rapidly at room temperature to give a thick black tar and was therefore stored at −80° in the dark.

Registry No.—**1**, 116-11-0; **2**, 128-08-5; **3a**, 32730-64-6; **3b**, 26562-24-3; **3c**, 32730-66-8; **4a**, 32730-67-9; **4b**, 26562-25-4; **4c**, 32730-69-1; **5a**, 32730-70-4; **5b**, 126-38-5; **5c**, 32730-72-6; **6a**, 78-95-5; **6b**, 598-31-2; **6c**, 3019-04-3; **7a**, 32827-44-4; **7b**, 32730-75-9; **7c**, 32730-76-0.

Acknowledgment.—We thank the Science Research Council (London) for a research studentship to G. G.

Alkaline Hydrolysis of Phosphoramidothioate Esters[1]

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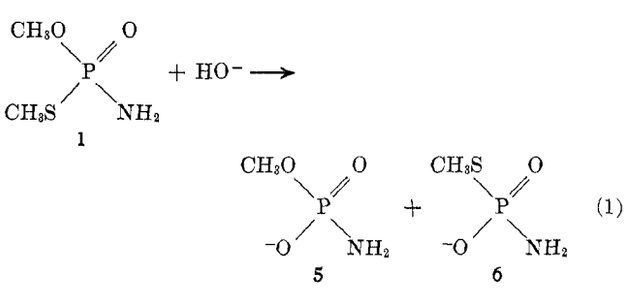
Received April 29, 1971

Products from the alkaline hydrolysis of *O*-methyl *S*-methyl phosphoramidothioate and its *N*-methyl and *N,N*-dimethyl derivatives were determined by analysis of pmr spectra and by glc. In aqueous potassium hydroxide *O*-methyl *S*-methyl phosphoramidothioate is hydrolyzed by P–O bond cleavage to give potassium *S*-methyl phosphoramidothioate as the major product while in the less polar solvents, methanol and acetone, P–S bond cleavage occurred to give mainly potassium *O*-methyl phosphoramidate. In ethanolic or propanolic potassium hydroxide the main products were potassium *O*-ethyl and *O*-propyl phosphoramidate, respectively, and dimethyl sulfide. Kinetic analysis showed that in water the second-order rate constants for P–O and P–S bond cleavage of *O*-methyl *S*-methyl phosphoramidothioate are 8.4 and 0.6 M^{-1} min^{-1}, respectively. Both rate constants and the relative rates of P–O/P–S bond cleavage decreased markedly with sequential substitution of the amido protons with methyl groups, and the *N,N*-dimethyl derivative hydrolyzed virtually exclusively by P–S bond cleavage but at a rate some 10^3 times slower than P–S cleavage in unsubstituted phosphoramidothioate. Exclusive P–S bond cleavage in the *N,N*-dimethylphosphoramidothioate evidently occurs by a normal concerted SN2 reaction in which the best leaving group departs. In phosphoramidothioates containing at least one amido proton the results are rationalized in terms of two competing processes, an addition–elimination reaction on phosphorus leading to P–O bond cleavage and an elimination reaction involving the amido proton to give P–S bond cleavage.

O-Methyl *S*-methyl phosphoramidothioate[2,3] (Monitor, Chevron Chemical Co.) is a relatively simple organophosphorus ester which is currently under development as a potential insecticide. Monitor or **1** is highly toxic to a variety of insects,[4] producing typical cholinergic symptoms of intoxication. In an earlier investigation[4] on the mode of action of **1** and related esters it was suggested that the alkylthiolate moiety was released when the cholinesterase enzyme was inhibited by the phosphoramidothioate ester. Subsequently, however, examination of the reaction between **1** and hydroxide ion has shown that methylthiolate ion is not always the major product but methoxide also is liberated, the relative amounts depending on the conditions of the reaction. Because of the possible connection between alkaline hydrolysis rates and anticholinesterase activity, an examination of the alkaline hydrolysis of **1** and its *N*-methyl (**2**) and *N,N*-dimethyl (**3**) analogs was initiated. Product and kinetic analyses were undertaken to sort out the various individual reactions and to assess quantitatively their relative importance in the overall hydrolysis reaction. Particular attention was given to the effect of sequential substitution of methyl groups on the nitrogen atom and of solvent on the specific rates of P–O and P–S bond cleavage.

Results

Products of Alkaline Hydrolysis.—Pmr spectra of the products obtained from the hydrolysis of *O*-methyl *S*-methyl phosphoramidothioate (**1**) with equimolar amounts of potassium hydroxide in water and in 50% aqueous acetone showed that two monoanionic products were obtained, one by P–S cleavage giving *O*-methyl phosphoramidate anion (**5**) and the other by P–O cleavage giving *S*-methyl phosphoramidothioate anion (**6**). In water the major product obtained was **6**, since analysis of the pmr integrals for P–OCH_3 protons



(1)

(doublet centered at δ 3.7, J = 11 Hz) and P–SCH_3 protons (doublet centered at δ 2.2, J = 12 Hz) showed a ratio of **5**:**6** of 1:4.5. In 50% aqueous acetone, however, **5** was the major product, and the ratio of **5**:**6** in this case was 5.1:1. Support for the ratio of products obtained by integration of pmr spectra was provided by glc analysis after remethylation of the mixture of **5** and **6** with diazomethane. Remethylation of **5** and **6** gave dimethyl phosphoramidate (**4**), retention time 1.75 min, and **1**, retention time 3.50 min, respectively, and the ratio of these products was virtually identical with the ratio of **5**:**6** obtained by proton integration. Confirmation of product ratios by glc, therefore, allowed the use of pmr as the major means of product analysis.

Data for product analysis by pmr after alkaline hydrolysis of **1** in a variety of solvent systems are given in Table I. The results indicate that the solvent strongly influences the relative percentages of **5** and

(1) This investigation was supported in part by the U. S. Public Health Service Research Grant No. EP 00806 from the Environmental Protection Agency; The Rockefeller Foundation; and Cotton Incorporated.

(2) Chevron Research Corp., Netherlands Patent Application 6,602,588 (Jan 2, 1967); *Chem. Abstr.*, **67**, 10691y (1967).

(3) W. Lorenz, G. Schrader, G. Unterstenkoefer, and I. Hammermann, A. G. Belgian Patent 666,143 (Dec 30, 1965); *Chem. Abstr.*, **65**, 16864 (1966).

(4) G. B. Quistad, T. R. Fukuto, and R. L. Metcalf, *J. Agr. Food Chem.*, **18**, 189 (1970).

TABLE I
SALT DISTRIBUTION IN ALKALINE HYDROLYSIS OF *O*-METHYL *S*-METHYL PHOSPHORAMIDOTHIOATE IN VARIOUS ORGANIC–WATER SOLVENT MIXTURES AT 23°

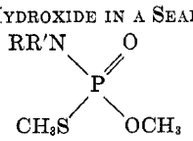
% Organic solvent in aqueous mixture (v/v)	% Salt containing— P-OCH_3	P-SCH_3
Methanol 100	93	7
95	86	14
90	79	21
85	76	24
80	67	33
75	63	37
65	50	50
50	40	60
0	18	82
Acetone 50	83	17
Mesityl oxide 10, ethanol 30	33	67
Propionaldehyde 50, ethanol 25	80	20
Formaldehyde[a] 30	100	
Acetophenone 20, ethanol 60	25	75
Acetonitrile 50	23	77
2-Butanone 45, ethanol 10	60	40
Ethanol 100	7.5	12.5
	80[b]	
Propanol 100	10	22.5
	67.5[c]	
Benzaldehyde 25, ethanol 20	83	17

[a] Extensive polymerization occurred. [b] P-OC_2H_5. [c] P-OC_3H_7.

