1082. *The Reactivity of Organophosphorus Compounds. Part IX.*[1] *The Reaction of Thionates with Alkyl Iodides.*

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The reaction, $EtO{\cdot}P(\colon S)XY + RI \longrightarrow RS{\cdot}P(\colon O)XY + EtI$, where X and Y are R, RO, RS, or R_2N, has been investigated. Kinetic measurements and qualitative experiments based on analyses of products have shown that the reaction proceeds most readily when X and Y are amino- or substituted amino-groups and, in all cases, is accelerated when conducted in solvents of high dielectric constant. The preparative consequences are discussed.

ALKYLATION of simple phosphorothionates was first reported by Emmett and Jones,[2] who noted that trimethyl phosphorothionate, $(MeO)_3PS$, on heing heated gave the isomeric

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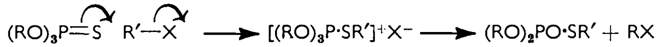
[1] Part VIII, Cadogan and Moulden, preceding paper.

[2] Emmett and Jones, *J.*, 1911, **99**, 713.

thiolate, $(MeO)_2PO\cdot SMe$. About the same time Pishchimuka[3] described the formation of *S*-butyl diethyl phosphorothiolate in the reaction of triethyl phosphorothionate with n-butyl iodide: $(EtO)_3PS + Bu^nI \longrightarrow (EtO)_2PO\cdot SBu^n + EtI$. Both reactions required vigorous conditions to ensure good conversions, and synthetic exploitation has been slight, although Kabachnik and his co-workers[4] recently demonstrated that dialkyl alkylphosphonothionates rearrange to the isomeric thiolates in the presence of the appropriate

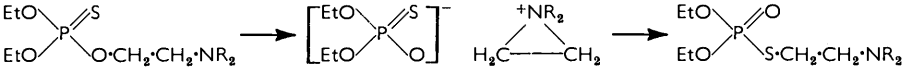
$$(RO)_2PS\cdot R'' + R'Br \longrightarrow (RO)(R'S)PO\cdot R'' + RBr$$

alkyl halide at high temperatures. They restricted the reaction (i) to the case of R = R'. The common mechanism of these reactions is almost certainly of the type:



$$(RO)_3P{=}S \quad R'{-}X \longrightarrow [(RO)_3P\cdot SR']^+X^- \longrightarrow (RO)_2PO\cdot SR' + RX \quad . \quad . \quad . \quad . \quad \text{(i)}$$

where R'X is $(MeO)_3PS$ in the first case and Bu^nI in the second. The reaction would, therefore, be expected to occur more readily with a highly electrophilic α-carbon atom in R'X and/or a highly nucleophilic sulphur atom in the phosphorothionate. Evidence concerning the first factor is available. It has been shown in this investigation and elsewhere[5] that triethyl phosphorothionate is much more slowly isomerised by heat to the corresponding thiolate than is the trimethyl analogue, in which the alkyl groups are more electrophilic. On the other hand, the isomerisation of 2-dialkylaminoethyl diethyl phosphorothionates (I) to the corresponding thiolates,[6] and that of the 2-ethylthioethyl analogue[7] to *S*-2-ethylthioethyl diethyl phosphorothiolate, occurs very readily.

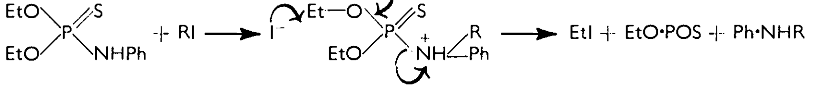


(I)

The driving force in these reactions is the ease of ionisation of these compounds which is a result of the stability of the intermediate ethyleniminium (or sulphonium) ions. The overall effect is therefore that of a thionate containing a highly electrophilic alkyl group.

Little is known of the factors which influence the nucleophilicity of the $\geqslant P{=}S$ group, and it was our intention, by a study of the effect of substituent groups in the phosphorothionate on the ease of its reaction with alkyl halides, to measure such factors.

The reaction of thionates with alkyl iodides has now been extended to phosphoroamidates (II), such as diethyl *N*-cyclohexylphosphoroamidothionate (II; $X = EtO$, $Y = NH\cdot C_6H_{11}$) and ethyl *NN'*-dicyclohexylphosphorodiamidothionate (II; $X = Y = NH\cdot C_6H_{11}$). In theory, amidothionates could react in two ways with alkyl iodides: at the sulphur atom as described in equation (i), and at the nitrogen atom, thus:



since it has been shown[8] that in certain circumstances the nitrogen atom of phosphoramidates is appreciably nucleophilic.

However, when an alkoxyl group (generally ethoxyl) was present in the thionate, *S*-alkyl compounds corresponding to the alkyl iodide used were obtained, and no evidence in favour of participation of the nitrogen atom in the reaction was found. The structures

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[3] Pishchimuka, *J. Russ. Phys. Chem. Soc.*, 1912, **44**, 1406.

[4] Kabachnik, Mastryukova, and Kurochkin, *Bull. Acad. Sci. U.S.S.R.*, 1956, 185.

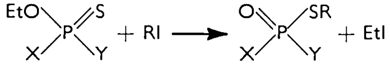
[5] Walling and Rabinowitz, *J. Amer. Chem. Soc.*, 1959, **81**, 1243.

[6] Fukoto and Stafford, *J. Amer. Chem. Soc.*, 1957, **79**, 6083; Tammelin, *Acta Chem. Scand.*, 1957, **11**, 1738.

[7] Fukoto and Metcalf, *J. Amer. Chem. Soc.*, 1954, **76**, 5103.

