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STEREOCHEMISTRY OF THE REACTION BETWEEN PHOSPHORYL COMPOUNDS AND PHOSPHORUS PENTASULPHIDE (P_4S_{10})[1]

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Abstract—Phosphorus pentasulphide converts optically active phosphonothiolates into the corresponding phosphonodithioates with predominant retention of configuration at the phosphorus atom. Reaction of the optically active methylpropylphenylphosphine oxide was found to afford racemic methylpropylphenylphosphine sulphide.

PHOSPHORUS PENTASULPHIDE, P_4S_{10}, is frequently used for the conversion of the phosphoryl group P(O) into thiophosphoryl group P(S).[2-4] Our interest in the synthesis and transformations of optically active thiophosphoryl compounds[5-8] has led us to examine the reaction of the optically active phosphoryl compounds with P_4S_{10}. This reaction is of interest for two reasons: the possibility of finding a new route to optically active thiophosphoryl compounds and the stereochemistry of the reaction itself.

The recent communications of Aaron *et al.*[9, 10] on stereospecific reactions of P_4S_{10} with O-isopropyl methylphosphonate and with some phosphonothiolates. Me(i-PrO)P(O)SR. (where R = Ph. i-Pr), prompted us to report our own results. We have studied the conversion of P(O) into P(S)-group in the optically active O,S-diethyl ethylphosphonothiolate (II), O-isopropyl S-ethyl methylphosphonothiolate (VI) and methylpropylphenylphosphine oxide (IX).

The phosphonothiolates II, $[\alpha]_D$ − 70·90°, and VI $[\alpha]_{578}$ − 63·90° (benzene), were obtained from EtI and (−) O-ethyl ethylphosphonothioic acid (I), $[\alpha]_D$ − 14·50°, and (−) O-isopropyl methylphosphonothioic acid (V), $[\alpha]_D$ − 14·10°, respectively.

Treatment of (−)-O,S-diethyl ethylphosphonothiolate (II), $[\alpha]_D$ − 70·90°, with an excess of P_4S_{10} in the presence of dimethylaniline at 120–130° for 2 hr gave (−) O,S-diethyl ethylphosphonodithioate (III), $[\alpha]_D$ − 72·00°. The pure ester (III) (100% by GLPC) was isolated from the mixture with 37% yield.

The stereochemical course of the reaction and its stereospecificity have been established by carrying out additional chemical correlations. They include the conversion of the (−) acid I, $[\alpha]_D$ − 14·50°, into (−) O-ethyl ethylphosphonochloridothionate (IV), $[\alpha]_D$ − 70·00°, and its subsequent reaction with ethylmercapto-anion affording the (+) ester (III), $[\alpha]_D$ + 62·40°. According to our previous investigations both the reactions proceed apparently with inversion of configuration at the phosphorus atom.[5, 7]

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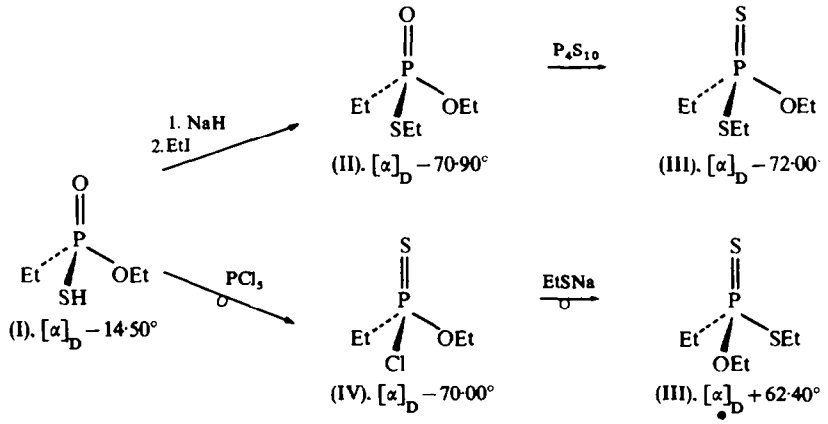
All transformations used to assign the stereochemistry of the reaction with P_4S_{10} are summarized in Scheme 1.

