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STEREOCHEMISTRY OF NUCLEOPHILIC SUBSTITUTION REACTION AT A THIOPHOSPHORYL CENTRE—IV[1]

CHEMICAL PROOF OF WALDEN INVERSION*

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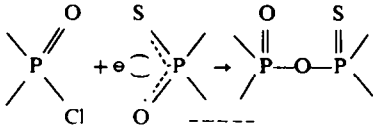
Abstract—Optically active pyrophosphonothionates (II, III and IV) have been obtained in the reaction between optically active O-ethyl ethylphosphonothioic acid (I) and 2-chloro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan, diethyl phosphorochloridate and O,O-diethyl phosphorochloridothionate respectively. It has been found that alkaline hydrolysis of these anhydrides occurs with full inversion of configuration at the thiophosphoryl centre. The reaction is discussed from the point of view of stereochemistry and the reaction mechanism.

IT IS now generally accepted that, in spite of numerous analogies, there are many important differences between the organic chemistry of phosphorus and of carbon.[2,3] For example, in considering the mechanism of nucleophilic substitution at a tetracovalent P atom, the bimolecular reaction rule is not a sufficient criterion for ascribing the S_N2-P mechanism. In the case of phosphorus compounds the essential complicating factor is the question whether the 3d orbitals are, or are not involved. In addition to the transition state characteristic of S_N2-P reactions, one may consider, for a bimolecular reaction, the formation of a pentacovalent intermediate such as is appropriate to a steady state approximation for unstable intermediates. It may therefore be expected that considerable information as to the intimate details of the mechanism at a phosphorus centre can be gained by examining the stereochemistry of optically active chiralic phosphorus compounds.

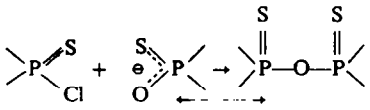
The chemistry of thiopyrophosphate systems has been the subject of systematic investigations at this laboratory. It has been found that these substances are suitable for stereochemical studies of nucleophilic substitution reactions.[4–6] The present paper shows how advantage can be taken of certain properties of optically active pyrophosphonothionates in order to demonstrate chemically an inversion of configuration at the thiophosphoryl centre during alkaline hydrolysis.

The phosphorylation of the phosphorothioic acid anion, leading to the formation of a pyrophosphorothionate, occurs through the direct attack of a P atom on the O atom of the ambident thioacid anion, and not through the isomerization of the less stable system P(O)-S-P(O)[4].



* Dedicated to Prof. J. Suszko on the occasion of his 80th birthday.

The thiophosphorylation reaction have to occur similarly,[7] since the known stability of isomeric system P(S)–S–P(O) excludes the possibility of its isomerization.[8,9]

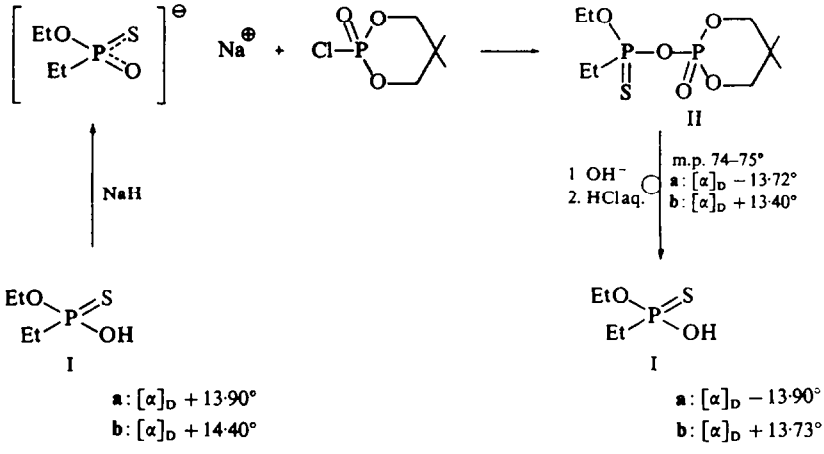


The above statements are fundamental from the point of view of the stereochemistry of pyrophosphorothionates. Phosphorylation and thiophosphorylation of optically active phosphorothioic acid anion should lead to optically active pyrophosphonothionates with the same configuration, and of the same optical purity as the original thioacid.

