

Organophosphorus Compounds. Part CL.¹ Synthesis of ' Stable ' Tetra-*O*-alkyl *sym*-Monothiopyrophosphates

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Oxophosphoranesulphenyl chlorides react readily with dialkyl phosphites giving, in high yield, simple and mixed *sym*-thiopyrophosphates $(RO)_2P(O)-S-P(O)(OR')_2$, uncontaminated by any catalyst for the ready isomerization into the unsymmetrical isomers, $>P(O)-O-P(S)<$, which has marred earlier procedures. The reaction involves nucleophilic attack by the phosphorus atom on the sulphur atom of the sulphenyl chloride and formation of a quasi-phosphonium complex. Some side reactions resulting from the great reactivity of *sym*-monothiopyrophosphates are also described.

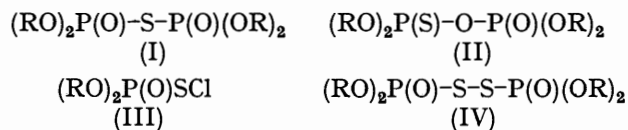
TETRA-*O*-ALKYL *sym*-MONOTHIOPYROPHOSPHATES (I) and their structural analogues have received much attention in this laboratory. In our early research we were only able to postulate the intermediacy of structure (I) in

¹ Part CXLIX, A. Koziara and A. Zwierzak, *Tetrahedron*, 1970, **26**, 3527.

some reactions leading to *asym*-monothiopyrophosphates (II).² Later we obtained stereochemical proof of the

² (a) J. Michalski, M. Mikołajczyk, and A. Skowrońska, *Chem. and Ind.*, 1962, 819; (b) Cz. Krawiecki and J. Michalski, *J. Chem. Soc.*, 1960, 881; (c) J. Michalski, J. Mikołajczyk, B. Młotkowska, and A. Skowrońska, *Bull. Acad. polon. Sci., Ser. sci. chim.*, 1963, **12**, 695.

intermediate formation of structure (I),³ and only recently 'unstable' *sym*-monothiopyrophosphates were synthesized by the reaction of piperidinesulphenyl chloride with dialkyl phosphites, in high yield,⁴ and by



condensation of dialkoxyoxophosphoranesulphenyl chloride (III) with trialkyl phosphites.⁵ In the latter reaction the yield of (I) is low (*ca.* 20%), the main products being phosphorochloridates and phosphorothionates. The products (I) from both reactions are very unstable with respect to rearrangement [(I) → (II)]. Although the *asym*-isomers (II) are expected to be more stable thermodynamically than (I) by *ca.* 8.5 kcal mol⁻¹,⁶ such a ready isomerization is surprising. We now describe a synthetic method in which the catalysed isomerization (I) → (II) and side reactions due to the high reactivity of (I) towards nucleophilicities are eliminated.

We have previously^{2a} described the condensation of dialkoxyoxophosphoranesulphenyl chlorides (III) with dialkyl phosphites but were not able to prove the formation of (I) at that time. However we have reinvestigated this reaction in detail and our results demonstrate that the *sym*-monothiopyrophosphates (I) can be prepared by this method under carefully chosen conditions and are much more stable than previously supposed.

Oxophosphoranesulphenyl chloride reacts readily with dialkyl phosphites in inert solvents, for example light petroleum or benzene. The reaction is noticeably exothermic and in order to secure a pure product (I) in high yield it must be carried out between 0 and +5°. Hydrogen chloride is removed *in vacuo* below 10° and all operations are carried out under strictly anhydrous conditions. The purity of thiopyrophosphates formed depends to a great extent on the purity of the starting oxophosphoranesulphenyl chlorides. The latter are best prepared directly before being used, without prior distillation, from pure substrates such as monothio-acids⁷ or phosphonothionates.⁸ All synthetic operations should be performed as quickly as possible. For this reason it is advisable not to exceed a 0.05 mol scale. The purity of *sym*-monothiopyrophosphates was checked by ³¹P n.m.r. spectroscopy. Tetraisopropyl monothiopyrophosphate (I; R = Prⁱ) can be distilled *in vacuo* at 80° without any isomerization to (II; R = Prⁱ). The procedure described is well suited for the synthesis of mixed thiopyrophosphates (I).