[8] Cadogan, *J.*, 1957, 1079.

of the resulting thiolates (III) were confirmed by analyses, infrared spectrography, and independent syntheses, in two cases, and in appropriate cases the presence of a P·SEt



(II) (III) . . . . (ii)

group in the product was confirmed by the formation of *S*-ethyl-*S*-toluene-*p*-sulphonamido-*N*-toluene-*p*-sulphonylsulphidimine [1] (IV).

Qualitative experiments indicated that the amidothionates reacted much more readily in reaction (ii) than did triethyl phosphorothionate under comparable conditions. More accurate kinetic experiments have confirmed this, as shown in Table 1, in which mean values are given for the constant obtained for reactions of propyl iodide with a series of thionates.

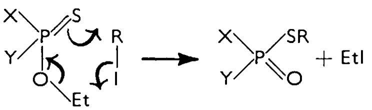
TABLE 1.

Reactions of thionates EtO·P(:S)XY with Pr^{n}I (10 mol.) at 105°.

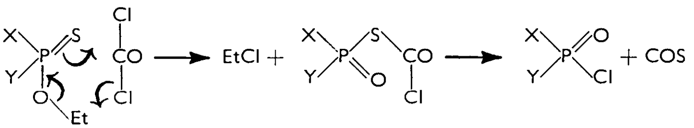
X	Y	$t_{\frac{1}{2}}$ (hr.)	10^5k (sec.$^{-1}$) *
NH·C_6H_{11}	NH·C_6H_{11}	0·48	40
NH·C_6H_4Me-*p*	NH·C_6H_4Me-*p*	2·6	7·5
EtO	NH_2	3·5	5·5
EtO	NH·C_6H_{11}	5·5	3·5
EtO	Piperidino	6·9	2·8
EtO	NH·C_6H_4Me-*p*	14	1·4
EtO	Me	23	0·85
EtO	Ph	32	0·60
EtO	EtO	43	0·45
EtO	EtS	55	0·35
EtO	Cl	*ca.* 15 days	—

* Pseudounimolecular reaction.

The results show that the presence of groups such as NH_2, NHR, NR_2, and NHAr strongly facilitates the reaction of thionates with alkyl iodides, diamidates being particularly reactive. Within the limits of our experiments it can also be seen that thionates containing less powerful electron-donating groups such as methyl, ethoxyl, and thioethyl react less readily, while the chloridothionate, containing the strongly electron-attracting chlorine atom, is effectively unreactive. *OO*-Diethyl hydrogen thiophosphite $(EtO)_2PHS$, also reacted very slowly with propyl iodide, to give ethyl iodide, but in a non-first-order process, indicating that the basic reaction is different in this case. The order of activation of the process by substituent groups is therefore: R_2N, etc. $>$ R $>$ RO $>$ RS. The lower reactivity of triethyl phosphorothionate than of diethyl methylphosphonothionate is interesting since it suggests greater electron repulsion by the methyl than by the ethoxyl group. A complete explanation of the differences in reactivity must await a more exhaustive kinetic analysis and would even then require a knowledge, so far unavailable, of the stereochemistry of the transition state in each case. The observed greater reactivity of the sulphur atom in phosphonothionates than in phosphorothionates is in accord with the only results concerning nucleophilic reactions of thionates. It has been shown [9] that the phosphonothionates react readily with carbonyl chloride, whereas phosphorothionates and phosphorothiolothionates do not. It is probable, therefore, that both types of reaction follow similar paths which can be schematically represented thus:



. . . . (iii)



. . . (iv)

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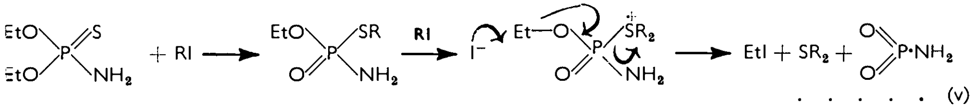
[9] Cadogan, *J.*, 1961, 3067.

By analogy with the ease with which the reactions of amidothionates and alkyl iodides occur it is predicted that the reactions of the former with carbonyl chloride should also occur readily, but no relevant experimental evidence is available. Regardless of whether the conversion of thionates into thiolates proceeds as described in equation (i) or by a concerted process as outlined in equation (iii), the presence of alkyl groups more electrophilic than ethyl would probably facilitate the overall reaction. This view is supported by the observation that, in the reaction of benzyl diethyl phosphorothionate with propyl iodide, debenzylation occurs 2·5 times more readily than de-ethylation.

In the reactions of thionates with propyl iodide the first-order plot for the formation of ethyl iodide was linear over most of the reaction. In the case of diethyl phosphoramidothionate slight curvature of the plot corresponding to an increased rate of formation of the iodide was observed, suggesting that further reaction between newly formed thiolate and propyl iodide had occurred:



. . . . . (v)

This is supported by the observation that ethyl *S*-propyl phosphoramidothioate (III; R = Prⁿ, X = EtO, Y = NH_2) with propyl iodide gives ethyl iodide at a slow but significant rate ($k_1 = 4{\cdot}2 \times 10^{-6}$ sec.$^{-1}$; $t_{\frac{1}{2}} = 46$ hours), and by isolation from the reaction of diethyl phosphoramidothionate (II; X = EtO, Y = NH_2) and methyl iodide of a small quantity of trimethylsulphonium iodide, formed presumably from dimethyl sulphide [equation (v); R = Me]. Such a process would also account for Emmett and Jones's observation[2] that the reaction of trimethyl phosphorothiolate with methyl iodide gave trimethylsulphonium iodide.

TABLE 2.

Reaction of thionates with PrⁿI (10 mol.) in solvents (10 mol.).

