Tetrahedron. Vol 28, pp. 3855 to 3865. Pergamon Press 1972. Printed in Great Britain

CONFIGURATION OF THE OPTICALLY ACTIVE PHOSPHORUS THIOACIDS—I[1]

CHEMICAL CORRELATION OF THE CONFIGURATION OF O-ALKYL ALKYL-PHOSPHONOTHIOIC ACIDS

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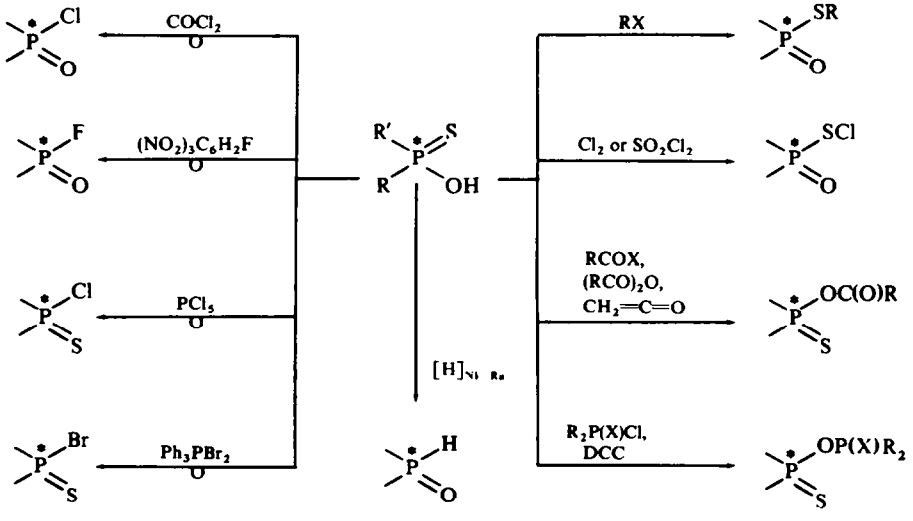
(*Received in the UK 25 March 1972; Accepted for publication 12 April 1972*)

Abstract— Chirality of the P atom in O-alkyl methylphosphonothioic acids, Me(RO)P(S)OH (R=Me,-Et,Pr^n.Bu^n), O-alkyl ethylphosphonothioic acids Et(RO)P(S)OH (R=Me,Et), O-alkyl isopropylphosphonothioic acids Pr^i(RO)P(S)OH (R=Me,Et) was correlated with that of (+)*R*-O-isopropyl methylphosphonothioic acid, Me(Pr^{i}O)P(S)OH. The chemical correlation was based on the synthesis of optically active O,O-dialkyl alkylphosphonothionates, R(RO)(R'O)P(S), from suitably substituted phosphonothioic acids via the corresponding O-alkyl alkylphosphonochloridothionates, R(RO)P(S)Cl. It has been shown that all the dextrorotatory O-alkyl alkylphosphonothioic acids have the *R* configuration.

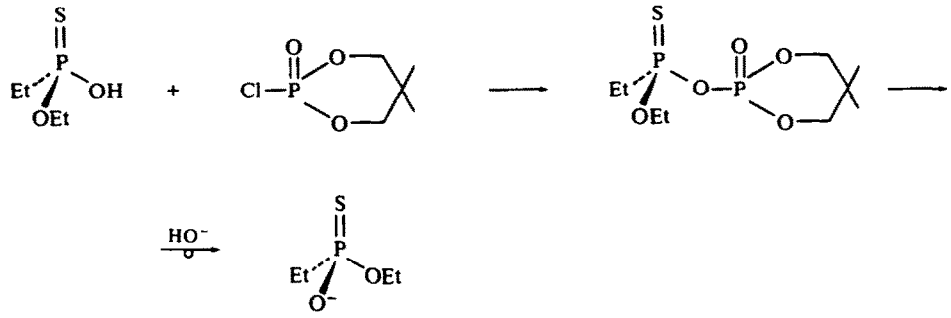
Additionally it has been demonstrated that alkaline hydrolysis occurs with inversion of configuration at the P atom connected with the isopropyl group.