6 produced and, in the case of the methanol–water system, an increasingly larger amount of P–O bond cleavage was obtained with increasing amounts of water; *e.g.*, 5:6 in absolute methanol was 93:7 compared to 18:82 in water.

When **1** was treated with an equimolar amount of potassium hydroxide in absolute ethanol or propanol, the major product was neither **5** nor **6** but the potassium salt of *O*-ethyl and *O*-propyl phosphoramidic acid, respectively. Further, distillation of the reaction mixture containing 1-propanol or ethanol as a solvent gave a low-boiling fraction (37–40°) which was identified by glc and pmr as dimethyl sulfide. Dimethyl sulfide also was isolated by the same procedure in varying quantities after the treatment of **1**, *O*-methyl *S*-methyl *N*-methylphosphoramidothioate (**2**), and *O*-methyl *S*-methyl *N*,*N*-dimethylphosphoramidothioate (**3**) with potassium hydroxide in water (Table II). Dimethyl sulfide apparently is formed

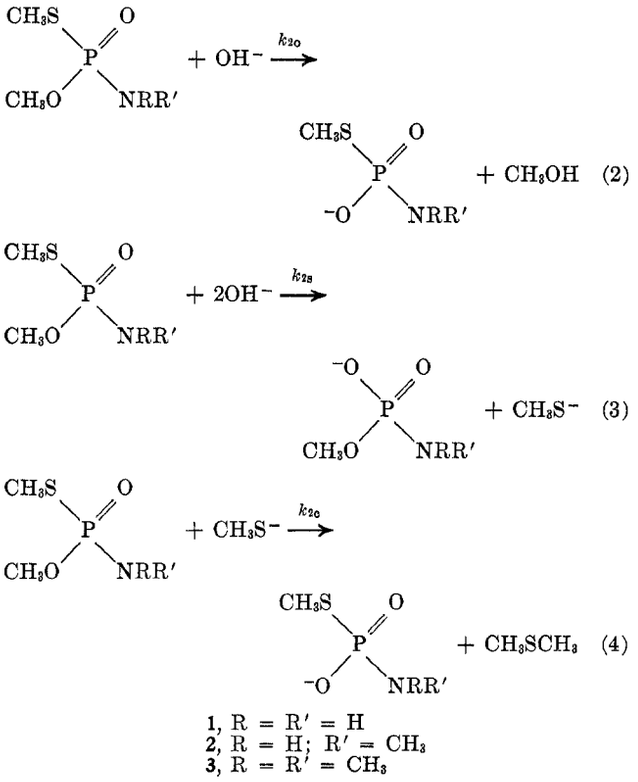
TABLE II
PRODUCT DISTRIBUTION AFTER HYDROLYSIS OF PHOSPHORAMIDOTHIOATES BY AQUEOUS POTASSIUM HYDROXIDE IN A SEALED AMPOULE



R	R′	Temp, °C	Reaction time, hr	% Salt containing— P-OCH_3	P-SCH_3	% MeOH	% CH_3SCH_3
H	H	23	4	18	82	75	10
H	CH_3	23	16	52	48	30	19
CH_3	CH_3	23	96	50	50	13–15[a]	[b]
CH_3	CH_3	96	14	42	58	24	32

[a] Reaction mixture was distilled to obtain methanol in high concentration for glc. [b] Reaction at atmospheric pressure; dimethyl sulfide was not determined.

from the reaction between methylthiolate anion, produced by P–S bond cleavage, and the starting ester. O-Demethylation by thiolate anions has been demonstrated by others.[5] Therefore, the reactions involved in the decomposition of **1** and related esters by hydroxide ion may be depicted as follows (eq 2–4). Here



(2)

(3)

(4)

1, R = R′ = H
2, R = H; R′ = CH_3
3, R = R′ = CH_3

k_{2o}, k_{2s}, and k_{2c} are the specific second-order rate constants for P–O, P–S, and C–O bond cleavage, respectively.

Evidently, *S*-methyl phosphoramidothioate anion (**6**) may be produced in two ways, from replacement by hydroxide ion according to eq 2 or from O-demethylation by methylthiolate ion according to eq 4. The extent of **6** (or its *N*-methyl and *N*,*N*-dimethyl equivalent) formed by replacement of methoxide by hydroxide ion was determined by glc analysis for methanol in the reaction mixture. Quantitative data showing the relative amounts of the various products produced after treatment of **1**, **2**, and **3** by equimolar aqueous potassium hydroxide are presented in Table II. The results indicate that the O-demethylation reaction to produce **6** or its *N*-alkyl derivatives becomes increasingly important with sequential methylation of nitrogen.

Finally, in order to determine whether potassium hydroxide treatment of **1** produced methanol by P–O or C–O bond cleavage, the reaction was carried out in water enriched with $H_2{}^{18}O$. The liberated methanol was examined by mass spectrometry and no significant ^{18}O incorporation was found, indicating that hydrolysis occurred by P–O bond cleavage.

Kinetic Analysis.—Equations 2–4 provide an example in which the second-order reactions are both parallel and in series.[6] By restricting the conditions of the reactions it was possible to evaluate the various rate constants with reasonable confidence.

Hydrolysis of *O*-Methyl *S*-Methyl Phosphoramidothioate (1).—Under conditions of high concentrations

(5) B. Miller, *Proc. Chem. Soc.*, 303 (1962).
(6) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1961, p 178.

of 1 compared to hydroxide, the values for the overall pseudo-first-order rate constant k_1 were obtained by following hydroxide ion consumption from estimation of the change in pH. Under these conditions eq 4 may be omitted in the kinetic analysis of 1 since hydroxide ion is not involved in this equation. Figure 1 shows the plot of pH *vs.* time based on the relation $pH = -k_1t/2.303 + pH_0$ where pH_0 is the initial pH and k_1 is the overall pseudo-first-order constant at constant phosphoramidothioate concentration. Also, $k_1 = k_{1o} + ak_{1s}$ where k_{1o} and k_{1s} are the pseudo-first-order constants for P–O and P–S cleavage, respectively. The value of the coefficient a depends on the pH of the solution; *i.e.*, a is 2 at pH substantially greater than the pK_a of methanethiol (10.7) and a is 1 at pH lower than 10.7. From the slope of the line, the values for the overall pseudo-first-order constant k_1 and overall second-order constant k_2 at 27° was calculated to be 0.96 min^{-1} and 9.6 M^{-1} min^{-1} (1 was 0.1 M), respectively.

The value of k_{2o}, the second-order constant for P–O bond cleavage, was determined directly by following methanol production under second-order conditions of 1 and hydroxide ion as shown in Figure 2. The plot was reasonably linear up to about 65% reaction and k_{2o} was calculated to be 8.4 M^{-1} min^{-1} at 27°. From the relationship $k_2 = k_{2o} + 2k_{2s} = 9.6$ M^{-1} min^{-1}, k_{2s} was calculated to be 0.6 M^{-1} min^{-1}. Values for k_{2o} and k_{2s} are given in Table III.