From the theoretical point of view, one of the most characteristic and interesting reactions of pyrophosphorothionate systems is their degradation as a result of an attack by nucleophilic reagents. Previous observations on compounds with identical substituents at both P atoms clearly indicated that the phosphoryl centre was a preferred point of nucleophilic attack.[4,5] During nucleophilic substitution reactions in optically active compounds of this type, the phosphorus thioacid residue plays only the part of the leaving group. Further investigations showed that the direction of attack is determined by the nature of the substituents at the P atoms and by the nature of the reaction medium.[10]

The compound obtained by the phosphorylation of the sodium salt of the optically active O-ethyl ethylphosphonothioic acid (I) by the action of 2-chloro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan is especially interesting.

SCHEME A



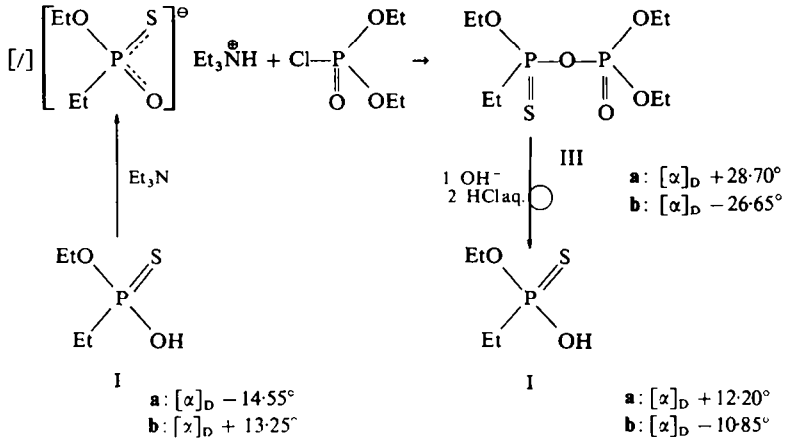
The thiophosphoryl centre P(S) in the anhydride (II) should be prone to attack by nucleophilic reagents both as a result of the electronic effect on substituting the OEt group by the Et group, and of the known steric effect of the neopentyl glycol group. This is particularly noticeable in the alkaline hydrolysis reaction, which, as can be seen from the above scheme, leads to the formation of the acid (I) with the same optical

purity as the original acid, and with a reversed configuration. Somewhat lower value of optical rotation $[\alpha]_D$ in experiment (b) is due to the fact that crude anhydride (II) (+) was used in the hydrolysis. This anhydride, after crystallization has an optical rotation $[\alpha]_D$ +14·30°.

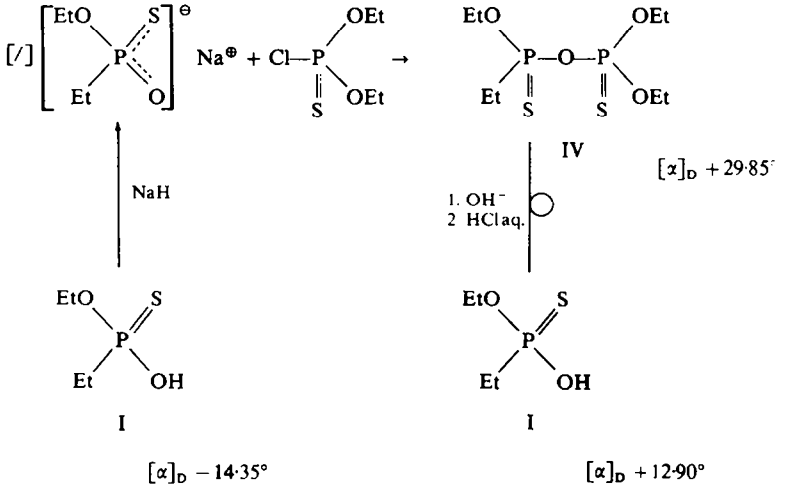
Taking into account the fact that reaction in which the anhydride (II) is formed occurs without inversion of configuration at the chiral P atom, the formation of the thioacid (I), with the opposite optical rotation and the same optical purity as the original thioacid proves full Walden inversion and selective attack of the OH^- ion on the thiophosphoryl centre.

Analogous reactions were also carried out on two other systems: triethyl ethylphosphonothionate (III, scheme B) and triethyl ethylphosphonodithionate (IV, scheme C).