	Dielectric	$(EtO)_2PS{\cdot}NH{\cdot}C_6H_{11}$		$(EtO)_2PPhS$	
Solvent	constant	$t_{\frac{1}{2}}$ (hr.)	10^5k (sec.$^{-1}$)	$t_{\frac{1}{2}}$ (hr.)	10^5k (sec.$^{-1}$)
PrⁿI	5	5·5	3·5	32	0·6
$Me_2{\cdot}CH{\cdot}NO_2$	25	2·4	8·0	15	1·3
$Ph{\cdot}NO_2$	33	2·2	8·6	14	1·4
Me·CO·NHMe	166	0·49	39·0	5·3	3·6

The use of solvents of increasing dielectric constant [nitromethane or 2-nitropropane ($\varepsilon = 25$), nitrobenzene (33), or *N*-methylacetamide (166)[10]] appreciably increased the rates of the reaction of thionate with propyl iodide without affecting the nature of the products (Table 2). The use of such solvents, particularly of nitromethane, which as a low-boiling liquid facilitates the isolation of the products, considerably enhances the usefulness of this route to compounds previously difficult to prepare. The formation of diethyl *S*-methyl phosphorothioate from methyl iodide and triethyl phosphorothionate for example, requires several weeks at the boiling point of the iodide, 5 days in the presence of nitromethane, and 45 minutes in the presence of *N*-methylacetamide at 105°. The use of the *N*-methylacetamide as a solvent also appreciably increased the rate of thermal isomerisation of triethyl phosphorothionate to thiolate, a process usually difficult to effect.[5]

O-Dealkylation occurs in all of the reactions discussed above. This, coupled with the high reactivity of diamides, suggested that phosphorothioic triamides and related compounds not containing alkoxyl groups should react readily with alkyl iodides to give

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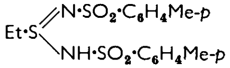
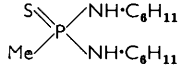
[10] Leader and Gormley, *J. Amer. Chem. Soc.*, 1951, **73**, 5731; Williams, Ellard, and Dawson, *ibid.*, 1957, **79**, 4652.

products of a type not isolable from similar reactions of phosphoramidothioic esters. In accord with this, hexa-*N*-ethylphosphorothioic triamide (V) and *NN'*-dicyclohexylmethylphosphonothioic diamide (VI) with methyl iodide readily gave stable crystalline monomethiodides.

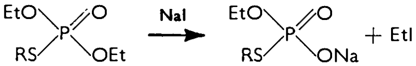

(IV)

$(Et_2N)_3PS$
(V)


(VI)

Although the exact structure of these adducts, which dissociate when heated *in vacuo*, has not been established, the methyl group is probably associated with the sulphur atom of the thionate, as in $[(Et_2N)_3P{\cdot}SMe]^+I^-$, since aqueous hydrolysis of the *NN'*-dicyclohexylmethylphosphonothioic diamide methiodide gives a strong odour of methanethiol. The triamide methiodide, when heated with triethylamine, gave triethylamine methiodide and hexa-*N*-ethylphosphorothioic triamide. Similar adducts of trimethylphosphine sulphide and methyl iodide have been described.[11]

Pertinent to the foregoing discussion are the reactions of sodium iodide with phosphorothioates. In agreement with the above observations *O*- rather than *S*-dealkylation of triethyl and *S*-benzyl diethyl phosphorothiolates by sodium iodide in ethyl methyl ketone readily occurs:


. . . . (vi)

In the case of triethyl phosphorothionate, however, sodium *OS*-diethyl phosphorothioate, rather than the expected *OO*-diethyl ester, was isolated. Plainly, in this case, *O*-dealkylation first occurs to give ethyl iodide and the bidentate *OO*-diethyl phosphorothioate ion, which further reacts by way of the more nucleophilic form, $(EtO)_2P(\dot{:}O)S^-$, to give triethyl phosphorothiolate with the regeneration of sodium iodide. Reaction as in (vi) then gives the observed product.

$$(EtO)_3PS \xrightarrow{I^-} EtI + [(EtO)_2POS]^- \longrightarrow (EtO)_2PO{\cdot}SEt + I^- \longrightarrow [(EtO)(EtS)PO_2]^- + EtI$$

EXPERIMENTAL

Extracts were dried over magnesium sulphate. The light petroleum used had b. p. 40—60° The infrared spectra in the region 2—15 μ were obtained by using a Perkin-Elmer model 21 double-beam spectrophotometer fitted with a rock-salt prism. Those in the region of 15—25 μ were recorded on a Hilger H.800 double-beam spectrophotometer fitted with a potassium bromide prism. Liquids were examined as capillary films between potassium bromide plates, and solids in potassium chloride or bromide discs. The provision of these facilities by Mr. L. C. Thomas, and his help in the interpretation of the spectra, which was in part based on his unpublished correlations, are gratefully acknowledged.

Preparation of Compounds.—Triethyl phosphorothionate and phosphorothiolate were prepared as described in Part VIII.[1] Diethyl methylphosphonothionate, b. p. 78°/10 mm., n_D^{25} 1·4605, was prepared by the reaction of methylphosphonothioïc dichloride with ethanolic sodium ethoxide (Found: C, 35·4; H, 7·8. Calc. for $C_5H_{13}O_2PS$: C, 35·7; H, 7·8%). Hoffmann, Wadsworth, and Weiss [12] reported b. p. 46°/2·3 mm., n_D^{25} 1·4619. *Diethyl phenylphosphonothionate*, b. p. 163°/20 mm., 96°/0·05 mm., n_D^{25} 1·5370, was similarly prepared (50%) from phenylphosphonothioic dichloride (Found: C, 52·6; H, 6·6. $C_{10}H_{15}O_2PS$ requires C, 52·2; H, 6·6%). *Benzyl diethyl phosphorothionate* was prepared by boiling diethyl phosphorochloridothionate (50 g.) in benzene (100 ml.) with a solution of sodium benzyloxide [formed from benzyl alcohol (32 g.) and sodium (6·9 g.)] in benzene (300 ml.) for 2 hr. Benzene (200 ml.) was removed by distillation, light petroleum (300 ml.) was added, and the mixture filtered

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[11] Hantzsch and Hibbert, *Ber.*, 1907, **40**, 1508.