TABLE III
SECOND-ORDER RATE CONSTANTS FOR P–O (k_{2o}) AND P–S (k_{2s}) CLEAVAGE OF PHOSPHORAMIDOTHIOATES IN AQUEOUS POTASSIUM HYDROXIDE AT 27°

	k_{2o}, M^{-1} min^{-1}	k_{2s}, M^{-1} min^{-1}
$(CH_3O)(CH_3S)P(O)NH_2$	8.4	0.6
$(CH_3O)(CH_3S)P(O)NHCH_3$	1.0×10^{-3}	4.4×10^{-2}
$(CH_3O)(CH_3S)P(O)N(CH_3)_2$		1.5×10^{-4}

Effect of Acetone on Hydrolysis of 1.—The effect of acetone on the values of the pseudo-first-order constants k'_{1o} and k'_{1s} under conditions of constant pH for P–O and P–S cleavage is shown in Table IV. Because of

TABLE IV
PSEUDO-FIRST-ORDER RATE CONSTANTS IN AQUEOUS ACETONE FOR THE ALKALINE HYDROLYSIS OF O-METHYL S-METHYL PHOSPHORAMIDOTHIOATE AT pH 10, μ = 0.2 M

% Acetone (v/v)	$k'_{1s} \times 10^3$, min^{-1}	$k'_{1o} \times 10^3$, min^{-1}	Calcd from CH_3SH release ($t_{1/2}$)	Calcd from HO^- consumption
0				3.0
10	1.6	5.0	6.9	
20	3.1	5.5	8.6	
30	4.2	5.9	10.6	10.1
40	6.2	6.0	12.5	12.2

interference by acetone in the glc analysis of methanol, it was not possible to determine k'_{1o} directly in solvents containing acetone. Therefore, k'_{1o} was calculated from the values of k'_1 (overall pseudo-first-order constant at constant pH) and k'_{1s} was determined at pH 10.0 in aqueous solvents containing 0–40% acetone and sodium carbonate as the buffer. k'_{1s} was calculated from the relationship below (eq 5) by following

$$\frac{[CH_3SH]}{[A_0]} = \frac{k'_{1s}}{k'_1}(1 - e^{-k'_1t}) \quad (5)$$

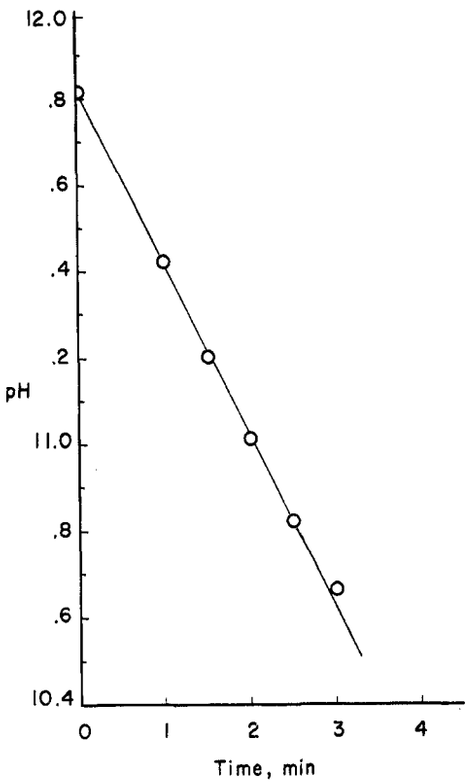


Figure 1.—Plot showing rate of hydroxide ion decrease at 27°; O-methyl S-methyl phosphoramidothioate (1) is 0.1 M.

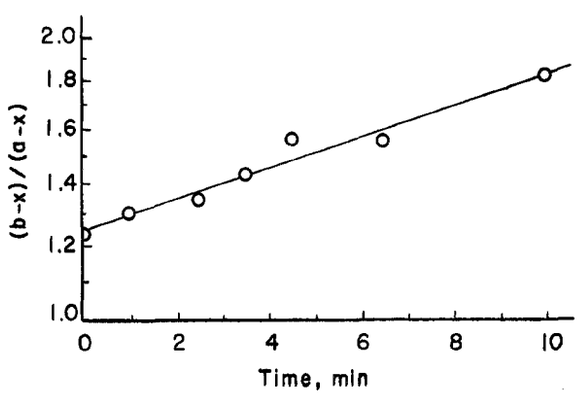


Figure 2.—Second-order plot showing rate of P–O bond cleavage from estimation of methanol formation at 27°; a = 2.0×10^{-2} M O-methyl S-methyl phosphoramidothioate (1), $b = HO^- = 2.4 \times 10^{-2}$ M, x = methanol concentration.

methanethiol formation where $[A_0]$ is the initial concentration of 1. A plot of $[CH_3SH]/[A_0]$ *vs.* $(1 - e^{-k'_1t})$ gave the linear relationship shown in Figure 3 and k'_{1s} was calculated from the slope. The value of k'_1 was determined from the amount of base needed to maintain a pH of 10.0 using a micrometer-driven syringe containing standardized aqueous potassium hydroxide. k'_1 also was calculated from the relationship $t_{1/2} = \ln 2/k'_1$ which follows from eq 5 where $t_{1/2}$ is the time required to liberate one-half of the total amount of methanethiol released. The data in Table IV show good agreement between the values of k'_1 obtained by estimation of potassium hydroxide consumption and that calculated from the $t_{1/2}$ value for methanethiol release.

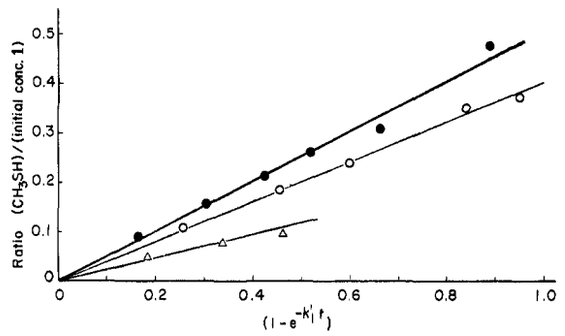


Figure 3.—Plots showing the rate of P–S bond cleavage of *O*-methyl *S*-methyl phosphoramidothioate (**1**) according to eq 5 in aqueous acetone at 27°: initial concentration of **1** = 8×10^{-3} *M*; ●, 40% acetone; ○, 30% acetone; △, 10% acetone.

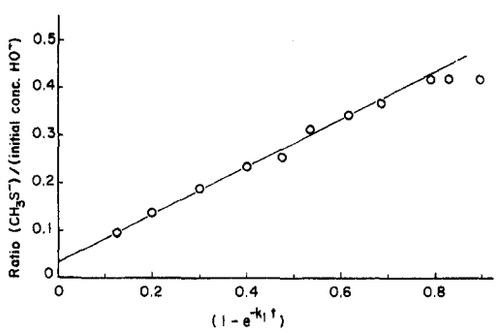


Figure 4.—A plot showing the rate of P–S bond cleavage of *O*-methyl *S*-methyl *N*-methylphosphoramidothioate (**2**) according to eq 13 at 27°: **2** = 0.5 *M*, HO^- = 2.48×10^{-2} *M*.

Hydrolysis of *O*-Methyl *S*-Methyl *N*-Methylphosphoramidothioate (2).—The overall rate of reaction between *O*-methyl *S*-methyl *N*-methylphosphoramidothioate (**2**) and hydroxide ion determined by estimating change in pH was approximately 110-fold slower than **1**, with a pseudo-first-order rate (excess of **2**) constant k_1 of 4.45×10^{-2} min^{-1} and a second-order rate constant k_2 of 8.9×10^{-2} M^{-1} min^{-1}. Because of the slow rate of reaction between **2** and hydroxide ion, loss of **2** by dealkylation (eq 3) was significant and it was possible to determine k_{1c} (the pseudo-first-order rate constant for C–O cleavage) as well as k_{1o} and k_{1s}. Kinetic analysis was accomplished by imposing again, as in the case of **1**, pseudo-first-order conditions, *i.e.*, high concentrations of **2** relative to hydroxide ion. Under these conditions, eq 2, 3, and 4 may be designated as follows

$$A + B \xrightarrow{k_{1o}} C \quad (6)$$

$$A + B \xrightarrow{k_{1s}} D \quad (7)$$

$$A + D \xrightarrow{k_{1c}} G \quad (8)$$

where A = **2**, B = hydroxide ion, C = methanol, D = methylthiolate ion, and G = dimethyl sulfide. From eq 6, 7, and 8, and since A is constant, eq 9 and 10 may be obtained.

$$\frac{-d[B]}{dt} = k_1[B] = k_{1o}[B] + 2k_{1s}[B] \quad (9)$$

$$\frac{d[D]}{dt} = k_{1s}[B] - k_{1c}[D] \quad (10)$$

Since $[B] = [B_0]e^{-k_1 t}$, where $[B_0]$ is the initial hydroxide ion concentration, eq 10 becomes eq 11.

$$\frac{d[D]}{dt} = k_{1s}[B_0]e^{-k_1 t} - k_{1c}[D] \quad (11)$$

This first-order differential equation has the following solution.

$$[D] = \frac{k_{1s}[B_0]}{k_{1c} - k_1}(e^{-k_1 t} - e^{-k_{1c} t}) \quad (12)$$

When k_{1c} is small compared to k_{1s}, integration of eq 11 results in eq 13.

$$\frac{[D]}{[B_0]} = \frac{k_{1s}}{k_1}(1 - e^{-k_1 t}) \quad (13)$$

This equation is similar to eq 5 where $[B_0]$ (initial hydroxide ion concentration) is substituted for $[A_0]$ (phosphoramidothioate concentration).