SCHEME 1

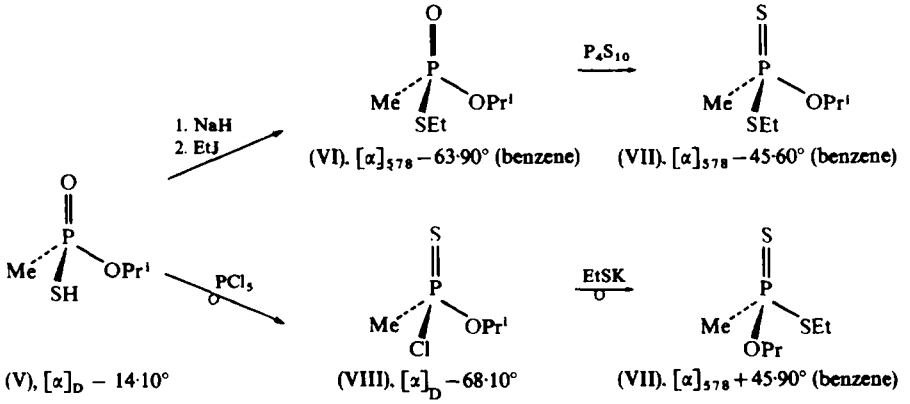


Since S-ethylation of acid I involves no change in configuration at phosphorus, the comparison of the rotation of the resulting O,S-diethyl ethylphosphonodithioates (III) obtained by each route indicates that the reaction of O,S-diethyl ethylphosphonothiolate (II) with P_4S_{10} must have occurred with retention of configuration at phosphorus.

Taking into account that (−) chloride IV. $[\alpha]_D$ − 70·00°, obtained from the (−) acid I. $[\alpha]_D$ − 14·50°, is at least 80·7% optically pure[5] and assuming the fully stereospecific conversion of (−) chloride IV into (+) phosphonodithioate III, the stereospecificity of the reaction discussed may be estimated at 96%.

Similarly, the reaction of (—) O-isopropyl S-ethyl methylphosphonothiolate (VI). $[\alpha]_{578}$ —63·90° with P_4S_{10} under the same conditions afforded (—) O-isopropyl S-ethyl methylphosphonodithioate (VII). $[\alpha]_{578}$ −45·60° (benzene). Assignments of the stereochemical direction of the reaction and degree of stereospecificity were based on an analogous reaction sequence shown in Scheme 2. It clearly indicates

SCHEME 2



that the reaction of the (−)ester VI with P_4S_{10} occurs with predominant retention of configuration at phosphorus.

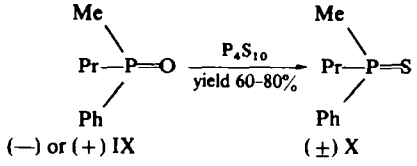
As the optical purity of the O-isopropyl methylphosphonochloridothionate (VIII) was unknown its synthesis and alkaline hydrolysis were carried out in independent experiments.[6]

$$\underset{\text{(−) V. } [\alpha]_D -14{\cdot}10^\circ}{\text{Me(i—PrO)P(S)OH}} \xrightarrow[O]{PCl_5} \underset{\text{(−) VIII. } [\alpha]_D -85{\cdot}80^\circ}{\text{Me(i—PrO)P(S)Cl}} \xrightarrow[O]{HO^-} \underset{\text{(−) V. } [\alpha]_D -12{\cdot}25^\circ}{\text{Me(i—PrO)P(S)OH}}$$

Reaction of O-isopropyl methylphosphonothioic acid (V). $[\alpha]_D$ −14·10°. with PCl_5 in petroleum ether at −10° gave O-isopropyl methylphosphonochloridothionate (VIII). $[\alpha]_D$ −85·80°. Alkaline hydrolysis of (−) VIII gave (−)acid V. $[\alpha]_D$ −12·25°. This result indicates that the optical rotation of the pure (−)chloride VIII can be tentatively assigned as $[\alpha]_D$ −98·9°.*

On the basis of these data the stereospecificity of the conversion VI→VII may be estimated at 84%.