[12] Hoffmann, Wadsworth, and Weiss, *J. Amer. Chem. Soc.*, 1958, **80**, 3945.

through Celite 545. Distillation and redistillation gave a product (30 g.), b. p. 130°/0·2 mm., n_D^{25} 1·5120 (Found: C, 50·9; H, 7·0. $C_{11}H_{15}O_3PS$ requires C, 50·75; H, 6·6%).

OO-Diethyl hydrogen phosphorothioite, b. p. 86°/20 mm., n_D^{25} 1·4600 (Found: C, 32·0; H, 7·3. Calc. for $C_4H_{11}O_2PS$: C, 31·2; H, 7·2%), was prepared (46%) by the method of Krawiecki and Michalski [13] who reported b. p. 75—76°/14 mm., n_D^{20} 1·4608. *OOS*-Triethylphosphorodithioate, b. p. 127°/15 mm., n_D^{25} 1·5019, was prepared (70%) by reaction of potassium *OO*-diethyl phosphorodithioate [14] with methanolic ethyl bromide.

Ethyl *P*-methyl-*N*-phenylphosphonamidothionate was prepared as follows: Dry ($MgSO_4$) triethylamine (6·8 g.) in ethanol (3·1 g.) and dry (Na) benzene (30 ml.) was added dropwise to methylphosphonothioic dichloride (10 g.) in dry benzene (80 ml.), and the mixture was boiled under reflux for 6 hr. On the next day, after filtration, the solution was washed with water (3 × 50 ml.) and dried. Distillation of the solution gave ethyl methylphosphonochloridothionate (7·2 g., b. p. 103°/70 mm., n_D^{25} 1·4930. Hoffmann, Wadsworth, and Weiss [12] reported b. p. 41°/4·0 mm., n_D^{25} 1·4950. A mixture of aniline (4·1 g.) and triethylamine (4·5 g.) in dry benzene (30 ml.) was added to the foregoing chloridate (7·2 g.) in benzene (80 ml.). After 3 hr. at the b. p. the mixture was filtered, was washed with water (3 × 50 ml.), and dried. Distillation gave *ethyl* P-*methyl*-N-*phenylphosphonamidothionate* (7·25 g.), b. p. 125°/0·05 mm., n_D^{25} 1·5770 (Found: C, 49·5; H, 6·5. $C_9H_{14}NOPS$ requires C, 50·2; H, 6·6%).

OS-Diethyl *N*-cyclohexylphosphoramidothioate was prepared by the addition of ethanethiol (20·8 g.) in ether (Na-dry; 50 ml.) to ethyl phosphorodichloridate (54·3 g.) and triethylamine (33·8 g.) in dry ether (300 ml.), followed by boiling for 2 hr.; cyclohexylamine (67 g., 2 mol.) was then added in dry ether (100 ml.). After a further 2 hr. at the b. p. the mixture was filtered, washed with water (2 × 100 ml.), and dried. Distillation gave a poor yield (19%) of material of b. p. 140°/0·25 mm., m. p. 53—54°.

Amidates derived from diethyl phosphorochloridothionate were prepared by reaction of the appropriate amine (2 mol.) with the chloridothionate (1 mol.) in a suitable boiling solvent, followed by washing and purification. *Diethyl* N-*cyclohexylphosphoramidothionate*, prepared (52%) in ether (2 hr.), had b. p. 121°/0·75 mm., n_D^{25} 1·4920 (Found: C, 47·6; H, 8·9. $C_{10}H_{22}NO_2PS$ requires C, 47·8; H, 8·8%). *Diethyl* N-p-*tolylphosphoramidothionate*, prepared (40%) in toluene (17 hr.), had m. p. 38° (from light petroleum) (Found: C, 51·0; H, 6·5. $C_{11}H_{18}NO_2PS$ requires C, 51·0; H, 7·0%). Diethyl phosphoramidothionate, prepared (87%) by passing ammonia through an ether solution of the chloridate for 4 hr., had b. p. 132°/20 mm., $n_D^{26.5}$ 1·4842 (Found: C, 28·5; H, 7·4. Calc. for $C_4H_{12}NO_2PS$: C, 28·4; H, 7·2%). Mel'nikov and Zen'kevich [15] reported b. p. 112—115°/9 mm., n_D^{20} 1·4828. *Ethyl* NN'-*dicyclohexylphosphorodiamidothionate*, prepared (53%) from ethyl phosphorodichloridothionate [16] (1 mol.) and cyclohexylamine (4 mol.) in ether at room temperature, had m. p. 76° (from aqueous ethanol) (Found: C, 55·7; H, 9·7. $C_{14}H_{29}N_2OPS$ requires C, 55·3; H, 9·6%). *Ethyl* NN'-*di*-p-*tolylphosphorodiamidothionate*, which could not be prepared by the previous method, was obtained as follows: Ethyl phosphorodichloridite (11·8 g.) in dry ether (100 ml.) was added dropwise to *p*-toluidine (34·4 g.) in dry ether (300 ml.). After removal of the hydrochloride by filtration, sulphur (2·6 g.) was added in small portions. Removal of the solvent at 40 mm. left a viscous liquid which, on treatment with boiling ethanol, deposited sulphur (0·4 g.), which was collected. After 7 days at 0° crystals (6%), m. p. 107°, were deposited (Found: C, 60·2; H, 6·6. $C_{16}H_{21}N_2OPS$ requires C, 60·0; H, 6·6%).