Figure 4 gives the plot of $[CH_3S^-]/[OH_0^-]$ *vs.* $(1 - e^{-k_1 t})$. Expected linearity was obtained over the major portion of the reaction from which k_{1s} at 27° was calculated as 2.20×10^{-2} min^{-1}. From the relation $k_1 = k_{1o} + 2k_{1s} = 4.45 \times 10^{-2}$ min^{-1} the value of k_{1o} was calculated as 5×10^{-4} min^{-1}. The corresponding second-order rate constants k_{2o} and k_{2s} given in Table III were obtained by dividing the values of k_{1o} and k_{1s} by 0.5 *M* (initial concentration of **2**). It should be noted that the line in Figure 4 does not pass through the origin. This was interpreted as being attributable to localized hydrolysis when the potassium hydroxide solution was mixed with the compound. This corresponds to about 7% reaction.

The value of k_{1c} was calculated by using eq 12 with the aid of a computer. By setting the value of k_1 to 4.45×10^{-2} min^{-1}, estimated values of k_{1s} and k_{1c} were substituted in eq 12 until the calculated values of methylthiolate ion concentration at different time intervals coincided with the experimental values. Best fit of the data was obtained when k_{1s} was 2.2×10^{-2} min^{-1} and k_{1c} was 3.6×10^{-3} min^{-1}. Figure 5 shows the relationship between the curve calculated from eq 12 and the observed curve after correction for localized hydrolysis.

Hydrolysis of *O*-Methyl *S*-Methyl *N*,*N*-Dimethylphosphoramidothioate (3).—The rate of hydrolysis of **3** was much slower than that of **2** under identical first-order conditions of excess phosphoramidothioate over base with a pseudo-first-order constant k_1 for the disappearance of hydroxide ion of 1.4×10^{-4} min^{-1}. No methanethiol was detectable at any time during the course of the reaction, indicating that the rate of reaction between methanethiolate ion and **3** to form dimethyl sulfide was considerably faster than the initial reaction between hydroxide ion and **3**. k_{1c}, the pseudo-first-order rate constant for methyl-oxygen bond cleavage for **2** and **3** under the same condition, should be similar, and based on the value of $k_{1c} = 3.6 \times 10^{-3}$ min^{-1} obtained for **2**, the dealkylation reaction for **3** should be approximately 25-fold faster than the initial reaction.

Analysis of products after reaction between **3** and potassium hydroxide showed that P–O cleavage was much slower than P–S cleavage (23°) and this coupled with the above information gives the order $k_{1c} > k_{1s} \gg k_{1o}$. By making the assumption that k_{1o} is negligibly small compared to k_{1s}, the kinetics of the reac-

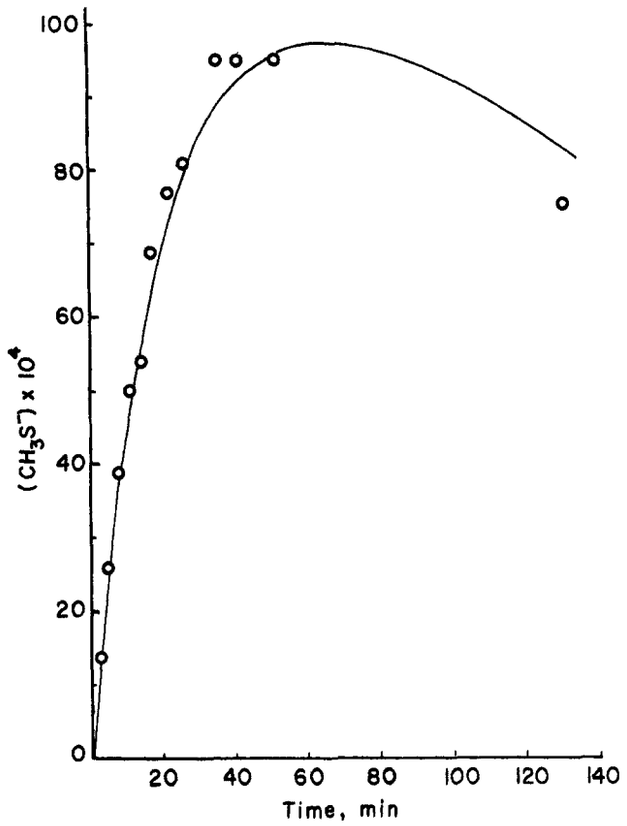
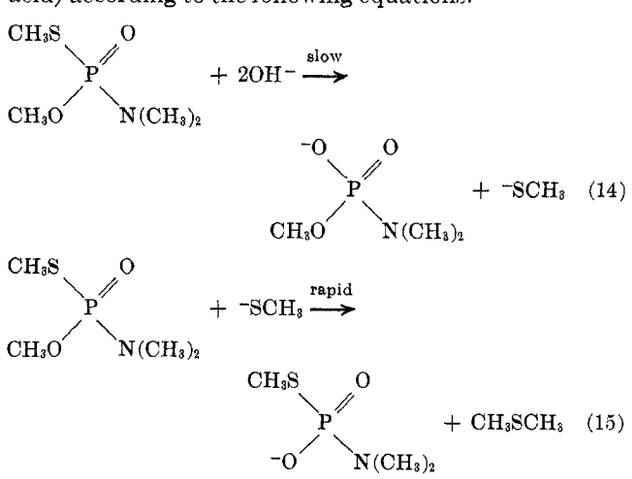


Figure 5.—A curve showing the relationship between the amount of methylthiolate calculated from eq 12 (solid line) and the experimental values (O) during the reaction between *O*-methyl *S*-methyl *N*-methylphosphoramidothioate and hydroxide ion.

tion may be approximated to a second-order situation with the provision that 2 mol of **3** are consumed (1 mol by P–S cleavage in the rate-determining step and 1 mol by a rapid dealkylation reaction) with 2 mol of hydroxide ion (1 mol for P–S cleavage and 1 mol for rapid neutralization of the resulting phosphoramidic acid) according to the following equations.