SCHEME B



SCHEME C



The slightly lower optical purity of the acid (I), in comparison to the changes of scheme (A), obtained during alkaline hydrolysis in the last two cycles may be explained by the possibility of partial attack on the second P atom, which causes the formation of small amounts of acid (I) with the same configuration as the original acid.

The studies of Hudson and Green gave the first indication that alkaline hydrolysis at a thiophosphoryl centre occurs which an inversion.[7] The present work gives definite evidence inversion of configuration as a result of the attack by ion OH^- on thiophosphoryl centre; other investigation have shown that inversion occurs during the attack of nucleophilic reagents on thiophosphoryl centre[4–6, 11–13]—this leads us to suppose that inversion of configuration is a rule for S_N2–P reaction at a thiophosphoryl centre.

The fact that full of inversion configuration occurs in the reactions under discussion is very important in considering the reaction mechanism. It make it possible to assume, for S_N2–P reactions a transition state in the shape of a trigonal bipiramid in which bonds are made and are broken synchronously. The formation of a pentacovalent adduct as an intermediate does not seem probable, for in this case racemization would be expected as a result of pseudorotation of the trigonal bipiramid.[14–17] Because of the structure and chemical properties similarity between thiophosphoryl and phosphoryl compounds these arguments can be applied to both classes of compounds.

EXPERIMENTAL

Optical activity measurements were made with a Hilger and Watts polarimeter (sensitivity ±0·01°), occasionally a Perkin–Elmer 141 photopolarimeter (sensitivity ±0·002°) was used. Neat compounds were examined in all cases. M.ps and b.ps are uncorrected. Organic extracts were dried over $MgSO_4$ and evaporated under reduced press. Benzene was dried over NaH and distilled. Et_3N was dried over KOH. 1,2-Dimethoxyethane was dried over $CaCl_2$, followed by Na and distilled, b.p. 82–83°.

O-ethyl ethylphosphonothioic acid (I; b.p. 57–59°/0·08 mm, n_D^{22} 1·4900) was obtained and resolved into optical antipodes according to Aaron's *et al.*[18]

2-Chloro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan m.p. 101–102° was obtained by the procedure of Stec and Zwierzak.[19] Diethyl phosphorochloridate (b.p. 89–90°/18 mm, n_D^{22} 1·4160) was obtained as described by Fiszer and Michalski.[20] O,O-diethyl phosphorochloridothionate was obtained according to Fletcher's *et al.* method.[21]

Reaction of (+) O-*ethyl ethylphosphonothioic acid* (I) *with* 2-*chloro*-2-*oxo*-5,5-*dimethyl*-1,3,2-*dioxaphosphorinan.* To the stirred suspension of (+) sodium O-ethyl ethylphosphonothioate obtained from I (4·62 g, 0·03 mole $[\alpha]_D^{20}$ +13·906°) and NaH (0·72 g, 0·03 mole), in 1,2-dimethoxyethane (30 ml), 2-chloro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan (6 g, 0·03 mole) in 1,2-dimethoxyethane (20 ml) was added dropwise at 0°. The reaction mixture was stirred for 6 hr at room temp. After removal of the solvent benzene was added and precipitated NaCl filtered off. The benzene soln was washed with water and dried. Evaporation of the solvent left a solid, which was crystallized from benzene–ligroine (1:1) to give 6·7 g (74%) of impure (−)-II, m.p. 72–75° $[\alpha]_D^{20}$ −13·208°. Recrystallization of II afforded analytically pure sample m.p. 74–75° (racemic compound have m.p. 72–73°) $[\alpha]_D^{20}$ −13·720°. (Found: C, 35·60; H, 6·77; P, 20·23, requires: C, 35·75; H, 6·66; P, 20·49%).

Reaction of (−) O-*ethyl ethylphosphonothioic acid* (I) *with* 2-*chloro*-2-*oxo*-5,5-*dimethyl*-1,3,2-*dioxaphosphorinan.* The soln of 2-chloro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan (5·45 g, 0·027 mole) in 1,2-dimethoxyethane (20 ml) was added dropwise to the stirred suspension of (−) sodium O-ethyl ethylphosphonothioate in 1,2-dimethoxyethane (30 ml), prepared from I (4·2 g, 0·027 mole $[\alpha]_D^{20}$ −14·400°) and NaH (0·65 g, 0·027 mole) at 0°. The reaction mixture was worked up as described to give 6·8 g (84%) of (+)-II, m.p. 71–75° $[\alpha]_D^{20}$ +13·426°. After crystallization from benzene–ligroine (1:1), it melted at 74–75° $[\alpha]_D^{20}$ +14·302°.