NN'-*Dicyclohexylmethylphosphonothioic diamide*, obtained in 53% yield from methylphosphonothioic dichloride (1 mol.) and cyclohexylamine (4 mol.), had m. p. 115° after recrystallisation from benzene–light petroleum (Found: C, 56·9; H, 9·6. $C_{13}H_{27}N_2PS$ requires C, 56·9; H, 9·9%).

Hexa-N-*ethylphosphorothioic Triamide*.—Phosphorus trichloride (34·4 g.) in dry ether (100 ml.) was added dropwise to an ice-cooled solution of diethylamine (146 g.) in ether (300 ml.). The reaction was extremely vigorous. After 3 hr. the hydrochloride was removed and the filtrate was evaporated under reduced pressure. Sulphur (8 g.) was added portionwise (0·25 g.) at $<25°$ to the residue in light petroleum (200 ml.). The resulting solution was filtered through Celite 545 and evaporated under reduced pressure to leave a red liquid (61·5 g.). Distillation

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[13] Krawiecki and Michalski, *J.*, 1960, 881.

[14] Cadogan and Thomas, *J.*, 1960, 2248.

[15] Mel'nikov and Zen'kevich, *J. Gen. Chem. U.S.S.R.*, 1955, **25**, 793.

[16] *Inorg. Synth.*, 1953, **4**, 75.

of the product, which occurred with much charring, gave the triamide as a pale red oil (48%), b. p. 104°/0·025 mm., $n_D^{23.5}$ 1·5040 (lit.,[17] b. p. 120—121°/0·1 mm., n_D^{20} 1·5052) (Found: C, 51·5; H, 11·3. Calc. for $C_{12}H_{30}N_3PS$: C, 51·6; H, 10·8%).

Reactions of Thionates with Alkyl Iodides.—(i) *Isolation of products.* (*a*) The reactions were effected by boiling a mixture of the thionate (1 mol.) and alkyl iodide (5—10 mol.) until reaction was complete, as shown by the appearance of P=O absorption in the infrared spectrum. The corresponding *S*-alkyl compound was isolated by distillation alone and/or recrystallisation as necessary. The method is exemplified by the reaction of methyl iodide with diethyl phosphoramidothionate: The amidate (4·9 g.) and methyl iodide (18·2 g.) were boiled under reflux for 4¾ hr. When cool, the colourless crystals which had been deposited were collected and washed with methyl iodide (3 ml.). Crystallisation from benzene gave trimethylsulphonium iodide (0·1 g.), m. p. and mixed m. p. 202—206° (correct infrared spectrum). Light petroleum was added to the mother liquors to precipitate O-*ethyl* S-*methyl phosphoramidothiolate*, which on recrystallisation from benzene–light petroleum had m. p. 67·5° (4 g., 89%) (Found: C, 23·4; H, 6·1. $C_3H_{10}NO_2PS$ requires C, 23·2; H, 6·5%).

Similar reactions are summarised in Table 3.

TABLE 3.

Details of the reaction $EtO{\cdot}P(:S)XY + RI \longrightarrow RS{\cdot}P(:O)XY + EtI$.

					Properties of RS·P(:O)XY						
X	Y	R in RI	Time (hr.)	Yield (%)	M. p.	B. p./mm.	Found (%) C	Found (%) H *	Formula	Reqd. (%) C	Reqd. (%) H
EtO	NH_2	Et	22	66	51° [1]	—	28·4	7·1	$C_4H_{12}NO_2PS$	28·4	7·1
EtO	NH_2	Pr^n	18	55	—	122—128°/ 0·05 [a]	33·0	7·6	$C_5H_{14}NO_2PS$	32·8	7·7
EtO	$NH{\cdot}C_6H_{11}$	Et	22	83	61	130°/0·25	47·9	8·7	$C_{10}H_{22}NO_2PS$	47·8	8·8
EtO	$NH{\cdot}C_6H_{11}$	Pr^n	19	98	30—32	—	49·6	8·9	$C_{11}H_{24}NO_2PS$	49·8	9·1
EtO	$NH{\cdot}C_6H_4Me$-*p*	Me	23	98	88·5— 91·5	—	49·3	6·9	$C_{10}H_{16}NO_2PS$	49·0	6·6
EtO	$NH{\cdot}C_6H_4Me$-*p*	Et	36	86	59—61	137—140°/ 0·025	51·0	7·0	$C_{11}H_{18}NO_2PS$	51·0	7·0
$NH{\cdot}C_6H_{11}$	$NH{\cdot}C_6H_{11}$	Pr^n	3	91	158 [1]	—	56·2	9·8	$C_{15}H_{31}N_2OPS$	56·6	9·8
$NH{\cdot}C_6H_4Me$-*p*	$NH{\cdot}C_6H_4Me$-*p*	Pr^n	12	90	161 [2]	—	61·3	6·6	$C_{17}H_{25}N_2OPS$	61·1	6·9
EtO	Me	Pr^n	92	51	—	106°/10 [b]	39·7	8·6	$C_6H_{15}O_2PS$	39·6	8·3
EtO	Ph	Pr^n	8 days	78	—	116°/0·01 [c]	54·3	7·0	$C_{11}H_{17}O_2PS$	54·1	7·0
$NH{\cdot}C_6H_{11}$	$NH{\cdot}C_6H_{11}$	Me	24 [3]	71	175	—	54·1	9·1	$C_{13}H_{27}N_2OPS$	53·8	9·4
EtO	Piperidino	Pr^n	41·5	66	—	106—110°/ 0·05 [d]	48·2	8·8	$C_{10}H_{22}NO_2PS$	47·8	8·8

* Recryst. from (1) benzene–light petroleum, (2) aq. EtOH. [3] Reaction at room temperature. n_D^{25} (*a*) 1·4906, (*b*) 1·4718, (*c*) 1·5365, (*d*) 1·4919.