OPTICALLY active phosphorus monothioacids constitute a class of compounds which have played an important part in the development of the dynamic stereochemistry of phosphorus. Due to their reactivity and the ambident character of the monothioacid anion various optically active phosphoryl, P(O)- and thiophosphoryl, P(S)-compounds can be prepared by stereospecific reactions of phosphorus thioacids. The most important optically active derivatives of phosphorus thioacids are shown in Scheme 1.[2]

SCHEME 1

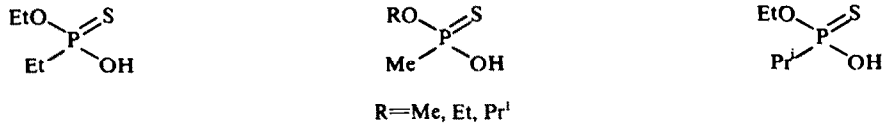


It is of interest that Walden cycle for phosphorus has been devised on the basis of reactions of optically active phosphorus thioacids.[3]



This very short review shows that optically active phosphorus thioacids can be regarded as key compounds and that the elucidation of their absolute configuration may be of great value in chemical and biochemical studies.

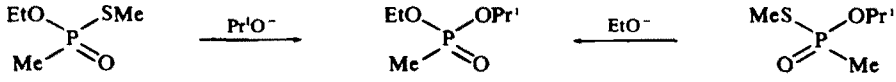
The relative configurations of phosphorus thioacids were mentioned for the first time in an early work of Aaron,[4] who resolved the following O-alkyl alkylphosphonothioic acids.



R=Me, Et, Pr^i

According to Aaron the configurations of the levorotatory enantiomers of these acids are the same. This conclusion was drawn from the fact that the optically active derivatives synthesized from the (−)thioacids are more potent inhibitors of cholinoesterase enzymes than their corresponding enantiomers.

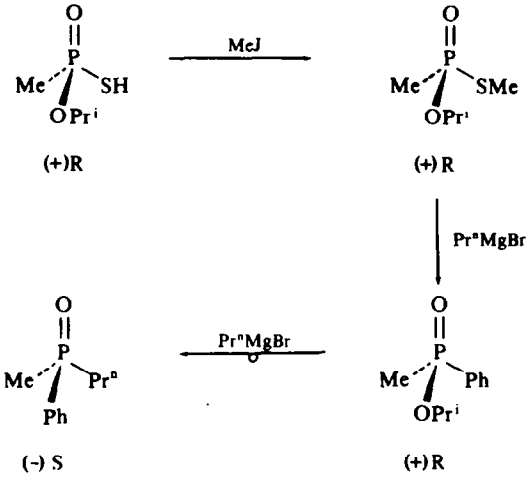
The similarity of configurations of the levorotatory isomers of O-isopropyl methylphosphonothioic acid and O-ethyl methylphosphonothioic acid was also indicated by the following chemical transformations:[5]



Benschop *et al.*[6] were able to establish for the first time the correlation between (+)O-isopropyl methylphosphonothioic acid and (−)S-methyl-n-propylphenylphosphine oxide. It can be seen from the scheme that the conversion of (+)phosphonothioic acid into (−)S-phosphine oxide was achieved via methylation and two successive

reactions with Grignard reagents. The first reaction does not involve any change of configuration at the P atom. According to recent results reported by Mislow *et al.*[7] and by Benschop[8] the stereospecific conversion of phosphonothiolates into phosphinates takes place with retention of configuration at the P atom.† Since the reaction of phosphinates with Grignard reagents is accompanied by inversion of configuration at the P atom,[9] it follows that (+)O-isopropyl methylphosphonothioic acid has the absolute configuration (R).‡

SCHEME 2



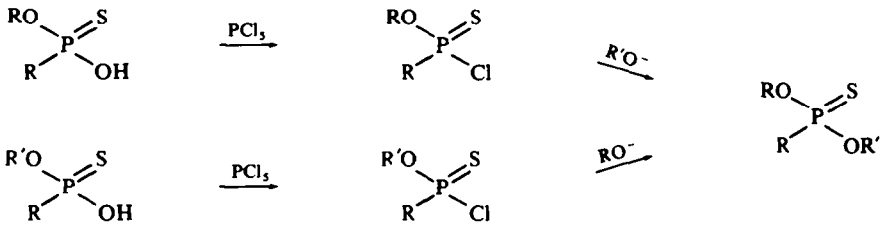
We have investigated methods of determining the absolute configurations of the optically active phosphorus thioacids. In the present paper we describe the chemical correlations in the series of O-alkyl alkylphosphonothioic acids, using (+)R-O-isopropyl methylphosphonothioic acid as the reference compound.