We have already referred to the need for special

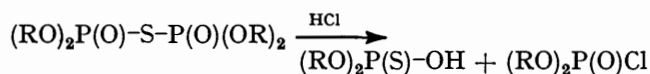
³ J. Michalski, M. Mikołajczyk, and A. Ratajczak, *Bull. Acad. polon. Sci., Ser. sci. chim.*, 1965, **13**, 277.

⁴ J. Michalski, M. Mikołajczyk, and B. Mlotkowska, *Chem. Ber.*, 1969, **102**, 90.

⁵ J. Michalski and A. Skowrońska, *J. Chem. Soc. (C)*, 1970, 703.

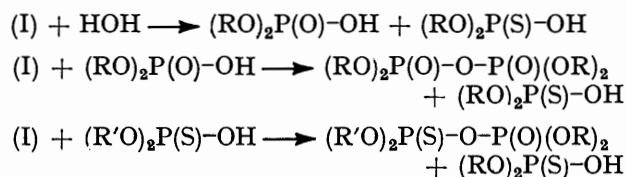
⁶ R. F. Hudson, 'Structure and Mechanism in Organophosphorus Chemistry,' Academic Press, London and New York, 1956, p. 123.

precautions in order to avoid reactions resulting from the high reactivity of (I). Hydrogen chloride cleaves *sym*-monothiopyrophosphates (I) with formation of the corresponding phosphorothioic acid and phosphorochloridate. The reaction is slow below 10° in neutral



solvents. It is notable that hydrogen chloride does not cause isomerization of (I) to (II) under the reaction conditions. *sym*-Monothiopyrophosphates (I) also react with an excess of dialkoxyoxophosphoranesulphenyl chloride (III), yielding bisdialkoxyphosphinoyl disulphides (IV). This reaction is very slow below 10° under the conditions of the synthesis of (I), and can be almost completely excluded by the addition of the reagents in the right sequence.

When moisture is present the products of hydrolysis and subsequent formation of tetra-alkyl pyrophosphates and *asym*-monothiopyrophosphates (II) are observed (Scheme 1).



SCHEME 1

The foregoing reactions exemplify the high reactivity of (I) and are relevant to the work of Zwierzak,⁹ who, in his paper on the reaction of thionyl chloride with diethyl phosphite, suggested the transient formation of (III; R = Et) and its subsequent reaction with an excess of phosphite. The numerous products were explained in terms of a dynamic equilibrium between phosphonium complexes, which can collapse in various different ways. The reaction was performed at rather a high temperature (40 °C) and most of the products observed are in our opinion due to secondary reactions of (I) with various species present in the reaction mixture.

We have now shown that the isomerization (I) → (II) is subject to nucleophilic catalysis. The most effective catalysts examined were tertiary amines and monothio-acid anions (Scheme 2). Both catalytic processes can be considered as nucleophilic displacements of the *S_N2(P)* type.¹⁰ The monothiopyrophosphates (I) are potent phosphorylating agents owing to the excellence of the leaving group present [the anion (RO)₂P(S)O⁻ is very stable and the P-S bond is of low energy]. The action of the tertiary amine leads to an intermediate ion pair which reacts according to the 'hard-hard' principle with the formation of (II) and

⁷ Borecka and J. Michalski, *Roczniki Chem.*, 1957, **31**, 1167.

⁸ J. Michalski, B. Pliszka-Krawiecka, and A. Skowrońska, *Roczniki Chem.*, 1963, **37**, 1479.

⁹ A. Zwierzak, *Tetrahedron*, 1969, **25**, 5177.

¹⁰ A. J. Kirby and S. G. Warren, 'The Organic Chemistry of Phosphorus,' Elsevier, Amsterdam, 1967, p. 22.