(*b*) For reactions carried out in solvents, in general, an excess (10—20 mol.) of an equimolar mixture of alkyl iodide and nitromethane or *N*-methylacetamide was used. Ethyl *p*-methyl-*N*-phenylphosphonamidothionate (2·15 g.), for example, ethyl iodide (8·2 g., 5 mol.), and nitromethane (3·1 g., 5 mol.) were boiled under reflux for 18 hr. Removal of the solvents left *S*-ethyl *P*-methyl-*N*-phenylphosphonamidothioate, which on recrystallisation from benzene-methanol (trace) had m. p. 155° (72%). Triethyl phosphorothionate (5 g., 1 mol.) on reaction with methyl iodide (35 g., 10 mol.) in nitromethane (15 g., 10 mol.) was similarly converted into *diethyl* S-*methyl phosphorothiolate* (3 g., 65%) b. p. 106°/8 mm., n_D^{23} 1·4557 (Found: C, 33·0; H, 7·2. $C_5H_{13}O_3PS$ requires C, 32·6; H, 7·1%).

Experiments carried out in *N*-methylacetamide are exemplified by the following: Ethyl *NN'*-dicyclohexylphosphorodiamidothionate (1·0 g.), propyl iodide (6 g.), and *N*-methylacetamide (2·5 g.) were heated on a steam bath for 20 min. Water (50 ml.) was added and the product was extracted into 1 : 1 chloroform–benzene (2 × 125 ml.). The dried extracts were evaporated to 50 ml. and light petroleum (150 ml.) was added. The crystals (82%) of *S*-propyl *NN'*-dicyclohexylphosphorodiamidothioate which were precipitated had m. p. 158°, undepressed on admixture with a specimen prepared in the absence of *N*-methylacetamide.

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[17] Stuebe and Lankelma, *J. Amer. Chem. Soc.*, 1956, **78**, 976.

The results of similar experiments with other thionates are summarised in Table 4. The physical constants of the products were identical with those obtained as described in Table 3.

(ii) *Structures.* The structures of the thiolates formed in the above reactions were further confirmed by examination of the relevant infrared spectra, when the presence of P–S–C (1258—1271 cm.$^{-1}$)[12] and P=O (8·15 μ) and absence of P=S (12·05 μ) were established in each case. The m. p. of *OS*-diethyl *N*-cyclohexylphosphoramidothiolate, prepared as described in Table 3, was undepressed on admixture with a sample prepared from ethyl phosphorodichloridate as described above, as was that of *S*-ethyl *P*-methyl-*N*-phenylphosphonamidothiolate on admixture with an authentic sample prepared by Cadogan's method.[9] The presence of the P·SEt group in *OS*-diethyl phosphoramidothioate was confirmed as follows: A solution of chloramine-T (6·2 g., 2 mol.) in 3 : 7 aqueous ethanol (30 ml.) was added portionwise (5 ml.) to *OS*-diethyl phosphoramidothioate (2 g., 1 mol.) in 3 : 7 aqueous ethanol (30 ml.). A colourless solid was at once precipitated and, after 2 hr. at 20°, was collected and washed with ethanol and light petroleum. Recrystallisation from ethanol gave *S*-ethyl-*S*-toluene-*p*-sulphonamido-*N*-toluene-*p*-sulphonylsulphidimine, m. p. 195° (decomp.) (1·7 g., 40%) undepressed on admixture with a specimen prepared as described by Cadogan and Moulden.[1] *OS*-Diethyl *N*-cyclohexylphosphoramidothioate similarly gave *S*-ethyl-*S*-toluene-*p*-sulphonamido-*N*-toluene-*p*-sulphonylsulphidimine, m. p. and mixed m. p. 193·5°.

TABLE 4.

Reactions of thionates, $\mathrm{EtO{\cdot}P({:}S)XY}$ with alkyl iodides in the presence of solvents at the b. p.

X	Y	Solvent	R in RI	Time (hr.)	Yield (%) of $\mathrm{RS{\cdot}P({:}O)XY}$
EtO	$\mathrm{NH_2}$	$\mathrm{MeNO_2}$	Et	10	72
EtO	$\mathrm{NH{\cdot}C_6H_{11}}$	$\mathrm{MeNO_2}$	Et	14	80
EtO	$\mathrm{NH{\cdot}C_6H_{11}}$	Me·CO·NHMe	Et	2·5	52
$\mathrm{NH{\cdot}C_6H_{11}}$	$\mathrm{NH{\cdot}C_6H_{11}}$	$\mathrm{MeNO_2}$	$\mathrm{Pr^n}$	1·25	86
$\mathrm{NH{\cdot}C_6H_{11}}$	$\mathrm{NH{\cdot}C_6H_{11}}$	Me·CO·NHMe	$\mathrm{Pr^n}$	0·3[1]	82
EtO	EtO	Me·CO·NHMe	Me	0·75[2]	68
EtO	EtO	$\mathrm{MeNO_2}$	Me	120	65
EtO	Me	Me·CO·NHMe	$\mathrm{Pr^n}$	22	30
EtO	Me	$\mathrm{MeNO_2}$	$\mathrm{Pr^n}$	42·5	84
EtO	Ph	$\mathrm{MeNO_2}$	$\mathrm{Pr^n}$	96	80
EtO	Piperidino	$\mathrm{MeNO_2}$	$\mathrm{Pr^n}$	19	90
Me	NHPh	$\mathrm{MeNO_2}$	Et	18	72

[1] At 100°. [2] At 105°.