Hydrolysis of (−)*2-ethylethoxyphosphinothioyl-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan* (II). Hydrolysis of (−)-II (6·1 g, 0·02 mole $[\alpha]_D^{20}$ −13·720°) was effected by stirring for 12 hr with the soln of NaOH (8·0 g, 0·20 mole) in water (80 ml) and dioxan (15 ml) at room temp. The reaction mixture was extracted with benzene (2 × 20 ml). The water layer was acidified with conc HCl (30 ml) at 0°. The precipitated 2-hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan was filtered off, washed with $CHCl_3$ and dried (0·8 g, m.p. 170–172°) Crude I was extracted with $CHCl_3$ (6 × 20 ml) from the mother liquor. After removal of the solvent the residue was distilled *in vacuo* to give 2·1 g (79%) of I, b.p. 53–54°/0·05 mm, n_D^{24} 1·4890, $[\alpha]_D^{20}$ −13·900°. (Found: C, 31·15; H, 7·15; P, 19·83; Calc. for $C_4H_{11}O_2PS$: C, 31·16; H, 7·19; P, 20·09%). The water soln was then evaporated *in vacuo* and the residue extracted with acetone. Evaporation of solvent left a solid, which was crystallized from water and dried over P_2O_5 to afford the next crop (1·2 g) of 2-hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan, m.p. 170–172°. Total yield of this acid was 2·0 g (74·5%). (Found: C, 36·06; H, 6·60; P, 18·22. Calc. for $C_5H_{11}O_4P$: C, 36·15; H, 6·67; P, 18·62%).

Hydrolysis of (+)*2-ethylethoxyphosphinothioyl-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan* (II). The (+)oxide II (4 g, 0·013 mole $[\alpha]_D^{20}$ +13·426°) was hydrolysed as described immediately above to give 1·6 g (79%) of (+)-I, b.p. 52–53°/0·03 mm, n_D^{21} 1·4900 $[\alpha]_D^{20}$ +13·739°, and 1·55 g (70%) of 2-hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan m.p. 170–172°.

(+) *and* (+) O,O,O-*Triethyl ethylpyrophosphonothionates* (III) *from* (+) *and* (−) O-*ethyl ethylphosphonothioic acids* (I). The soln of (−)-I (4·1 g, 0·0266 mole $[\alpha]_D^{20}$ −14·55°) in benzene (10 ml) was cooled to −5°. Triethylamine (2·69 g, 0·0266 mole) followed by diethyl phosphorochloridate (4·58 g, 0·0266 mole), were then added dropwise with stirring at 0°. After the addition had been completed, stirring was continued for 0·5 hr at 0°. The reaction mixture was left overnight at room temp. Benzene (20 ml) was then added and triethylamine hydrochloride filtered off. Benzene soln was washed with water and dried. Evaporation of the solvent left an oil, which was distilled *in vacuo* to give (+)-III (5·8 g, 80%), b.p. 79–80°/0·01 mm, n_D^{21} 1·4595 $[\alpha]_D^{20}$ +28·70°.

According to this procedure (−)-III (5·3 g, 73%), b.p. 82–84°/0·05 mm, n_D^{22} 1·4590, $[\alpha]_D^{20}$ −26·65°, was obtained from (+)-I (4 g, 0·026 mole $[\alpha]_D^{20}$ +13·25°).

Optically active (+) and (−) O,O,O-triethyl ethylpyrophosphonothionates have identical properties with analytically pure racemic compound b.p. 85–87/0·08 mm, n_D^{22} 1·4595. (Found: C, 33·3; H, 6·9; P, 21·10. Calc. for $C_8H_{20}O_5P_2S$: C, 33·1; H, 6·9; P, 21·13%).