RESULTS AND DISCUSSION

Our correlation method is based on the synthesis of optically active phosphonochloridothionates from phosphorus pentachloride and suitably substituted thiophosphonic acids (the configurations of which are to be correlated), and the alkoxide displacement at the asymmetric P atom in the phosphonochloridothionates giving the same optically active phosphonothionate. The general approach is shown in the scheme below:

† Benschop *et al.*[6] have originally assumed that the inversion of configuration occurs during this conversion and they have assigned *S* configuration to (+)O-isopropyl methylphosphonothioic acid.

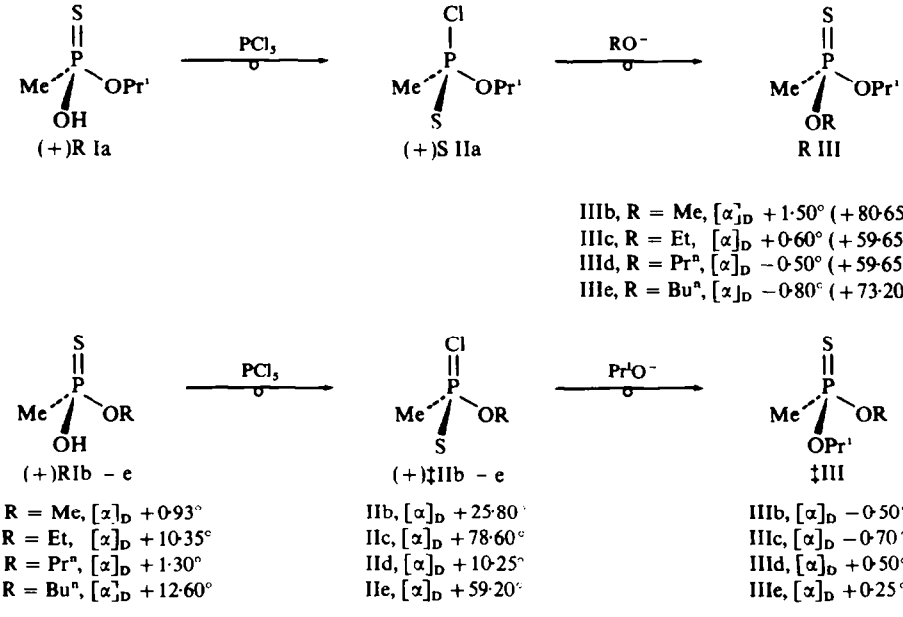
‡ In view of this fact our earlier assignments of absolute configurations to O-ethyl ethylphosphonothioic acid,[10] O-methyl methylphosphonothioic acid[11] and O-ethyl methylphosphonothioic acid [11] must be revised.



According to previous investigations, both reactions proceed with inversion of configuration at the P atom.[12] Therefore, the configurations of the phosphonothionates prepared by this method are readily correlated with those of their precursor thioacids and the configurational correlation between both thioacids can be established. The configurational correlations between thioacids are established by this method even without information on the stereochemical course (i.e., inversion or retention) of both reactions, provided that the reaction course remains the same when different phosphonothioic acids and phosphonochloridothionates are used.

O-Alkyl methylphosphonothioic acids. The chemical correlation of (+)R-O-isopropyl methylphosphonothioic acid (Ia) with other O-alkyl methylphosphonothioic acids (Ib–d), Me(RO)P(S)OH, (R = Me, Et, Pr^n, Bu^n) is shown in Scheme 3.

SCHEME 3



† The values given in parantheses refer to the (+)chloride (IIa) used for the synthesis of the phosphonothionates (III).