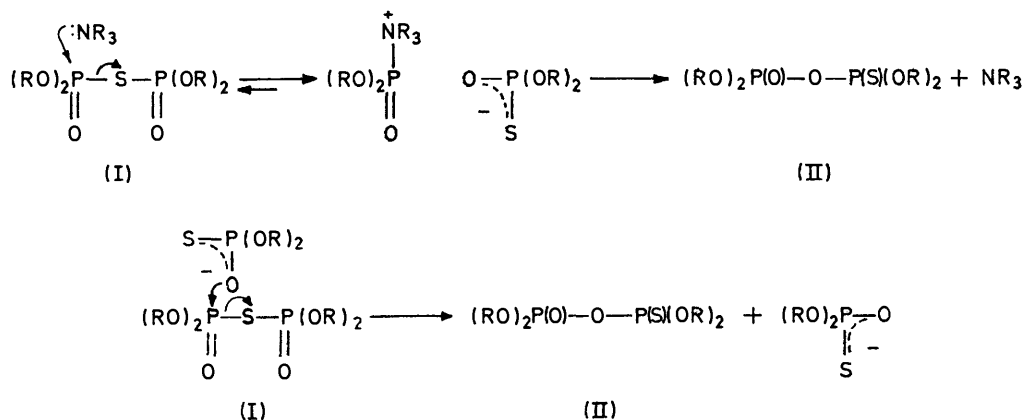
regeneration of the amine. The monothio-acid anion is phosphorylated directly with formation of (II) and regeneration of the catalyst. Amine hydrochlorides and trialkyl phosphites also can catalyse the isomerization (I) \rightarrow (II). Our previous method of synthesis of (I), based on the reaction of phosphites with piperidinesulphenyl chloride, leads to the formation of piperidine hydrochloride, which acts as isomerization catalyst and is extremely difficult to remove completely from (I). In our opinion this is the reason for the low stability of (I) prepared by this method.

We suggest an ionic mechanism for our synthetic reaction, involving nucleophilic displacement by dialkyl

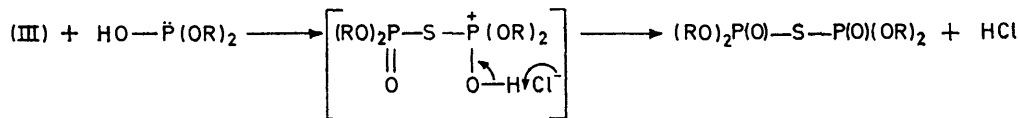
EXPERIMENTAL

Benzene was dried over sodium hydride and freshly distilled before use. I.r. spectra were recorded with a U.R. 10 (Zeiss) spectrophotometer for liquid films. ^{31}P N.m.r. spectra were measured on a JEOL C-60H spectrometer, operating at 24.3 MHz, for neat liquids, with 85% phosphoric acid as external reference. A heteronuclear spin decoupler (INM-SD-HC) was used for precise ^{31}P chemical shift determination. The purity of the products was determined from integrated ^{31}P n.m.r. spectra. Identity of compounds with authentic materials was established by comparison of i.r. spectra and ^{31}P n.m.r. chemical shift values.

Trialkyl and dialkyl phosphites were prepared by



SCHEME 2



SCHEME 3

phosphite at the sulphur atom of the oxophosphoranesulphenyl chloride. It seems reasonable to suppose that the dialkyl phosphite reacts in the tricovalent form.¹¹ The intermediate quasi-phosphonium complex may break down by the removal of a proton, forming the *sym*-thiopyrophosphate (I). The situation here is different from that observed for the reaction of oxophosphoranesulphenyl chlorides with trialkyl phosphites. In the latter case the analogous quasi-phosphonium complex may react in one of two ways, undergoing either dealkylation by chloride ion leading to *sym*-thiopyrophosphates, or nucleophilic attack by a chloride ion on the phosphoryl group leading to a mixture of phosphorochloridate and tri-*O*-alkyl phosphorothioate. The second process is dominant. In the reaction represented by Scheme 3, deprotonation is expected to be faster than dealkylation or nucleophilic attack of chloride ion on either an alkyl or the phosphoryl group.

conventional methods.^{11,12} Trialkyl phosphorothioates were obtained by addition of sulphur to trialkyl phosphites.¹³ Dialkoxyoxophosphoranesulphenyl chlorides were synthesized according to ref. 8, from pure trialkyl phosphorothioates. Crude dialkoxyoxophosphoranesulphenyl chlorides were analysed by ^{31}P n.m.r. spectroscopy and used directly for the reactions. Diethyl hydrogen phosphate was prepared by oxidation of diethyl phosphite with potassium permanganate.¹⁴ Dialkyl hydrogen phosphorothioates were prepared by addition of sulphur to dialkyl phosphites.¹⁵ Authentic tetra-alkyl *asym*-thiopyrophosphates were prepared according to ref. 16.