(iii) *Kinetic measurements.* The following reaction was studied: thionate + $\mathrm{Pr^nI} \longrightarrow$ thiolate + EtI. In the presence of a ten-fold excess of $\mathrm{Pr^nI}$ this was of the first order in thionate. The rate of formation of ethyl iodide was measured by gas–liquid chromatography.

Measurements were made with a Perkin-Elmer " Fraktometer " model 116, fitted with a high-sensitivity dual thermal conductivity detector. All injections were made using a precision liquid sample introduction system in which a current of nitrogen carrier gas by-passed from the main supply discharged the sample from a pipette into the injection block. Only one pipette (20 μl.) was used; it was filled by capillary action. A 2-m. column packed with silicone oil (DC.200) on Celite was used; it was used at 89° with a nitrogen flow of 18 ml./min. in early experiments and at 96° with a flow of 10 ml./min. in later experiments. The relative retention times under these conditions were $\mathrm{Pr^nI}$ 1·5, EtI 1·0. Calibrations appropriate to the conditions and compounds used were made frequently, with solutions of ethyl iodide in propyl iodide in the range 0—9 mole % and ethyl iodide, in equimolar mixtures of propyl iodide and added solvent, in the range 0—5 mole %. In all cases a plot of ethyl iodide peak height against concentration was linear. By the use of such calibrations the concentrations of ethyl iodide and propyl iodide present in reaction mixtures were readily determined without tedious measurement of the areas of the relevant peaks on the chromatogram. Preliminary experiments were also performed to ensure that the sensitivity of the response did not vary appreciably with the bridge voltage of the detector.

In the kinetic experiments the reaction mixtures used were in the range 8—9 mole % for thionates in pure propyl iodide, and 4·4—4·6 mole % when added solvents were used in equimolar proportions to the propyl iodide. Eight samples (*ca.* 1 ml. each) of the mixture were then sealed into tubes (9 × 30 cm.), being placed at the bottom of the tube by use of a long pipette and cooled in ice-salt; the tubes were then quickly sealed. These samples were kept in a thermostat at 105° for appropriate times and cooled in ice. Injections of this ice-cold mixture were made until consistency was obtained, usually within 5%, 3—5 injections being taken. The propyl iodide was effectively constant in concentration and was therefore used as an internal normalisation standard. The results were calculated on the basis of $\ln (P_0/P) = kt$, where P_0 = initial concentration of thionate, and P = concentration of thionate at time t.

The concentration of ethyl iodide was obtained from the peak height recorded on the chromatogram after correction, by means of the calibration graph. This concentration is effectively the same as that of thionate consumed.

In theory, ethyl iodide formed in this process can react with unchanged thionate, to give the corresponding ethyl thiolate and more ethyl iodide (equation ii). This reaction, which would escape detection by our analysis, is very unlikely at the concentrations used and is excluded by the product analyses described (Tables 3 and 4).

The results, which in each case are mean values obtained from several experiments, are summarised in Tables 1 and 2. A typical experiment is described in Table 5.

TABLE 5.

Reaction at 105° of PrI with $(EtO)_2P(:S)\cdot NH\cdot C_6H_{11}$ (8·75 molar %).

t (hr.)	0	0·25	1·25	2·25	3·25	4·25	5·4
EtI peak height	0	2·2	8·6	15·2	20·9	24·9	29·8
[EtI], molar %	0	0·3	1·25	2·25	3·1	3·7	4·45
[P = S] ,, ...	8·75	8·45	7·5	6·5	5·65	5·05	4·3

(iv) *Reaction of benzyl diethyl phosphorothionate with propyl iodide.* The thionate (1 g.) and propyl iodide (3·25 g., 5 mol.) were heated in a sealed tube at 105° for 20 hr. Gas–liquid chromatography (2-m. "C" column, 102°, rate of flow 14 ml./min.) revealed ethyl iodide (1·3% of propyl iodide present). Analyses at 170° indicated the presence of benzyl iodide (3% of propyl iodide present) and diethyl *S*-*n*-propyl phosphorothiolate. Hence the ratio of debenzylation to de-ethylation is 5 : 2.

(v) *Reaction of ethyl* S-*propyl phosphoroamidothiolate with propyl iodide.* The experiment was followed kinetically as described above, with a 10 molar excess of propyl iodide at 105°. Under these conditions the reaction was of the first order in ethyl iodide. The rate constant in pure propyl iodide was $4{\cdot}2 \times 10^{-6}$ sec.$^{-1}$ ($t_{\frac{1}{2}} = 46$ hr.) and in equimolar propyl iodide-*N*-methylacetamide, $k = 1{\cdot}8 \times 10^{-5}$ sec.$^{-1}$ ($t_{\frac{1}{2}} = 11$ hr.).

*Reaction of Hexa-*N*-ethylphosphorothioic Triamide with Methyl Iodide.*—The triamide (2·79 g.) and methyl iodide (1·42 g.) were kept at room temperature for 17 hr. The pale yellow crystalline product was triturated with ether and then boiled with ether for 3 hr. and filtered, to give the ***triamide methiodide*** as a white powder, m. p. 82° (Found: C, 37·0; H, 7·6. $C_{13}H_{33}IN_3PS$ requires C, 37·0; H, 7·9%). The adduct was stable at 50°/0·05 mm. for 3½ hr. but a portion (0·31 g.) after 1½ hr. at 77°/0·05 mm. gave hexa-*N*-ethylphosphorothioic triamide (0·18 g., 89%; n_D^{25} 1·5036). A portion (1·0 g.) of adduct was boiled under reflux with triethylamine (5·0 g.) for 4 hr. Light petroleum (50 ml.) was added and the mixture was left overnight. The colourless solid (0·54 g., 95%) formed was collected and had m. p. 299° and mixed m. p. 301° with triethyl methyl ammonium iodide (m. p. 303°). The filtrate on distillation gave hexa-*N*-ethylphosphorothioic triamide (0·56 g., 86%; n_D^{23} 1·5037; correct infrared spectrum).

