilute solution, the present measurements, necessarily made at finite concentrations, had to be extrapolated to zero ionic strength. This was done in the following way.

The equilibrium constant for the ionization reaction under study (eq 1), K_a, may be written as

$$K_a = A_{H^+} \frac{[RPO_3^{2-}]}{[RPO_3H^-]} \frac{f^{2-}}{f^-} \qquad (2)$$

where A_{H^+} is the activity of the hydrogen ion, brackets denote concentrations on the molarity scale, and f^- and f^{2-} are molar activity coefficients of the mono- and dinegative ions, RPO_3H^- and RPO_3^{2-}. These activity coefficients may be expressed as

$$\log f = \frac{-Az^2I^{1/2}}{1 + I^{1/2}} + BI \qquad (3)$$

where A is an electrochemical constant (0.5115 $M^{-1/2}$), z is the charge number of the ion, I is the ionic strength of the solution, and B is a specific ion interaction constant.[9] Taking the logarithm of eq 2 and inserting values for the activity coefficients from eq 3 leads to

$$\log \frac{[RPO_3H^-]}{[RPO_3^{2-}]} + \mathrm{pH} + \frac{3AI^{1/2}}{1 + I^{1/2}} = (\mathrm{p}K_a)_{\mathrm{app}}$$
$$= \mathrm{p}K_a + (B^{2-} - B^-)I \qquad (4)$$

in which B^- and B^{2-} are specific interaction constants for the RPO_3H^- and RPO_3^{2-} ions. This expression predicts that

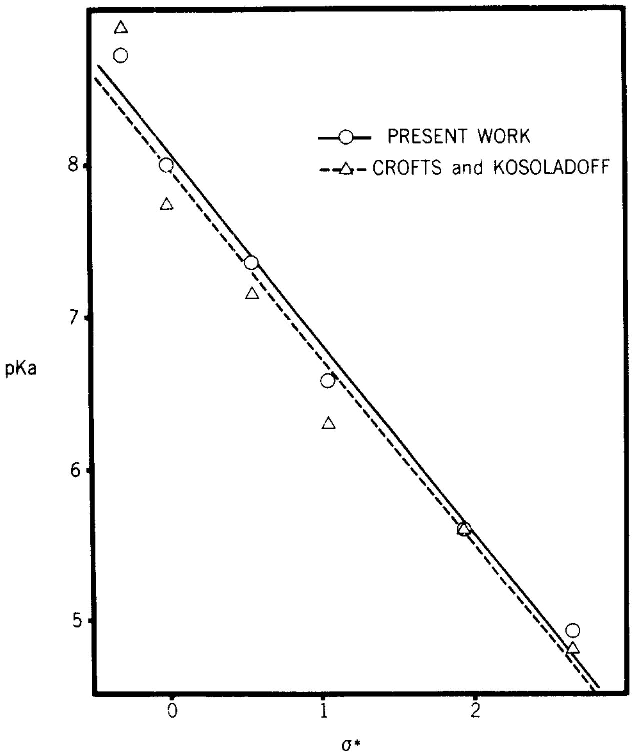

Figure 1. Equilibrium constants for the second ionization of alkylphosphonic acids correlated by the Taft equation.

$(pK_a)_{app}$, whose constituent quantities are all known, will be a linear function of ionic strength with the thermodynamic pK_a as its $I = 0$ intercept.

The data obtained here obey this relationship quite well. Least-squares analysis provides fits whose correlation coefficients are usually 0.98 or 0.99, and never less than 0.95, and whose slopes are generally 0.3 or 0.4; the latter is a reasonable magnitude for the difference $B^{2-} - B^{-}$.[10] These results are summarized in Table I. The average pK_a's listed there are simple unweighted means, and the error estimates given are standard deviations of these means. These probably do not take systematic errors adequately into account, and a more realistic estimate of the reliability of the present results may be 0.005–0.010 pK_a unit.