By using equimolar amounts of **3** and hydroxide ion the value for the second-order rate constant k_{2s} for P–S cleavage may be determined from eq 16 where

$$1/[OH^-] = 1/[OH^-_0] + 2k_{2s}t \quad (16)$$

$[OH^-]$ and $[OH_0^-]$ are the concentrations of hydroxide ion at time t and time zero, respectively. Figure 6

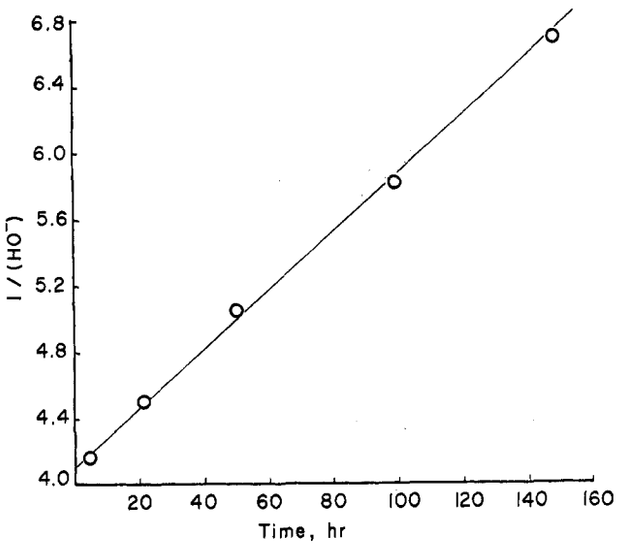


Figure 6.—A second-order plot of the reaction between *O*-methyl *S*-methyl *N*,*N*-dimethylphosphoramidothioate (**3**) and hydroxide ion.

gives the relation obtained when $1/[OH^-]$ is plotted against time from data obtained in a separate experiment using equimolar concentrations of **3** and hydroxide ion. The excellent straight line obtained over a 45% reaction range provides support for the assumptions made in the kinetic approach; *i.e.*, the overall reaction is second-order. From the plot, k_{2s} was found to be $1.5 \times 10^{-4}\ M^{-1}\ \text{min}^{-1}$ (27°).

The value of k_1 ($1.4 \times 10^{-4}\ \text{min}^{-1}$) obtained under the pseudo-first-order condition of excess phosphoramidothioate (**3** was 0.5 *M*) also is equal to $2k_{1s}$ since k_{1o} is negligible. From this relationship also k_{2s} may be calculated as $1.4 \times 10^{-4}\ M^{-1}\ \text{min}^{-1}$, in good agreement with the value obtained under second-order conditions.

Hydrolysis of *S*,*S*-Dimethyl Phosphoramidodithioate (7).—*S*,*S*-Dimethyl phosphoramidodithioate (**7**) was examined, since under alkaline conditions it can hydrolyze only by P–S bond cleavage without other competing reactions. The second-order rate constant k_2 for the reaction between **7** and aqueous potassium hydroxide (0.1 *M*) was $0.65\ M^{-1}\ \text{min}^{-1}$ at 25°. When the solvent was changed to 10% acetone–water (by volume), k_2 increased to $9.0\ M^{-1}\ \text{min}^{-1}$ and in 20% acetone–water k_2 was $19\ M^{-1}\ \text{min}^{-1}$. Thus, the addition of acetone caused an increase in k_2 similar to the effect of acetone on k'_{1s} observed with **1**.

Hydrolysis of *O*,*O*-Dimethyl Phosphoramidothioate (8).—Compared to simple trialkyl phosphorothionates, the rate of reaction between hydroxide ion and *O*,*O*-dimethyl phosphoramidothioate was relatively fast with a second-order constant for P–O cleavage of $1.1\ M^{-1}\ \text{min}^{-1}$ at 37°, a value which is about fivefold smaller than that obtained for dimethyl phosphoramidate ($5.0\ M^{-1}\ \text{min}^{-1}$) at the same temperature.[7]

Discussion

Effect of Solvent.—Because of the greater lability of the P–S bond,[8,9] the hydrolysis of **1** in aqueous potas-

(7) I. Öney and M. Caplow, *J. Amer. Chem. Soc.*, **89**, 6972 (1967).
(8) E. M. Thain, *J. Chem. Soc.*, 4694 (1957).
(9) D. C. Dittmer and O. B. Ramsay, *J. Org. Chem.*, **28**, 1268 (1963).

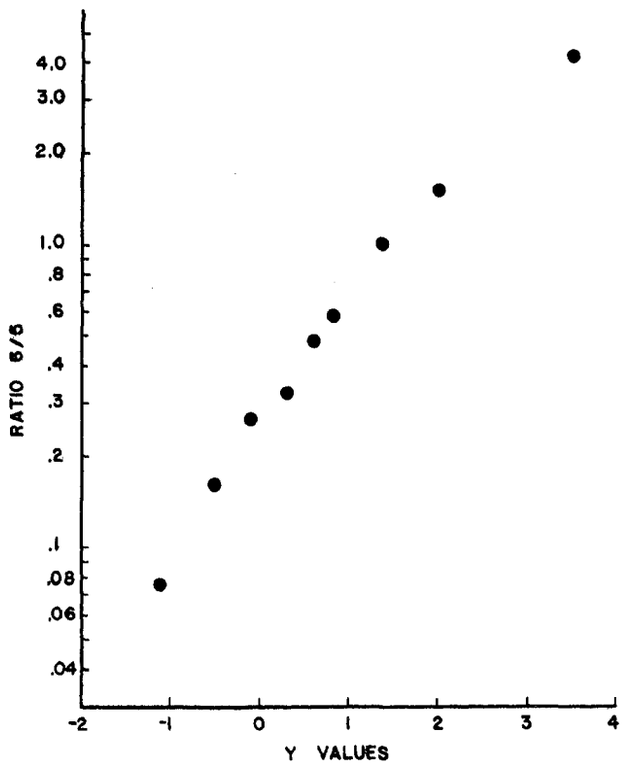


Figure 7.—Relation between Grunwald-Winstein Y values and the logarithm of the ratio of potassium *S*-methyl phosphoramidothioate (**6**) to *O*-methyl phosphoramidate (**5**).

sium hydroxide by predominantly P–O bond rather than P–S bond cleavage was unexpected. The ionizing capacity of the solvent evidently plays a dominant role in establishing the direction in which **1** is hydrolyzed by potassium hydroxide. The influence of solvent on the reaction is illustrated in Figure 7 which shows the relation between Grunwald-Winstein Y values for water–methanol[10,11] and the logarithm of the ratio of **6** to **5**. Although the product ratio in two parallel second-order reactions at any time is equal to the ratio of rate constants,[12] the value of **6**/**5** may only be considered as an approximation of the relative rate constants for P–O and P–S cleavage, since the same salt is obtained by O-demethylation and P–O cleavage. Figure 7 shows, however, that alkaline hydrolysis of **1** by P–O bond cleavage is favored in solvents of greater ionizing capacity. In less polar solvents P–S bond cleavage predominates, suggesting that the two competing reactions (P–O and P–S cleavage) occur by different mechanisms.

Table IV shows the effect of increasing amounts of acetone on the pseudo-first-order rate constants for P–O (k'_{1o}) and P–S (k'_{1s}) cleavage of **1** at pH 10.0. Figure 8 gives the relation between these constants and Grunwald–Winstein Y values for the relevant acetone–water mixtures. Although the relationship is clearly not linear, it does focus on the far greater dependency of k'_{1s} on solvent polarity; *e.g.*, k'_{1s} increases almost fourfold from 10% to 40% acetone while k'_{1o} remains virtually constant. Thus, in increasing apolar solvent P–S cleavage becomes increasingly important,

(10) E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, **70**, 846 (1948).
(11) E. Alexander, "Principles of Ionic Organic Reactions," Wiley, New York, N. Y., 1961, p 91.
(12) Reference 6, p 165.