Reaction of Dialkoxyoxophosphoranesulphenyl Chlorides (III) with Dialkyl Phosphites.—General procedure. The sulphenyl chloride (0.05 mol) in benzene (30 ml) was added dropwise to a solution of the dialkyl phosphite (0.05 mol) in benzene (30 ml). The temperature of the mixture was kept at 0–5° (ice-salt bath). The solvent was evaporated off below 10° and the residue was distilled *in vacuo*. The crude product and all fractions obtained

¹¹ A. H. Ford-Moore and I. M. Williams, *J. Chem. Soc.*, 1947, 1465.

¹² B. Fiszer, J. Michalski, and J. Wiczorkowski, *Roczniki Chem.*, 1953, **27**, 482.

¹³ A. Zwierzak, *Tetrahedron*, 1969, **25**, 5186.

¹⁴ A. Zwierzak, *Roczniki Chem.*, 1965, **39**, 1411.

¹⁵ M. I. Kabachnik and E. I. Golubeva, *Doklady Akad. Nauk S.S.S.R.*, 1955, **105**, 1258.

¹⁶ B. A. Arbuzov and I. J. Alimov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1954, 1038.

after distillation were examined by ^{31}P n.m.r. and i.r. spectroscopy.

(a) *Diethoxyoxophosphoranesulphenyl chloride with diethyl phosphite*. The pure sulphenyl chloride [n_{D}^{21} 1.4682, δ -17.8 (s) p.p.m.] and the phosphite [δ -6.9 (s) p.p.m.], gave tetra-*O*-ethyl *sym*-thiopyrophosphate (I; R = Et) (15.2 g), n_{D}^{20} 1.4625, ν_{max} 542 (P-S-P), 980, 1030 (P-O-C) and 1270 (P=O) cm^{-1} , δ -14.3 (s) p.p.m., contaminated with unchanged phosphite (3%). Distillation gave two fractions: (i) b.p. 30–60° at 0.05 mmHg (0.5 g), n_{D}^{21} 1.4405, consisting of diethyl phosphite (18%), diethyl phosphorochloridate (8%), δ -2.8 (s) p.p.m., and (I; R = Et) (74%); and (ii) b.p. 80–100° at 0.05 mmHg (13.1 g), n_{D}^{20} 1.4572, a mixture of (I; R = Et) (75%), tetra-*O*-ethyl *asym*-thiopyrophosphate (10%), $\delta_{\text{O-P}}$ +14.2 (d), $\delta_{\text{P-S}}$ -52.5 (d) p.p.m., $J_{\text{P-O-P}}$ 20.3 Hz, tetraethyl pyrophosphate (5%), δ +13 (s) p.p.m., *OOS*-triethyl phosphorothioate (6%), δ -26.5 (s) p.p.m., and di-*O*-ethyl hydrogen phosphorothioate (4%), δ -63.5 (s) p.p.m. (The value δ -56.7 p.p.m. for pure diethyl hydrogen phosphorothioate changes to -63.5 in a mixture with tetraethyl thiopyrophosphate.)

(b) *Di-isopropoxyoxophosphoranesulphenyl chloride with di-isopropyl phosphite*. The pure sulphenyl chloride [n_{D}^{22} 1.4610, δ -15.7 (s) p.p.m.] and the phosphite [δ -4 (s) p.p.m.] afforded tetra-*O*-isopropyl *sym*-thiopyrophosphate (I; R = Prⁱ) (18 g), n_{D}^{22} 1.4525, ν_{max} 542 (P-S-P), 985, 1010 (P-O-C), and 1270 (P=O) cm^{-1} , δ -12.5 (s) p.p.m. (Found: C, 40.05; H, 7.7; P, 17.3. $\text{C}_{12}\text{H}_{28}\text{O}_6\text{P}_2\text{S}$ requires C, 39.75; H, 7.8; P, 17.1%). The product was distilled *in vacuo* to give two fractions: (i) b.p. 30–70° at 0.01 mmHg (0.9 g), n_{D}^{20} 1.4430, composed of di-isopropyl phosphite (7%), di-isopropyl phosphorochloridate (10%), δ -0.7 (s) p.p.m., and (I; R = Prⁱ) (83%); and (ii) b.p. 80–96° at 0.01 mmHg (16 g), n_{D}^{23} 1.4520, identified as (I; R = Prⁱ) (96%) contaminated with tetraisopropyl pyrophosphate (2%), δ +15 (s) p.p.m., and di-isopropyl hydrogen phosphorothioate (2%), δ -61.5 (s) p.p.m.