Hydrolysis of (+) O,O,O-*triethyl ethylpyrophosphonothionate* (III). A soln of (+)-III (5·8 g, 0·02 mole $[\alpha]_D^{20}$ +28·10°) in dioxan (10 ml) was added with stirring to the soln of NaOH (7·5 g, 0·188 mole) in water (60 ml). The reaction mixture was stirred for 24 hr at room temp and then extracted with benzene (2 × 20 ml). The water layer was cooled, acidified with conc HCl (25 ml), and extracted with $CHCl_3$ (6 × 30 ml). The organic soln was dried and evaporated. The residue was distilled *in vacuo* to give two fractions: (a) 1·95 g, b.p. 52–53°/0·01 mm, n_D^{22} 1·4874 $[\alpha]_D^{20}$ +11·00° (b) 1·05 g, b.p. 92–110°/0·01 mm, n_D^{22} 1·4230. Fraction (a) was redestilled to give (+)-I b.p. 53–54°/0·01 mm, n_D^{22} 1·4894, $[\alpha]_D^{20}$ +12·20°. (Found: C, 30·85; H, 7·18; P, 19·17. Calc. for $C_4H_{11}C_2PS$: C, 31·16; H, 7·19; P, 20·09%).

The hydrolysis products were identified by ascending paper chromatography [Whatman paper No 1; solvent system: propanol–aq. ammonia–water (8:3:1)]. Chromatograms were developed by spraying with Ranes and Isherwood's reagent.[22] For product (a)-redestilled and (b), the respective R_f values were obtained: for (a) R_f 0·74 and for (b) R_f 0·65 and 0·74. Authentic samples of O-ethyl ethylphosphonothioic acid and diethyl phosphoric acid have R_f values 0·74 and 0·65 respectively.

Hydrolysis of (−) O,O,O-*triethyl ethylpyrophosphonothionate.* (−) O,O,O-Triethyl ethylpyrophosphonothionate $[\alpha]_D^{20}$ −26·65° was hydrolysed as desdribed above to give: fraction (a) b.p. 53–54°/0·05 mm, n_D^{23} 1·4885 $[\alpha]_D^{20}$ −9·20°, after redestillation b.p. 53–54°/0·05 mm, n_D^{23} 1·4895 $[\alpha]_D^{20}$ −10·85; fraction (b) b.p. 70–98°/0·05 mm, n_D^{24} 1·4290. Fraction (a) was identified chromatographically as O-ethyl ethylphosphonothioic acid and fraction (b) as a mixture two acids: diethyl phosphoric acid and O-ethyl ethylphosphonothioic acid.

(+) O,O,O-*Triethyl ethylpyrophosphonodithionate* (IV) *from* (−) O-*ethyl ethylphosphonothioic acid* (I). To the soln of (−) sodium O-ethyl ethylphosphonothioate, prepared from I (8·75 g, 0·57 mole $[\alpha]_D^{20}$ −14·35°) and NaH (1·37 g, 0·057 mole) in 1,2-dimethhoxyethane (50 ml), O,O-diethyl phosphorochloridothionate (12·4 g, 0·067 mole) was added at room temp. The mixture was stirred for 4 hr and then allowed to stand overnight. After removal of the solvent, benzene (50 ml) was added, the soln washed with water, dried and evaporated. The residue was distilled *in vacuo* to give 4·4 g of (+)-IV, b.p. 74–76°/0·01 mm, n_D^{22} 1·4880 $[\alpha]_D^{20}$ +29·85°. (Found: C, 31·4; H, 6·6; P, 20·5; Calc. for $C_8H_{20}O_4P_2S_2$: C, 31·3; H, 6·5; P, 20·2%).

Hydrolysis (+) O,O,O-*triethyl ethylpyrophosphonodithionate* (IV). Compound IV (4·4 g, 0·0144 mole $[\alpha]_D^{20}$ +29·85°) in dioxan (10 ml) was added to 12% NaOH aq (60 ml) at room temp. The mixture was stirred for 7 hr and then was left overnight. The soln was extracted with benzene (3 × 20 ml), acidified with conc HCl and extracted with $CHCl_3$ (5 × 20 ml). After removal of the solvent, the residue was distilled *in vacuo* to give two fractions:

(a) 1·28 g, b.p. 55–60°/0·05 mm, after redestillation was obtained analitically pure (+)-I (0·5 g), b.p. 55–56°0·05 mm, n_D^{20} 1·4890 $[\alpha]_D^{20}$ +12·90°. (Found: P, 20·2; requires P, 20·1%).

(b) 1·5 g, b.p. 60–70°/0·05 mm, which identified chromatographically as a mixture two acids: O,O-diethyl phosphorothioic acid and O-ethyl ethylphosphonothioic acid.

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