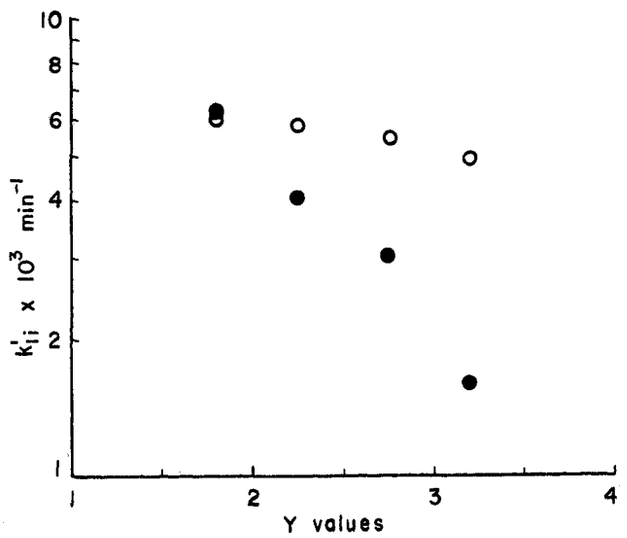


Figure 8.—Relationship between k_{1s} (●) and k_{1o} (○) and Grunwald-Winstein Y values for the alkaline hydrolysis of *O*-methyl *S*-methyl phosphoramidothioate in aqueous acetone.

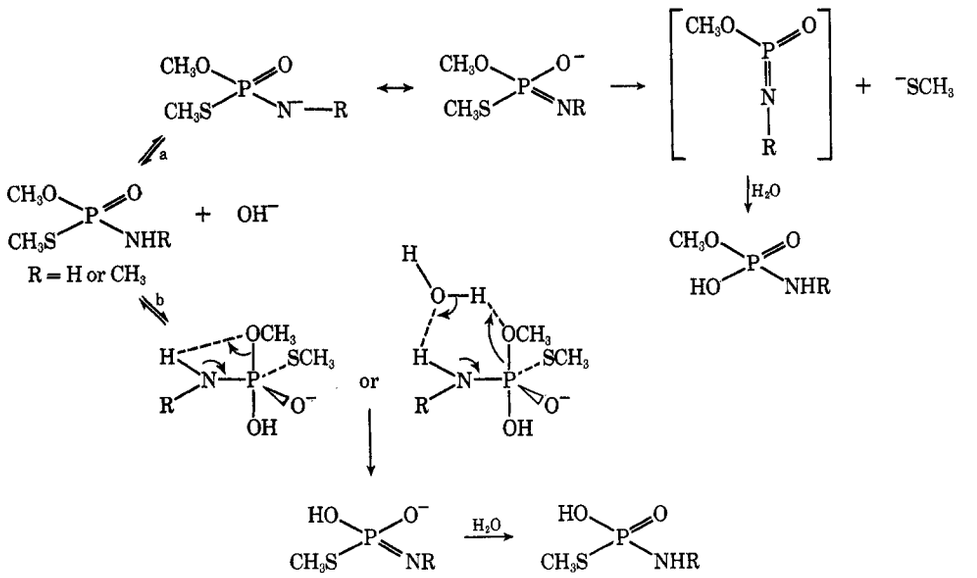
resulting eventually in a changeover in ratio of products.

The effect of acetone on the rate of P–S cleavage was even more pronounced in the alkaline hydrolysis of *S*,*S*-dimethyl phosphoramidodithioate (**7**). In water the second-order rate constant for the alkaline hydrolysis of **7** after correction for two methylthiolate leaving groups is 0.65 M^{-1} min^{-1} at 25°, virtually identical with the k_{2s} value of 0.6 M^{-1} min^{-1} for **1** at 27°. In alkaline solutions containing 10% and 20% acetone, the rate constant for **7** increased approximately 15- and 30-fold, respectively.

Effect of Methyl Substitution.—The values for the specific second-order rate constants for P–O (k_{2o}) and P–S (k_{2s}) bond cleavage for **1**, **2**, and **3** in aqueous potassium hydroxide at 27° in Table III show that there is a marked decrease in both k_{2o} and k_{2s} with sequential substitution of amido protons by methyl. In addition, the relative rates for P–O and P–S cleavage also decreased; *e.g.*, k_{2o}/k_{2s} was 14 for **1**, 0.023 for **2**, and presumably much smaller for **3**. Thus, **1** was hydrolyzed predominantly by P–O cleavage while P–S cleavage predominated with **2** and **3**.

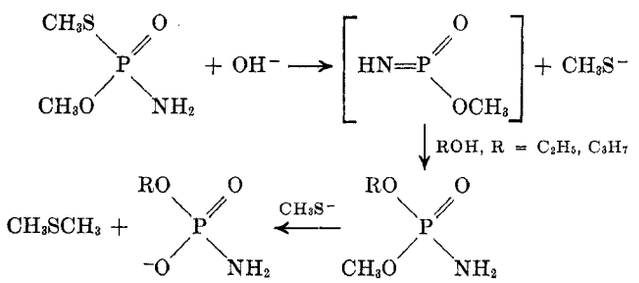
The value for k_2 of 5.0 M^{-1} min^{-1} (37°) previously reported for hydroxide ion catalyzed hydrolysis of dimethyl phosphoramidate[7] (**4**) is close to that for **1** at 27° and suggests that P–O cleavage in **1** and **4** occurs by a similar mechanism. Since compound **4** undergoes alkaline hydrolysis 10^4-fold faster than its *N*,*N*-dimethyl analog, a mechanism involving a metaphosphorimidate intermediate formed after removal of one of the nitrogen protons was suggested. In addition, a similar mechanism involving a phosphorimidate intermediate has been proposed by others[13,14] to account for the rapid hydrolysis of certain phosphoramidic chlorides. Our results, however, are difficult to rationalize in terms of a single process of this type alone. A plausible mechanism in which two different processes are taking place simultaneously may be suggested from the data: process a, which involves hy-

(13) P. S. Traylor and F. H. Westheimer, *J. Amer. Chem. Soc.*, **87**, 553 (1965).
(14) A. F. Gerrard and N. K. Hamer, *J. Chem. Soc. B*, 539 (1968).



droxide ion attack on the amido proton, leading to the phosphoramidothioate anion which decomposes in a rate-determining step to give P–S cleavage, and process b, which involves attack of hydroxide ion on the phosphorus atom, eventually resulting in P–O cleavage.

Process a, leading to P–S cleavage and phosphorimidate formation, is analogous to the mechanism proposed for base-catalyzed hydrolysis of phosphoramidic chlorides.[13,14] Direct support for this mechanism is found in results obtained from the analysis of products after base-catalyzed hydrolysis of **1** in absolute ethanol and propanol. The observation that **1** reacts with potassium hydroxide in absolute ethanol or propanol to give as major products dimethyl sulfide and the potassium salt of ethyl and propyl phosphoramidic acid, respectively, strongly indicates that this reaction proceeds through a metaphosphorimidate. In ethanol or propanol the intermediate is solvolyzed to give ethyl or propyl methyl phosphoramidate, which is in turn demethylated by methylthiolate anion to produce the respective products as shown below.



The finding that P–O cleavage predominates in highly polar solvents suggests that this reaction proceeds by a process involving hydroxide ion attack on the phosphorus atom, either by a concerted SN2 (P) or by an addition–elimination reaction. Although a concerted SN2 reaction may lead to P–O cleavage, it does not account for the preponderance of P–O over P–S cleavage, particularly since methylthiolate ion is a superior leaving group compared to methoxide ion. Thus, process b, leading to P–O cleavage, probably involves, at least in the case of **1** and **2**, the addition of the hydroxide ion to the phosphoramidothioate followed by a rapid elimination of the alkoxy group rather than a concerted SN2 type reaction. The addition step is expected to lead to a trigonal bipyramidal intermediate and from preference rules[15] the methoxy and hydroxy groups should occupy apical positions. With the methoxy group in an apical position, its departure may be assisted by the nitrogen proton either directly or indirectly by the intervention of a water molecule as indicated in the mechanism given above. The addition–elimination mechanism explains why P–O cleavage takes place with **1** and **2** but does not occur with **3** where the nitrogen atom is fully substituted with methyl groups. The exclusive cleavage of the P–S bond in **3** probably occurs by a concerted SN2 mechanism in which the best leaving group, *i.e.*, methylthiolate, is displaced by hydroxide ion.[8,9] This is the usual type of substitution reaction with most triesters of phosphoric acid.[16] The fact that the hydrolysis of **3** by P–S cleavage is approximately 3×10^3 times slower than that of **1** suggests different mechanisms for the hydrolysis of **1** and **3**.