(c) *Diethoxyoxophosphoranesulphenyl chloride with di-isopropyl phosphite*. The sulphenyl chloride [n_{D}^{22} 1.4676] and the phosphite gave di-*O*-ethyl di-*O*-isopropyl *sym*-thiopyrophosphate (16.5 g), n_{D}^{22} 1.4540, ν_{max} 540 (P-S-P), 990, 1020 (P-O-C), and 1270 (P=O) cm^{-1} , δ -12 [d, (PrⁱO)₂-P(O)S] and -14.3 [d, (EtO)₂P(O)S] p.p.m., $J_{\text{P-S-P}}$ 11.2 Hz, containing the phosphite (2%) and diethyl phosphorochloridate (3%). Distillation gave two fractions: (i) b.p. 40–75° at 0.05 mmHg (0.7 g), n_{D}^{23} 1.4250; and (ii) b.p. 80–100° at 0.05 mmHg (13.6 g), n_{D}^{22} 1.4496. Diethyl phosphorochloridate (31%), di-isopropyl phosphorochloridate (23%), di-isopropyl phosphite (21%), and the thiopyrophosphate (25%) were detected in fraction (i). Fraction (ii) was composed of the *sym*-thiopyrophosphate (90%), a mixture of tetraethyl and tetraisopropyl *asym*-thiopyrophosphates, δ +16.0 [d, (PrⁱO)₂P(O)] and -50.0 [d, (PrⁱO)₂P(S)O⁻] p.p.m., $J_{\text{P-O-P}}$ 20 Hz, and two diethyl di-isopropyl *asym*-thiopyrophosphates, δ +14.5 [d, (EtO)₂ and P(O)O] and -50.0 [d, (PrⁱO)₂P(S)O], $J_{\text{P-O-P}}$ 20.1 Hz, δ +15.7 [d, (PrⁱO)₂P(O)O⁻] and -52.5 [d, (EtO)₂P(S)O] p.p.m., $J_{\text{P-O-P}}$ 20.4 Hz (4%), a mixture of tetraethyl and tetraisopropyl pyrophosphates (3%), and a mixture of diethyl and di-isopropyl hydrogen phosphorothioates (3%).

(d) *Di-isopropoxyoxophosphoranesulphenyl chloride with diethyl phosphite*. The sulphenyl chloride [n_{D}^{22} 1.4605] and the phosphite afforded an oil (16.6 g), n_{D}^{22} 1.4550,

identified as di-*O*-ethyl di-*O*-isopropyl *sym*-thiopyrophosphate (96%), contaminated with unchanged phosphite (4%). Distillation gave the pure thiopyrophosphate (14.8 g), b.p. 90–95° at 0.01 mmHg, n_{D}^{23} 1.4545 (Found: C, 35.9; H, 7.2; P, 18.45. $\text{C}_{10}\text{H}_{24}\text{O}_6\text{P}_2\text{S}$ requires C, 35.9; H, 7.2; P, 18.55%).