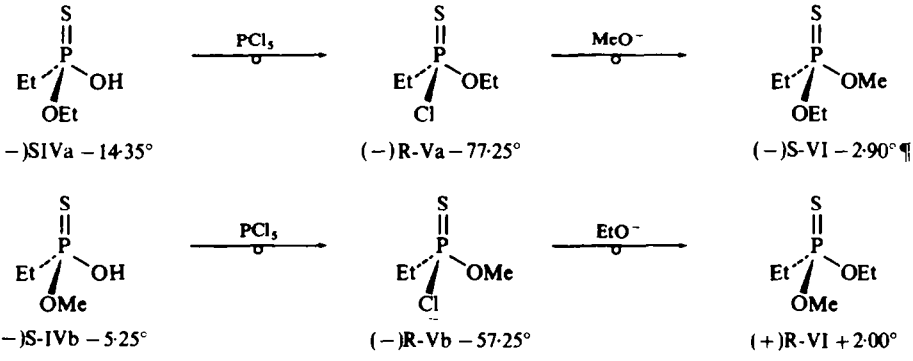
As indicated in the scheme, (+)R-phosphonothioic acid (Ia) has been converted into (+)S-O-isopropyl methylphosphonochloridothionate (IIa) by reaction with phosphorus pentachloride. Its reactions with alkoxides, RO^- (R = Me, Et, Pr^n, Bu^n) afforded the corresponding optically active O-alkyl O-isopropylphosphonothionates (III).*

Since the nucleophilic displacement of the chloride ion by an alkoxide ion proceeds with inversion of configuration, the chirality at phosphorus in all the synthesized thionoesters (III) must be R.

On the other hand, the same esters (III), but showing the opposite direction of rotation, and hence having the opposite configurations, i.e., S, have been obtained from the corresponding (+)O-alkyl methylphosphonothioic acids (Ib–e) via (+)O-alkyl methylphosphonochloridothionates (IIb–e). Comparison of the two routes to the phosphonothionates (III) indicates that all the (+)O-alkyl methylphosphonothioic acids (Ia–e) have R configuration.

O-*Alkyl ethylphosphonothioic acids.* (−)O-ethyl ethylphosphonothioic acid (IVa) was similarly correlated with (−)O-methyl ethylphosphonothioic acid (IVb). The reaction sequence shown below clearly indicates that both (−)phosphonothioic acids (IVa and IVb) have the same configuration.

SCHEME 4



¶ In our previous work[13] the configuration of (−)(VI) has been correlated with that of (−)IVa by means of the Pischschimuka reaction.

Taking into account the biochemical tests carried out by Aaron *et al.*[4] and the results of the asymmetric reduction of chiral sulphoxides by optically active thioacids (Ia and IVa)[10] we have assumed that (−)O-ethyl ethylphosphonothioic acid (IVa) has the S configuration. Therefore, the same configuration should be assigned to (−)thioacid (IVb).

Additional evidence in support of the S chirality of (−)thioacid (IVa) is provided by

* In contrast to highly rotating phosphonochloridothionates, the rotation values of the thionoesters are very small. For this reason crude phosphonothionates were treated with sodium hydroxide solutions in aqueous dioxane for several hours at room temperature in order to remove the small amounts of the unreacted optically active phosphonochloridothionates.

ORD measurements. The shapes of the ORD curves of both (−)thioacids (Ia and IVa) are almost identical (Fig 1), and a positive Cotton effect at *ca* 220 nm is observed.

O-Alkyl isopropylphosphonothioic acids. The above mentioned O-ethyl isopropylphosphonothioic acid (VIIa) has been resolved into optical antipodes by Aaron *et al.*[4]