Other evidence which is consistent with a mechanism postulating initial hydroxide attack on phosphorus to explain P–O bond cleavage is that *O,O*-dimethyl phosphoramidothioate (**8**) hydrolyzes approximately fivefold slower than the corresponding P=O analog in aqueous alkali, resulting exclusively in P–O cleavage. The difference in rates is consistent with the known deactivating effect of thiono sulfur[16] in reactions involving attack of a nucleophile on phosphorus. Further, the approximately threefold greater rate of P–O cleavage of **1** by hydroxide ion compared to dimethyl phosphoramidate (**4**) also is consistent with this mechanism owing to less d_π–p_π overlap between sulfur and phosphorus in **1**. In contrast, *O*-methyl *N*-cyclohexylphosphoramidothioic chloride has been reported[17] to hydrolyze substantially faster than its P=O derivative with elimination of chloride ion. These results have been rationalized on the basis of a mechanism involving hydroxide ion attack on amido proton with subsequent elimination of chloride, a good leaving group, and to the relative ease of formation

(15) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).
(16) J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).
(17) A. F. Gerard and N. K. Hamer, *J. Chem. Soc. B*, 369 (1969).

of P=S phosphorimidate compared to P=O phosphorimidate. It is unlikely, however, that P–O cleavage occurs by this type of mechanism because of the poor leaving ability of the methoxide moiety.[18]

The rate of P–O cleavage in the reaction between **1** and aqueous potassium hydroxide is more than tenfold greater than the rate at which **7** undergoes P–S cleavage under similar conditions. This may be attributed to the catalytic effect provided by the amido proton through hydrogen bonding with the leaving methoxyl moiety in the transition state. Catalytic effects of this type where a nucleophile attacks the reactive center and a proton assists the leaving group are known.[19] The substantial drop in rate of P–O cleavage of **2** compared to **1** may be attributed to steric interference by the methyl group combined with the decrease in the tendency of the amido proton to dissociate, hence decreasing proton assistance in the transition state.

The nature of the products obtained after alkaline hydrolysis of **1** or **2** depends on the relative rates of the two competing reactions a and b in the mechanistic scheme. The competition between these two reactions in different solvent systems bears a striking resemblance to the well-established competition between nucleophilic substitution and elimination reactions in the alkaline hydrolysis of alkyl halides, *e.g.*, 2-bromopropane.[20]

Finally, the discrepancy observed between the ratio of rate constants k_{2o}/k_{2s} and the ratio of products obtained experimentally from product analysis[1] for **2** and **3** deserves comment. Considering **2** first, product analysis after using equimolar amounts of **2** and potassium hydroxide in water gave a ratio of P–O to P–S cleavage of about 1:2. In contrast, the ratio k_{2o}/k_{2s} determined by using 50-fold more **2** than hydroxide ion was in the order of 1:44. Because of the high nucleophilicity of hydroxide ion toward phosphorus, it is possible that at the higher concentration of hydroxide the bimolecular mechanism leading to P–O cleavage benefits more than the elimination reaction leading to P–S cleavage. However, it was not possible to provide support for this statement owing to the complex nature of the kinetic analysis under second-order conditions.

In the case of **3** where the kinetic analysis precluded P–O cleavage, *i.e.*, the assumption was made that k_{2o} is negligibly small compared to k_{2s}, product analysis using equimolar amounts of **3** and potassium hydroxide showed that a significant amount of methanol was liberated, indicating P–O cleavage. The results here, however, are not directly comparable since product analysis for methanol was made after distillation of the reaction mixture to avoid the masking effect of dimethyl sulfide in the glc determination and to obtain methanol in high concentration. According to eq 14 and 15, half of the original amount of **3** should be in the form of the anion of methyl *N*,*N*-dimethylphosphoramidic acid after consumption of potassium hydroxide, and it is likely that during distillation of the reaction mixture C–O bond fission occurred by attack of water on the methyl carbon to produce methanol. Support for this possibility is found in the facile C–O bond cleavage of methyl and dimethylphosphoric acid in water at high temperature under neutral conditions.[21]

(18) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N. Y., 1965, p 280.

(19) J. Epstein, D. H. Rosenblatt, and M. M. Demek, *J. Amer. Chem. Soc.*, **78**, 341 (1956).

(20) K. A. Cooper, M. L. Dhar, E. D. Hughes, C. K. Ingold, B. J. MacNulty, and L. I. Wolf, *J. Chem. Soc.*, 2043 (1948).

Experimental Section

The phosphoramidothioate esters used in this study have been described previously.[4] The pmr spectrum of *O*-methyl *S*-methyl phosphoramidothioate (**1**) showed a doublet centered at δ 3.6 (J = 13 Hz) for $POCH_3$ protons and a doublet centered at δ 2.2 (J = 15 Hz) for $PSCH_3$ protons; *O*-methyl *S*-methyl *N*-methylphosphoramidothioate (**2**) showed a multiplet centered at δ 5.3 for the NH proton, a doublet centered at δ 3.7 for the $POCH_3$ protons (J = 13 Hz), a quartet centered at δ 2.5 for $PNCH_3$ protons, and a doublet centered at δ 2.2 for $PSCH_3$ protons (J = 15 Hz); *O*-methyl *S*-methyl *N*,*N*-dimethylphosphoramidothioate (**3**) showed a doublet centered at δ 3.6 for $POCH_3$ protons (J = 12 Hz), a doublet centered at δ 2.7 for $PN(CH_3)_2$ protons (J = 11 Hz), and a doublet centered at δ 2.2 for $PSCH_3$ protons (J = 14 Hz). Pmr spectra were obtained on a Varian T-60 spectrometer using deuteriochloroform or deuterium oxide as the solvent. Tetramethylsilane was used as the internal standard.

S,*S*-Dimethyl phosphoramidodithioate (**7**) was prepared as follows. Ammonia was passed into a solution of 10 g of *S*,*S*-dimethyl phosphorochloridodithioate,[22] bp 68–70° (0.05 mm), $n^{24}D$ 1.5734, in 150 ml of anhydrous toluene until cessation of precipitate formation. The mixture was warmed to 50° for 30 min and cooled, and the toluene-insoluble product and ammonium chloride were collected by filtration. The crude product was taken up in 30 ml of warm methanol and filtered to remove ammonium chloride, and toluene was added to the filtrate until crystallization occurred. Recrystallization from a methanol–toluene mixture gave 7.1 g of product (80%), mp 105–106°

Anal. Calcd for $C_2H_8NOPS_2$: C, 15.29; H, 5.10. Found: C, 15.66; H, 5.49.

Alkaline Hydrolysis.—All solvents used in this study were redistilled under nitrogen before use. In a typical hydrolysis reaction to determine products 1.41 g (0.01 mol) of **1** was dissolved in 10.0 ml of water (or appropriate solvent) to which was added 0.6 g of reagent grade potassium hydroxide in 10 ml of water and the mixture was allowed to stand in a 23° thermostated water bath for 4 hr. Removal of the solvent under reduced pressure produced a solid salt residue which was washed three times each with 5 ml of acetonitrile and dried at 0.02 mm pressure at 90° for 30 min. Analysis of the pmr spectra showed that the coupling of CH_3O (J = 11 Hz) and CH_3S (J = 12 Hz) protons with phosphorus in the two salts (**5** and **6**) was distinctly different from the coupling of CH_3O (J = 13 Hz) and CH_3S (J = 15 Hz) in the starting material (**1**).