(e) *Diethoxyoxophosphoranesulphenyl chloride with di-*n*-butyl phosphite*. The sulphenyl chloride [n_{D}^{20} 1.4682] and the phosphite [δ -7 (s) p.p.m.] gave di-*O*-ethyl di-*O*-butyl *sym*-thiopyrophosphate (19.3 g), n_{D}^{22} 1.4570, ν_{max} 538, (P-S-P), 985, 1025 (P-O-C), and 1275 (P=O) cm^{-1} , δ -14.5 p.p.m. (AB system) (Found: C, 39.65; H, 7.5; P, 16.85. $\text{C}_{12}\text{H}_{28}\text{O}_6\text{PS}$ requires C, 39.8; H, 7.75; P, 17.15%). Distillation gave two fractions: (i) b.p. 40–80° at 0.01 mmHg (0.6 g), n_{D}^{20} 1.4560, identified as diethyl phosphorochloridate (3%), dibutyl phosphorochloridate (3%), δ -3.5 (s) p.p.m., and the thiopyrophosphate (94%); and (ii) b.p. 80–100° at 0.01 mmHg, n_{D}^{23} 1.4552, consisting of a mixture of the thiopyrophosphate (90%), tetraethyl pyrophosphate (3%), tetrabutyl pyrophosphate (3%), δ +13.2 (s) p.p.m., diethyl hydrogen phosphorothioate (2%), and dibutyl hydrogen phosphorothioate (2%), δ -64 (s) p.p.m.

*Reaction of Tetra-*O*-ethyl sym-Thiopyrophosphate with Hydrogen Chloride*.—Anhydrous hydrogen chloride was passed through the thiopyrophosphate at room temperature for 2 h. ^{31}P N.m.r. analysis of the mixture showed the presence of diethyl phosphorochloridate (28%), diethyl hydrogen phosphorothioate (28%), the *sym*-thiopyrophosphate (8%), and tetra-*O*-ethyl *asym*-thiopyrophosphate (36%).

*Reaction of Tetra-*O*-ethyl sym-Thiopyrophosphate with Diethoxyoxophosphoranesulphenyl Chloride*.—Equimolar amounts of the reagents were mixed and kept at room temperature for 12 h. The products were identified (^{31}P n.m.r.) as diethyl phosphorochloridate (20%), bis-diethoxyphosphinoyl disulphide (24%), δ -20 p.p.m., the *sym*-thiopyrophosphate (17%), and the *asym*-thiopyrophosphate (30%).

*Reaction of Tetra-*O*-ethyl sym-Thiopyrophosphate with Diethyl Hydrogen Phosphate*.—The thiopyrophosphate (3.6 g, 0.01 mol) was added to the phosphate (0.78 g, 0.005 mol). After 2 days at room temperature the mixture was shown (^{31}P n.m.r.) to contain tetraethyl pyrophosphate (28%), diethyl hydrogen phosphate (14%), diethyl hydrogen phosphorothioate (28%), and the *sym*-thiopyrophosphate (30%).

*Reaction of Tetra-*O*-ethyl sym-Thiopyrophosphate with Di-isopropyl Hydrogen Phosphorothioate*.—Equimolar amounts of the reagents, heated at 65° for 8 h in a sealed tube, gave a mixture shown (^{31}P n.m.r.) to consist of diethyl di-isopropyl *asym*-thiopyrophosphate, tetraethyl *asym*-thiopyrophosphate, diethyl hydrogen phosphorothioate, di-isopropyl hydrogen phosphorothioate, *OOS*-triethyl phosphorothioate, and *S*-ethyl di-*O*-isopropyl phosphorothioate.

*Reaction of Tetra-*O*-ethyl sym-Thiopyrophosphate with the Triethylammonium Salt of Di-isopropyl Hydrogen Phosphorothioate*.—A solution of the thiopyrophosphate (7.0 g, 0.22 mol) in benzene (20 ml) was added to a solution of the salt in benzene (30 ml) [prepared from triethylamine (2.27 g, 0.22 mol) and di-isopropyl hydrogen phosphorothioate (4.3 g, 0.22 mol)]. The mixture was kept at room temperature for 24 h, then washed with water (2 × 10 ml), dried (MgSO_4), and evaporated. The ^{31}P n.m.r. spectrum showed that the crude material was a mixture of tetra-*O*-

ethyl *asym*-thiopyrophosphate (35%) and diethyl di-isopropyl *asym*-thiopyrophosphate (65%).

Reaction of Tetra-O-ethyl sym-Thiopyrophosphate with Triethylamine.—The thiopyrophosphate (3.06 g, 0.01 mol)

was mixed with triethylamine (1.01 g, 0.01 mol) and kept for 12 h at room temperature. Complete isomerization to the *asym*-isomer was observed (^{31}P n.m.r.).

[3/1752 Received, 20th August, 1973]