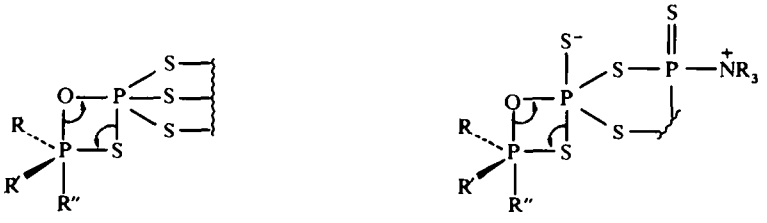
In contrast to the stereospecific reactions of phosphonothiolates, the reaction of the optically active methylpropylphenylphosphine oxide (IX) with P_4S_{10} leads to the racemic methylpropylphenylphosphine sulphide (X).



(−) or (+) IX (±) X

The changes of the reaction conditions such as: use of benzene as solvent and the absence of dimethylaniline have no influence on the stereochemistry of the latter reaction. In addition. the optically active phosphine sulphide (X) did not racemize on treatment with P_4S_{10} under conditions comparable to those of the conversion IX→X.

Although the mechanism of the reaction between phosphoryl compounds and P_4S_{10} is obscure, the retention of configuration at phosphorus during the conversion of phosphonothiolates into phosphonodithioates can be explained if the intervention of a four-membered cyclic intermediate of the types shown below is assumed.



The phosphoryl O–S exchange at phosphorus should take place in apical and equatorial positions. From the point of view of stereochemistry at phosphorus it resembles the Wittig and related reactions.[11, 12]

* Aaron *et al.*[9] have assumed (−) chloride (VIII) with an $[\alpha]_D$ + 69·9° obtained from (−) acid (V). $[\alpha]_D$ − 14·00° to be optically pure. In view of the results obtained here this is not the case and, therefore, the stereospecificities of the reactions investigated by the mentioned authors should be lower.

The loss of overall stereospecificity observed in the reaction between phosphine oxides and P_4S_{10} is presumably due to other mechanisms operating or to the different nature of the intermediate formed. Further experiments to elucidate the different stereochemical behaviour of phosphonothiolates and phosphine oxides are in progress.

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EXPERIMENTAL

Optical activity measurements were made with a Hilger and Watts polarimeter (sensitivity ±0·01°) or with a Perkin–Elmer 141 photopolarimeter (sensitivity ±0·002°). Rotations refer to neat compounds unless otherwise stated. The experiments with optically active materials were previously carried out on racemic compounds. Solvents were purified by conventional methods. Organic extracts were dried over $MgSO_4$.

O-ethyl ethylphosphonothioic acid (I) was resolved into optical antipodes according to Aaron *et al.*[13] O-isopropyl methylphosphonothioic acid (V) was resolved into optical antipodes *via* diastereomeric salts with (+) α-phenylethylamine.[14]

Optically active O-ethyl ethylphosphonochloridothionate (IV) was prepared according to Mickalski and Mikołajczyk.[5]

Optically active (−) methylpropylphenylphosphine sulphide (X) was prepared from (+) methylpropylphenylphosphine oxide (IX) by reduction with $SiHCl_3$ in the presence of Et_3N and addition of sulphur to the (−) methylpropylphenylphosphine formed.[15]

(−) O,S-*Diethyl ethylphosphonothiolate* (II) was prepared from EtI and sodium salt of the (−) acid I (10·8 g. 70·2 mmole). $[\alpha]_D$ − 14·50°. 79% yield. b.p. 55°/0·6 mm. n_D^{20} 1·4727. $[\alpha]_D$ − 70·90° (lit.,[16] b.p. 62°/0·9 mm. n_D^{22} 1·4720).

(−) O-*Isopropyl* S-*ethyl methylphosphonothiolate* (VI) was prepared similarly from EtI and (−) acid V (4·8 g. 31·2 mmole) $[\alpha]_D$ − 14·10°. 62% yield. b.p. 54°/1 mm. n_D^{20} 1·4668 $[\alpha]_{578}$ − 63·9 (benzene; c. 2.29).