Reaction in absolute ethanol or propanol (dried and distilled over magnesium) was carried out similarly by dissolving equimolar amounts of **1** and potassium hydroxide in solvent and allowing the mixture to stand for 4 hr. The reaction flask was attached to a 15-cm Vigreux column connected to a distillation head through which chilled water was passed and the mixture was heated to distil dimethyl sulfide, which was collected at 37–40°. Dimethyl sulfide was identified by pmr (singlet at δ 2.0) and by gas–liquid chromatography. The residual salts obtained after removal of ethanol or propanol were identified by pmr. Potassium ethyl phosphoramidate in deuterium oxide showed a multiplet at δ 4.0 for methylene protons and a triplet or a multiplet (depending on resolution) at δ 1.4 for methyl protons. Potassium propyl phosphoramidate showed a multiplet at δ 3.9 for OCH_2 protons, a multiplet at δ 1.7 for methylene protons, and a triplet at δ 1.0 for methyl protons.

Alkaline hydrolysis of **1** in ^{18}O-enriched water was carried out as described above using 1.5% ^{18}O water obtained from Bio Rad Laboratories, Richmond, Calif. After standing for 4 hr at 50°, the reaction mixture was heated to collect a water–methanol azeotropic mixture, which was examined in a Hitachi Perkin-

(21) W. C. Barnard, C. A. Bunton, D. R. Llewellyn, C. A. Vernon, and V. A. Welch, *J. Chem. Soc.*, 2670 (1961).

(22) T. W. Mastin, G. R. Norman, and E. A. Wellmuenster, *J. Amer. Chem. Soc.*, **67**, 1662 (1945).

Elmer Model RMO-693 double focus mass spectrometer. Analysis of the mass spectral data showed no significant incorporation of ^{18}O in methanol, *i.e.*, the $(M^+ + 2)$ peak for methanol had a relative abundance of only 0.28%.

Methanol and dimethyl sulfide were determined quantitatively by glc using an F & M Model 402 gas chromatograph equipped with hydrogen flame detector and a 6-ft 5% Carbowax Gas-Chrom Q column at 78°. For dimethyl sulfide determinations after hydrolysis of the phosphoramidothioate esters, the reactions were carried out in sealed ampoules and cooled in ice–water prior to glc analysis. Estimations of methanol and dimethyl sulfide were made by comparing peak areas obtained from standard solutions of methanol in water or dimethyl sulfide in a dimethyl sulfoxide–water mixture.

Methylation of **5** and **6** for glc analysis was carried out with diazomethane.[23] The sample to be esterified was dissolved in 1:9 methanol–ether, acidified with methanolic HCl, and treated with excess diazomethane at room temperature for 1 hr. The solution was concentrated and an aliquot was analyzed by glc using a hydrogen flame detector modified for thermionic detection of phosphorus by mounting a KCl pellet in the hydrogen jets. A 6-ft column containing 3.5% diethylene glycol succinate on SupelCoport (mesh size 80/100) at a temperature of 210° was used. Nitrogen, hydrogen, and air flow rates were 51, 41, and 40 ml/min, respectively.

Kinetic Methods. A. *O*-Methyl *S*-Methyl Phosphoramidothioate (1).—The overall rate of reactions between **1** and hydroxide ion (combined P–S and P–O cleavage) was determined under pseudo-first-order conditions (excess **1**) by following the drop in pH of the reaction mixture using a Corning Model 12 research pH meter equipped with an expanded scale accurate to ±0.005 pH unit. Reactions were carried out under nitrogen in a double-wall thermostated glass cell maintained at 27.0° and provided with a magnetic stirrer and glass electodes. Typically, to 19.6 ml of an aqueous solution containing 282 mg of **1** (2 mmol) was added 0.4 ml of 0.495 *M* aqueous sodium hydroxide and the rate was monitored by measuring the drop in pH.

5,5′-Dithiobis(2-nitrobenzoic) acid[24,25] (DTNB) was used to follow the rate of methanethiol release (P–S bond cleavage). Rates of P–S bond cleavage were determined under pseudo-first-order conditions in carbonate buffer at pH 10.0, ionic strength 0.2 *M*. Sealed ampoules initially containing 8×10^{-3} *M* **1** in carbonate buffer were removed at intervals from a constant-temperature bath and chilled in ice, and an aliquot was added to a solution consisting of 0.2 ml of 0.01 *M* DTNB in pH 7.0 phosphate buffer to make a final volume of 5.0 ml. The magnitude of the yellow color produced was estimated at 412 mμ in a Bausch and Lomb Spectronic-20 spectrophotometer. Amounts of methanethiol present in solution were determined from a standard curve.

Combined rates of P–S and P–O cleavage also were determined at constant pH. As hydrolysis of **1** occurred the amount of standard sodium hydroxide necessary to maintain the pH at the initial setting of 10.0 ± 0.1 was estimated by means of a manually operated micrometer-driven microsyringe. In experiments involving the effect of added acetone on pseudo-first-order hydrolysis rates, the pH of the initial alkaine solutions containing variable amounts of acetone (10, 20, 30, and 40% v/v) was standardized to equal the pH of a sodium carbonate buffer (pH 10.0 in water) containing the same amount of acetone. In these experiments the ionic strength was maintained constant at 0.2 *M* by the use of sodium chloride.

Rates of methanol release (P–O bond cleavage) were estimated by glc as previously described. For the hydrolysis of **1**, a 1-ml aliquot of a reaction mixture consisting of 2×10^{-2} *M* **1** and 2.4×10^{-2} *M* potassium hydroxide was withdrawn at different time intervals and acidified with 0.1 ml of 1 *N* hydrochloric acid, and a sample was analyzed by glc.

B. *O*-Methyl *S*-Methyl *N*-Methylphosphoramidothioate (2).—The overall pseudo-first-order rate of reaction between **2** and hydroxide ion was followed by the pH-drop method described above for **1**. Because of the slower rate of reaction of **2**, the initial concentration of this material was set at 0.5 *M*. P–S bond cleavage was estimated by DTNB reagent under the same pseudo-first-order conditions of excess **2** over potassium hydroxide used to determine overall rate except that the reactions were carried out in sealed ampoules as described for **1**. Ionic strength was maintained at 0.2 *M* with sodium chloride.

C. *O*-Methyl *S*-Methyl *N*,*N*-Dimethylphosphoramidothioate (3).—Because of its greater stability compared to **1** and **2**, estimation of the rate of hydrolysis of **3** was possible by titration with standardized hydrochloric acid of the amount of hydroxide ion remaining after different time intervals. Rate measurements were made under pseudo-first-order conditions identical with that described for **2** and also under second-order conditions of equimolar amounts (approximately 0.25 *M*) of potassium hydroxide and **3**.

D. *S*,*S*-Dimethyl Phosphoramidodithioate (7).—The rate of the reaction of **7** with hydroxide ion was followed by use of the DTNB reagent according to the method described for **1** and **2**. Hydroxide ion concentration was 0.1 *M* and **7** was 1×10^{-3} *M*.

E. *O*,*O*-Dimethyl Phosphoramidothioate (8).—The rate of hydrolysis of **8** was determined in equimolar concentrations of **8** and hydroxide ion (0.055 *M*) by titration with standardized hydrochloric acid. The reaction was carried out in a 20% ethanol–water mixture.

Registry No.—**1**, 10265-92-6; **2**, 28167-49-9; **3**, 25218-42-2; **5**, 32979-53-6; **6**, 32979-54-9; **7**, 32979-55-8; **8**, 17321-47-0; potassium hydroxide, 1310-58-3.

Acknowledgments.—We gratefully acknowledge valuable discussions with Dr. Lyle K. Gaston. We are indebted also to the granting agencies for financial support of this work.

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