Thermodynamic pK_a's seem not to have been determined before for any of the acids studied here, but some apparent pK_a values are available. These are due principally to Crofts and Kosolapoff,[6a,b] who carried out potentiometric titrations and used the relationship $pK_a' = pH + \log [RPO_3H^-]/[RPO_3^{2-}]$ to calculate their results. Comparison of this expression with eq 4 shows that this method leaves out the quantity $3AI^{1/2}/(1 + I)^{1/2} - (B^{2-} - B^{-})I$, whose evaluation requires knowledge of the ionic strength at which the measurements were made. Crofts and Kosolapoff do not specify this, but they do say that the mean concentration of phosphonic acids during their titrations was 0.005 M. From this, $I = 0.007–0.013$ M for 20–80% neutralization may be inferred, which leads to −0.12 to −0.14 for the difference $pK_a' - pK_a$. It is significant, therefore, that four of Croft and Kosolapoff's values are lower than the results obtained here: $pK_a' - pK_a = -0.26, -0.21, -0.29$, and -0.12 for $CH_3PO_3H^-$, $HOCH_2PO_3H^-$, $CH_2ClPO_3H^-$, and $CCl_3PO_3H^-$, respectively. For $CHCl_2PO_3H^-$, however, the difference is zero, and for $(CH_3)_3CPO_3H^-$ it is positive: $pK_a' - pK_a = +0.17$.

Additional apparent pK_a's of 5.58 and 4.71 are available for $CHCl_2PO_3H^-$ and $CCl_3PO_3H^-$.[4b] These are not inconsistent with the present results, but since neither the ionic strength nor the concentrations at which these values were obtained are specified, a more meaningful comparison is not possible.

The present results are correlated moderately well by the Taft equation.[11] Figure 1 shows the relationship obtained by least-squares analysis: $pK_a = (8.10 \pm 0.10) - (1.26 \pm 0.07)\sigma^*$. Although the correlation coefficient for this fit is good, $r = 0.994$, the average deviation from the line corresponds to a 30% difference in K_a or 0.13 pK unit; this is an order of magnitude greater than the estimated experimental uncertainty.

It is significant, however, that the apparent pK_a' values of Crofts and Kosolapoff give a considerably poorer correlation: $pK_a' = (7.98 \pm 0.21) - (1.24 \pm 0.15)\sigma^*$, $r = 0.973$, average deviation in K_a = 70% or 0.23 pK unit. It is interesting, on the other hand, that use of apparent pK_a's produces essentially no change in reaction constant; this is true even if the comparison is extended to a correlation based upon a much larger set of apparent pK_a's (22) which produced $\rho^* = 1.18$.[4b]

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Amplification of Cyanide Ion Production by the Micellar Reaction of Keto Oximes with Phosphono- and Phosphorofluoridates

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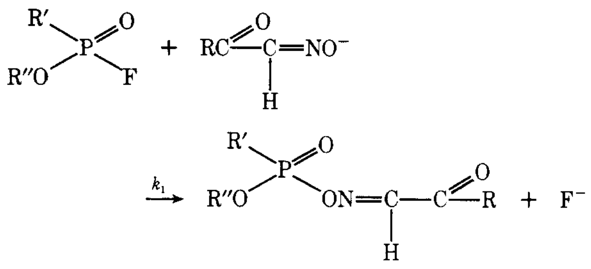
The reaction of keto oximes with phosphono- and phosphorofluoridates in alkaline aqueous solution proceeds according to the equations[1]



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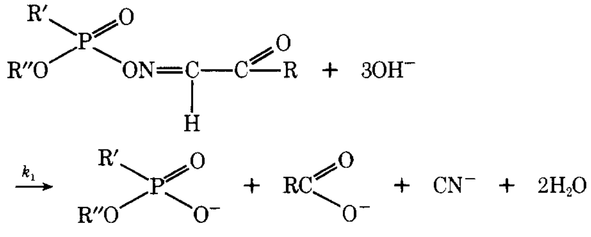

(2)