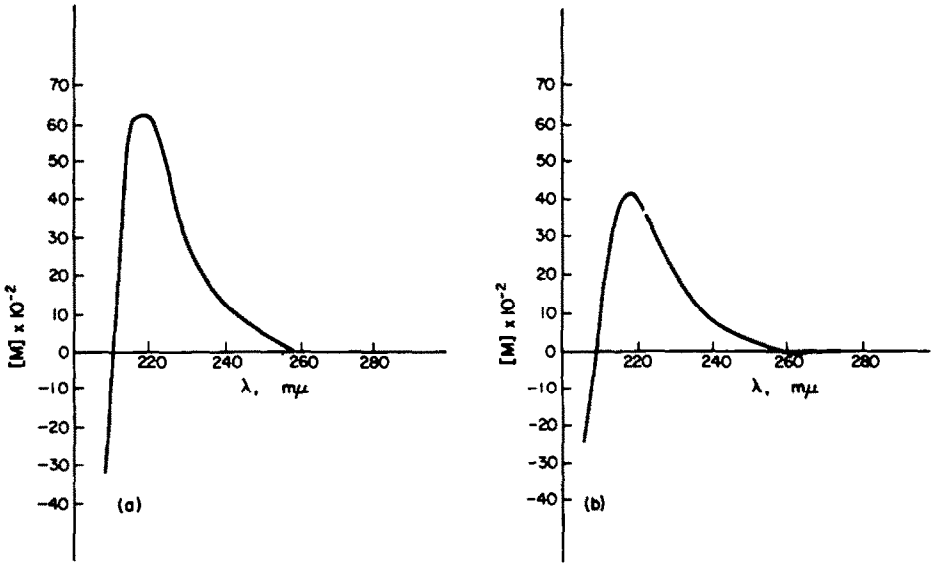
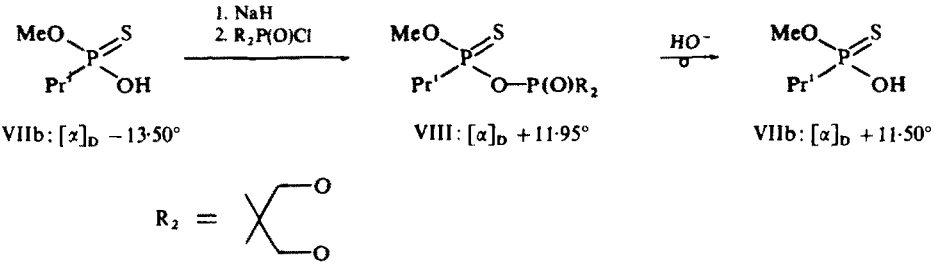


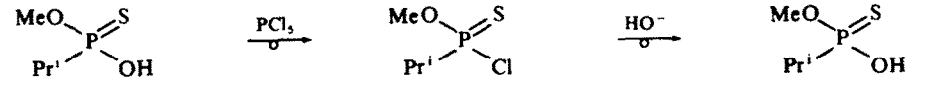
FIG 1. ORD curves of (a) (—)O-ethyl ethylphosphonothioic acid and (b) (—)O-isopropyl methylphosphonothioic acid measured in water

According to these authors the configuration of the levorotatory enantiomer is the same as that of the (−)S-O-isopropyl methylphosphonothioic acid (Ia). This fact made it possible for us to use this acid as a configurational standard in the correlation with O-methyl isopropylphosphonothioic acid (VIIb) which has been recently synthesized and resolved by diastereomeric salt formation with (−)α-phenylethylamine.[14]

The isopropyl group bonded directly to the P atom occupies the middle position between unbranched alkyl groups and the t-Bu group, which is known to force in some cases a retention mechanism during the nucleophilic substitution at phosphorus.[15] For this reason it was desirable to prove prior to the chemical correlations, the steric course of the nucleophilic displacement in such systems. Therefore we have synthesized (+)pyrophosphonothionate (VIII) by phosphorylation of the sodium salt of (−)O-methyl isopropylphosphonothioic acid (VIIb) with 2-chloro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan. The (+)anhydride (VIII) was then hydrolysed under alkaline conditions to give the thioacid (VIIb) having nearly the same optical purity as the starting thioacid and the reversed configuration. This shows definitely that alkaline hydrolysis proceeds with inversion of configuration at the P atom.



Another cycle involving the synthesis and alkaline hydrolysis of the optically active phosphonochloridothionate (IXb) strongly supports the assumption that the reaction of the (−)thioacid (VIIb) with phosphorus pentachloride as well as alkaline hydrolysis of the chloride (IXb) should proceed with inversion of configuration at the P atom bearing the isopropyl group.