Reaction of NN′-*Dicyclohexylmethylphosphonothioic Diamide with Methyl Iodide.*—The diamide (2·0 g.) and methyl iodide (5·0 g.) were kept at room temperature for 5 days. Removal of excess of methyl iodide, followed by treatment with ether as described in the previous experiment, gave ***methyl* NN′*-dicyclohexylmethylphosphonothioic diamide methiodide*** (2·1 g., 66%), m. p. 94—95° (Found: C, 40·9; H, 7·8. $C_{14}H_{30}IN_2PS$ requires C, 40·4; H, 7·3%). The adduct was completely converted into *NN′*-dicyclohexylmethylphosphonothioic diamide, m. p. and mixed m. p. 113° after 210 min. at 108°/0·1 mm., and after 6½ hr. at 84°/0·05 mm. A portion (0·62 g.) of the adduct was boiled under reflux in water (20 ml.) for 8 hr. The solution had pH

5—6. Methanethiol was evolved and removal of water left an unidentified solid which crystallised from ether–ethanol (0·17 g.; m. p. 194—196°) (Found: C, 43·5; H, 9·2%).

Isomerisation of Triethyl Phosphorothionate in N-*Methylacetamide.*—The thionate (1·0 g., 1 mol.) and *N*-methylacetamide (0·73 g., 2 mol.) were kept at 105° for 88 hr. Gas–liquid chromatography on a 2-m. "C" column at 190° with a flow rate of 12 ml./min. indicated that 16% of the thionate had isomerised to triethyl phosphorothiolate. The retention times relative to *N*-methylacetamide were $(EtO)_3PS$ 2·33, and $(EtO)_2PO{\cdot}SEt$ 3·56.

Reactions of Sodium Iodide with Phosphorothiolates.—(i) *With triethyl phosphorothiolate.* The ester (15 g.) and sodium iodide (11·4 g.) were boiled under reflux in ethyl methyl ketone (200 ml.) for 2 hr. The colourless needles (8·0 g.) which separated on cooling were washed with acetone and recrystallised from ethyl methyl ketone–acetone, to give *sodium* OS-*diethyl phosphorothiolate* in needles, m. p. 214° (Found: C, 25·6; H, 5·55. $C_4H_{10}NaO_3PS$ requires C, 25·0; H, 5·2%). The infrared spectrum exhibited bands attributable to PO_2^- and $EtS{\cdot}PO_2^-$ (1258—1271 cm.$^{-1}$.[12] The structure of the product was confirmed by its conversion into the 1,1,4,4-tetra-ethylpiperazinium derivative as follows: the sodium salt (2 mol.) in a small volume of hot methanol was added to 1,1,4,4-tetraethylpiperazinium dichloride [18] (1 mol.) in hot methanol. The cooled mixture was filtered, evaporated to a small volume, and diluted with acetone. Crystallisation from this mixture of solvents gave 1,1,4,4-tetraethylpiperazinium bis-(*OS*-diethyl phosphorothiolate) as needles (75%), m. p. 203° (after drying over P_2O_5 at 50°/0·01 mm. for 12 hr.), undepressed on admixture with an authentic specimen prepared as described by Cadogan and Thomas.[14]

(ii) *With triethyl phosphorothionate.* The ester (5 g.) and sodium iodide (4 g.) were boiled under reflux in ethyl methyl ketone (90 ml.) for 6½ hr. The crystals (0·5 g.) which separated on cooling recrystallised from ethyl methyl ketone–acetone, to give sodium *OS*-diethyl phosphorothiolate, m. p. and mixed m. p. 212—214° (correct infrared spectrum).

(iii) *With* S-*benzyl diethyl phosphorothioate.* The ester (2·3 g.) and sodium iodide (1·3 g.) in ethyl methyl ketone (30 ml.) similarly gave, after 1½ hr., a salt (0·8 g.), m. p. 200°, which was identified as sodium *S*-benzyl ethyl phosphorothioate by conversion, as described above, into 1,1,4,4-*tetraethylpiperazinium bis-*(S-*benzyl ethyl phosphorothiolate*) which, crystallised in colourless needles from acetone–methanol (trace), had m. p. 112° (after drying over P_2O_5 at 40°/0·01 mm. for 1 hr.), undepressed on admixture with an authentic specimen prepared as described below (Found: C, 54·3; H, 7·9. $C_{30}H_{52}N_2O_6P_2S_2$ requires C, 53·8; H, 7·8%).

SS-Dibenzyl ethyl phosphorodithiolate was first prepared as a viscous oil from toluene-α-thiol and ethyl phosphorodichloridate in the presence of triethylamine, as described by Cadogan and Thomas [14] for the preparation of *OSS*-triethyl phosphorodithiolate. The ester (6·9 g.) was then hydrolysed by shaking it with sodium hydroxide (2·8 g.) in water (50 ml.) and dioxan (20 ml.) for 2 hr. The mixture was extracted with ether and the pH of the aqueous portion was adjusted to 7. 1,1,4,4-Tetraethylpiperazinium dichloride (2·7 g.) was added and the solution was evaporated to dryness at 20 mm. The residue was extracted with boiling methanol (2 × 100 ml.), and the filtrate was evaporated to a small volume and diluted with acetone. Crystallisation from this mixture of solvents gave 1,1,4,4-tetraethylpiperazinium bis-(*S*-benzyl ethyl phosphorothiolate), m. p. 112°.

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[18] Cadogan, *J.*, 1955, 2971.