(+) O,S-*Diethyl ethylphosphonodithionate* (III) was obtained from (−) chloride IV (2 g. 13 mmole). $[\alpha]_D$ − 70·00° and EtSNa according to the procedure described previously:[7] (1·5 g. 58%, b.p. 45–47°/0·2. n_D^{22} 1·5223. $[\alpha]_D$ + 62·40°).

(−) O-*Isopropyl methylphosphonochloridothionate* (VIII). The (−) acid V. $[\alpha]_D$ − 14·10 . (4·65 g. 30·2 mmole) in petroleum ether (b.p. 40–60°. 5 ml) was added dropwise at −10° to the stirred suspension of PCl_5 (6·3 g. 30·2 mmole) and petroleum ether (25 ml). After stirring for 1 hr at 0° the mixture was filtered and solvent evaporated under reduced pressure. The residue was distilled *in vacuo* to give (−) chloride VIII. 1·7 g (33%) b.p. 22°/0·05 mm. n_D^{20} 1·4844. $[\alpha]_D$ − 85·80° (Found: C, 28·10; H, 5·99; P, 17·84. Calc. for $C_4H_{10}OPSCl$: C, 27·83; H, 5·84; P, 17·90%).

Hydrolysis of (−)O-*isopropyl methylphosphonochloridothionate* (VIII). The chloride VIII (1·7 g. 9·8 mmole). $[\alpha]_D$ −85·80°, was added to a solution of NaOH (2·8 g) in water (20 ml) and dioxane (5 ml). The mixture was stirred for 3 hr at 50–60° and left overnight at room temperature. The solution was then extracted with benzene (3 × 15 ml), acidified with conc HCl and extracted with $CHCl_3$ (4 × 15 ml). After removal of the solvent the residue was distilled *in vacuo* to give (−) acid (V). 1 g (66%). b.p. 46°/0·01 mm. n_D^{20} 1·4828. $[\alpha]_D$ − 12·25°; dicyclohexylamine salt m.p. 124–126° (lit.,[14] m.p. 126°).

(+) O-*isopropyl* S-*ethyl methylphosphonodithioate* (VII) *from* O-*isopropyl methylphosphonochloridothionate* (VIII). (−) Chloride VIII (1·5 g. 8·7 mmole). $[\alpha]_D$ − 68·10°. prepared from the (−) acid V. $[\alpha]_D$ − 14·10° was dissolved in dimethoxyethane (15 ml) and added dropwise at 5° to a suspension of EtSK (0·51 g K in 15 ml EtSH and 15 ml ether). The mixture was stirred for 6 hr at room temperature and allowed to stand overnight. The solvents were evaporated and water (20 ml) added. The water solution was extracted with benzene (3 × 15 ml). The organic solution was dried and evaporated. The residue was distilled *in vacuo* to afford (−) dithioester VII. 1·2 g (70%). b.p. 57°/0·7 mm. n_D^{20} 1·5158. $[\alpha]_{578}$ + 45·9° (benzene) c. 2·93). The purity of (−) VII checked by GLPC was 98%. (Varian chromatograph 10, Reoplex 10% columne 125°. N_2 20 ml/min). (Found: C, 37·48; H, 7·80; P, 15·42. Calc. for $C_6H_{15}OPS_2$: C, 36·32; H, 7·63; P, 15·63%).

(−) O,S-*Diethyl ethylphosphonodithioate* (III) *from* (−) O,S-*diethyl ethylphosphonohiolate* (II) *and*

P_4S_{10}. To (−) O,S-diethyl ethylphosphonothiolate (II) (3 g, 16·5 mmole), $[\alpha]_D$ −70·90, dimethylaniline (3·6 g, 30 mmole) and P_4S_{10} (6·6 g, 15 mmole) were added. The mixture was heated for 2 hr at 120°. After cooling HCl (15%, 20 ml) was added and the mixture allowed to stand overnight. The solution was extracted with benzene (4 × 20 ml). Organic layer was washed with diluted Na_2CO_3 soln. (2 × 15 ml) and water (2 × 10 ml). When the solvent had been removed the crude product was distilled to give (−) dithioester III. 1·2 g (37·5%), b.p. 49°/0·5 mm, n_D^{21} 1·5238, $[\alpha]_D^3$ −72·00°. The purity of (−) (III) checked by GLPC was 100% (Found: C, 36·44; H, 7·58; P, 15·66. Calc. for $C_6H_{15}OPS_2$: C, 36·32; H, 7·63; P, 15·63%).