The above experiments clearly indicate that the replacement of a simple unbranched alkyl group by isopropyl group does not change the steric course of the nucleophilic substitution at the P atom.

Finally the absolute configuration of (+)O-methyl isopropylphosphonothioic acid (VIIb) was deduced from the configurational correlations summarized in Scheme 5.

SCHEME 5

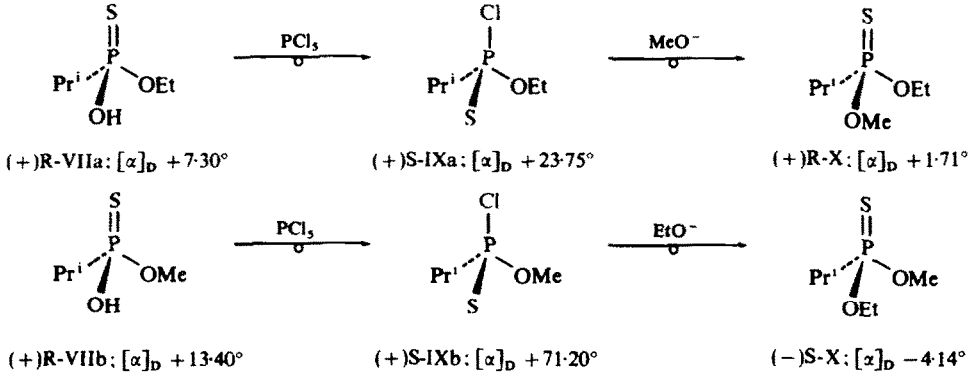


TABLE 1. OPTICALLY ACTIVE O-ALKYL ALKYLPHOSPHONOCHLORIDOTHIONATES, R(RO)P(S)Cl

Thioacid		Chloride						Literature data for racemic chloride
Formula	$[\alpha]_D$	Formula	$[\alpha]_D$	b.p./mmHg	n_D^{20}	Yield %	Elemental analysis %	
							Calc. for $C_4H_{10}OPSCl$:	b.p. 48/5[19]
Ia	+14·10	IIa	+80·65	77/15	1·4834	60·5	C, 27·83; H, 5·84; P, 17·94	
							Found: C, 27·10; H, 6·01; P, 17·70	n_D^{25} 1·4822
							Calc. for C_2H_6OPSCl:	b.p. 59/20[20]
Ib	+0·93*	IIb	+25·80	55/13	1·4996	53·5	C, 16·61; H, 4·18; P, 21·42	
							Found: C, 17·21; H, 4·44; P, 20·87	n_D^{19} 1·5001
							Calc. for C_3H_5OPSCl:	b.p. 65/15[20]
Ic	−10·50	IIc	−95·90	54/10	1·4930	65	C, 22·71; H, 5·08; P, 19·53	
							Found: C, 23·80; H, 4·95; P, 19·56	n_D^{20} 1·4991
							Calc. for $C_4H_{10}OPSCl$:	b.p. 86/20[20]
Id	+1·31*	IId	+10·25	66/12	1·4892	70	C, 27·83; H, 5·84; P, 17·94	
							Found: C, 27·96; H, 5·71; P, 18·26	n_D^{22} 1·4889
							Calc. for $C_5H_{12}OPSCl$:	b.p. 98/17[20]
Ie	+12·60	IIe	+59·20	26/0·05	1·4860	68	C, 32·18; H, 6·48; P, 16·60	
							Found: C, 32·50; H, 6·20; P, 16·30	n_D^{20} 1·4880
							Calc. for C_3H_8OPSCl:	b.p. 63/12[21]
IVb	−5·25	Vb	−57·25	20/0·05	1·5020	56	C, 22·71; H, 5·08; P, 19·53	
							Found: C, 23·10; H, 5·19; P, 20·38	
							Calc. for $C_5H_{12}OPSCl$:	
VIIa	+7·30	IXa	+23·75	68/2	1·4889	72	C, 32·18; H, 6·48; P, 16·60	
							Found: C, 32·14; H, 6·65; P, 16·68	
							Calc. for C_4H_8OPSCl:	
VIIb	+13·40	IXb	+71·20	72/4	1·4978	53·5	C, 27·83; H, 5·84; P, 17·94	
							Found: C, 28·45; H, 6·13; P, 17·78	

* $[\alpha]_{589}^{-}$.

TABLE 2. OPTICALLY ACTIVE O.O-DIALKYL ALKYLPHOSPHONOTHIONATES. R(RO)P(S)(OR')

Chloride			O,O-dialkyl alkylphosphonothionate					
n_D^{20}	Formula	$[\alpha]_D$	Formula	$[\alpha]_D$	b.p./mmHg	n_D^{20}	Yield	Elemental analysis %
	IIa	+80·60	IIIb	+1·50		1·4602	54·5	
	IIb	+25·80		−0·50	61/3	1·4608	41·5	Calc. for $C_5H_{13}O_2PS$: C, 35·70; H, 7·74; P, 18·43
								Found: C, 35·18; H, 7·80; P, 19·97
	IIa	+59·65	IIIc	+0·60	67/3	1·4560	38	Calc. for $C_6H_{15}O_2PS$: C, 39·55; H, 8·30; P, 17·00
	IIc	+78·60		−0·70		1·4560	39·5	Found: C, 39·37; H, 8·34; P, 17·10
	IIa	+59·65	IIId	−0·50	60/2	1·4546	33	Calc. for $C_7H_{17}O_2PS$: C, 42·83; H, 8·73; P, 15·78
	IId	+10·25		+0·50		1·4550	31	Found: C, 43·12; H, 8·38; P, 15·86
	IIa	+73·20	IIIe	−0·80	56/0·6	1·4570	48·5	Calc. for $C_8H_{15}O_2PS$: C, 45·69; H, 9·11; P, 14·73
	IIe	+59·20		+0·25		1·4564	40·5	Found: C, 45·88; H, 9·60; P, 14·45
	Va	−77·25	VI	−2·90		1·4678	69	
	Vb	−57·25		+2·00	44/3	1·4649	53	Calc. for $C_5H_{13}O_2PS$: C, 35·70; H, 7·74; P, 18·43
								Found: C, 35·90; H, 8·20; P, 18·46
	IXa	+23·75	X	+1·71*		1·4645	67·5	
	IXb	+71·20		−4·14*	44/1·5	1·4649	63	Calc. for $C_6H_{15}O_2PS$: C, 39·55; H, 8·29; P, 17·00
								Found: C, 39·55; H, 7·83; P, 17·44

* $[\alpha]_{589}$.

Since the absolute configuration of (+)(VIIa) is R, it follows from the above Scheme that the chirality of the P atom in (+)thioacid (VIIb) is also R, granted that the synthesis of the phosphonochloridothionates and chloride–alkoxide exchange take place with inversion of configuration.

The results of the present work indicate that the absolute configuration of all of (−)O-alkyl alkylphosphonothioic acids investigated here is S. It seems to us that the nature of alkyl group bonded directly or through oxygen to the P atom do not have significant influence on the relationship between the chirality of O-alkyl alkylphosphonothioic acids and their rotation sign. In this connection we suggest that (−)O-methyl t-butylphosphonothioic acid obtained recently by Krawiecka and Michalski[16] should have also configuration S.

Acknowledgement— We would like to express our gratitude to Dr. H. P. Benschop for kindly communicating to us his unpublished results concerning the absolute configuration of O-isopropyl methylphosphonothioic acid.

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 pure compounds unless otherwise stated. The experiments with optically active materials were previously carried out on racemic compounds. The chemical purity of O,O-dialkyl alkylphosphonothionates was checked by GLPC (Varian chromatograph 10).