(−) O-*Isopropyl* S-*ethyl methylphosphonodithioate* (VII) *from* (−) O-*isopropyl* S-*ethyl methylphosphonothiolate* (VI) *and* P_4S_{10}. According to the procedure described above from (−) ester VI (3 g, 16·5 mmole), $[\alpha]_{578}$ −63·9° (benzene; c, 2·29), dimethylaniline (3·6 g, 30 mmole) and P_4S_{10} (6·6 g, 15 mmole) the (−) dithioester VI was obtained with 12% yield (purity by GLPC, 97%), $[\alpha]_{578}$ −45·60° (benzene; c, 3·61).

Reaction of the optically active methylpropylphenylphosphine oxide (IX) *with* P_4S_{10}. (a) The mixture of (−) phosphine oxide (IX) (1·2 g, 6·6 mmole), $[\alpha]_{589}$ −12·00° (MeOH; c, 4·56), dimethylaniline (0·85 g, 7 mmole) and P_4S_{10} (2·2 g, 5 mmole) was heated for 2 hr at 120°, cooled to room temperature. HCl (15%, 20 ml) added and allowed to stand overnight. The solution was extracted with $CHCl_3$ (4 × 20 ml), the organic layer washed with diluted Na_2CO_3 soln (2 × 15 ml) and water (2 × 15 ml). Evaporation of solvent left a solid, crystallized from petroleum ether to afford methylpropylphenylphosphine sulphide (X), 0·8 g (61%), m.p. 59–61°, $[\alpha]_{589}$ 0° (MeOH: c, 3·03). (Found: C, 60·74; H, 7·50; P, 16·03 calc. for $C_{10}H_{15}PS$: C, 60·58; H, 7·61; P, 15·62%). (b) The (+) phosphine oxide (IX) (1·2 g, 6.6 mmole), $[\alpha]_{589}$ +4·5° (MeOH; c, 5·98) and P_4S_{10} (2·2 g, 5 mmole) were heated for 2 hr at 120°. Na_2CO_3 soln (25 ml) added and the phosphine sulphide (X) was extracted with $CHCl_3$ (4 × 20 ml). Evaporation of solvent and crystallization of crude product afforded phosphine sulphide (X), 1·1 g (84%), m.p. 59–61°, $[\alpha]_{589}$ 0° (MeOH; c, 4·48). (c) The mixture of (+) phosphine oxide (IX) (1.2 g, 6·6 mmole), $[\alpha]_{589}$ +4·5 (MeOH; c, 5·98), dimethylaniline (0·85 g, 7 mmole) and P_4S_{10} (2·2 g, 5 mmole) was refluxed in benzene (30 ml) for 2·5 hr. The benzene solution was washed with HCl (15%, 3 × 15 ml), diluted Na_2CO_3 soln (2 × 15 ml) and water (2 × 15 ml). After removal of solvent the crude product was crystallized from petroleum ether to give phosphine sulphide (X), 1 g (76%), m.p. 59–61°, $[\alpha]_{589}$ 0° (MeOH: c, 9·74).

Attempted racemization of (−) *methylpropylphenylphosphine sulphide* (X). The mixture of (−) phosphine sulphide (X) (1 g, 5·1 mmole), $[\alpha]_{589}$ −5·0° (MeOH; c, 2·16), dimethylaniline (0·7 g, 5·8 mmole) and P_4S_{10} (1·8 g, 4·05 mmole) was refluxed in benzene (25 ml) for 2·5 hr. The sulphide (X) was separated as described above; 0·6 g (60%), $[\alpha]_{589}$ −5·3° (MeOH; c, 3·35), m.p. 60–62°.

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