Compounds Ib, Ic, Ia and Ie were resolved into optical antipodes via diastereomeric salts with optically active α-phenyl ethylamine.[17] Compounds IVa,[18] IVb[4] and VIIa[4] were resolved with quinine. Synthesis and resolution of Id and VIIb will be described elsewhere.[14]

Optically active O-alkyl alkylphosphonochloridothionates were prepared from optically active O-alkyl alkylphosphonothioic acids and PCl_5 according to the general procedure.[12a] To the stirred suspension of PCl_5 and solvent (ether, methylene chloride, light petroleum) the soln of optically active thioacid was added at −10°. After stirring for 1 hr at 0° the mixture was filtered and solvent as well as $POCl_3$ were evaporated under reduced pressure. The residue was dissolved in ether and washed with dilute $NaHCO_3$aq and then with water. The ether soln was dried over $MgSO_4$. After removal of the solvent the crude O-alkyl alkylphosphonochloridothionates were distilled *in vacuo*. Their optical rotations, yields and other data are given in the Table 1.

Optically active O,O-*dialkyl alkylphosphonothionates* were prepared according to the general procedure.[12c] Optically active O-alkyl alkylphosphonochloridothionate was added dropwise to a soln of sodium alkoxide at 0°. The mixture was stirred for 1 hr at 0° and then allowed to stand overnight. After evaporation of the corresponding alcohol, benzene was added. The benzene soln was washed with water, dried and evaporated. Then the crude O,O-dialkyl alkylphosphonothionate was stirred with NaOHaq in aqueous dioxane for 5 hr at room temp. The ester was extracted with benzene (4 × 20 ml). The organic soln was dried and evaporated. The residue was distilled *in vacuo* to afford O,O-dialkyl alkylphosphonothionate. Optical rotations, yields and physical constants of O,O-dialkyl alkylphosphonothionates obtained by this procedure are summarized in Table 2.

(+)-2-*Methoxyisopropylphosphinothioyl*-2-*oxo*-5,5-*dimethyl*-1,3,2-*dioxaphosphorinan* (VIII). The soln of 2-chloro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan (4·05 g, 22·1 mmole) in 1,2-dimethoxyethane (20 ml) was added dropwise to a soln of the Na salt of VIIb (3·4 g, 22·1 mmole), $[\alpha]_D$ −13·50°. The mixture was stirred for 1 hr at room temp and worked up as described previously[3] to give 2·8 g (42%) of (+) (VIII), m.p. 63·5–65° (from benzene–ligroine) m.p. of the racemic product −73–75°, $[\alpha]_{589}$ +11·95°, $[\alpha]_{578}$ +12·42° (benzene: *c*, 2·31). (Found: C, 36·13; H, 6·98; P, 20·04%. Calc. for $C_9H_{20}O_5P_2S$: C, 35·75; H, 6·66; P, 20·49%).

Hydrolysis of (+)2-*isopropylmethoxyphosphinothioyl*-2-*oxo*-5,5-*dimethyl*-1,3,2-*dioxaphosphorinan* (VIII). To a soln of NaOH in water (2·4 g in 20 ml) and dioxane (5 ml) (+) VIII, $[\alpha]_D$ +11·95 (benzene *c*, 2·3), 2·7 g (8·9 mmole) was added. The mixture was stirred at room temp for 6 hr and then allowed to stand overnight and worked up as described previously[3] to give: 2-hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxa-

phosphorinan (0·5 g, m.p. 169–172°) and (+) VIIb, 0·7 g (51%), $[\alpha]_D$ +11·50°, b.p. 53/0·05, n_D^{20} 1·4922; the dicyclohexylamonium salt, $[\alpha]_{589}$ +4·10° (benzene, *c*, 0·78) m.p. 168–170°. (Found: C, 57·19; H, 10·55; N, 4·05. Calc. for $C_{16}H_{34}O_2PSN$: C, 57·28; H, 10·21; N, 4·17%).

Hydrolysis of (–)*O-methyl isopropylphosphonochloridothionate* (IXb). The (–)chloride IXb, $[\alpha]_D$ –58·25°, (1·2 g; 6·9 mmole) was added to a soln of NaOH in water (1·8 g in 15 ml) and dioxane (5 ml). The mixture was stirred at room temp for 3 hr and then was left overnight. After the usual isolation procedure[12a] we obtained (–)thioacid (VIIb), 0·7 g (66%), $[\alpha]_D$ –7·10°, n_D^{20} 1·4921. (Found P, 19·70. Calc. for $C_4H_{11}O_2PS$: 20·00%).

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