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THE SYNTHESIS AND STEREOCHEMICAL ASPECTS OF OPTICALLY ACTIVE PHOSPHOROTHIONATES

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Abstract—Optically active phosphorothionates (**10–20**) were synthesised via the following sequence of reactions:
(1) ephedrine-methyl-1-naphthylphosphorothionate diastereoisomers using (−) ephedrine hydrochloride→(**2**) methyl-1-naphthyl-phosphorothioic acid (+) and (−) enantiomers→(**3**) methyl-1-naphthyl-chloridophosphorothionate (−) and (+) enantiomers using PCl_5→ (**4**) methyl-1-naphthyl alkyl (aryl) phosphorothionates (+) and (−) enantiomers using various nucleophiles.
(−)-Methyl-n-butyl-1-naphthylphosphorothionate (**16**) was then used to investigate the stereochemical consequences of a sequence of reactions with PCl_5 (**23**) and methoxide anion (**16'**), being reactions at the P atom, involving two inversions (Walden-type), and with trimethylamine (**20**, **20'**) and methyliodide (**21**, **21'**), involving retention, and with diazomethane resulting in retention (**16''**, **21''**). Thus the optical purity of **16** was confirmed by the diazomethane reaction.

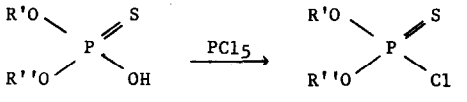
Optically active phosphorus compounds where the P atom is chiral are important in the study of certain enzymatic reactions.[1,2] In this study some enantiomeric phosphorothiono triesters have been synthesised. Reactions where the asymmetric phosphorus centre is unaffected and reactions where the optically active phosphorus centre is affected have been used in correlating configurations of the different enantiomeric intermediates.

Nucleophilic displacement reactions at chiral thiophosphoryl centres are generally stereospecific and occur with inversion of configuration at the P atom.[3] Reaction of a P(V) halide with optically active phosphonothionic acid has been shown to be at least 98% stereospecific and to have proceeded with inversion of configuration at the chiral P atom.[4,5] Triphenyl phosphorus dibromide (Ph_3PBr_2) when reacted with (O-ethyl)ethyl-phosphonothioc acid reacts similarly to P(V) with inversion to produce (O-ethyl)ethyl-phosphonobromidothioate of optical purity ≥94%.[6]

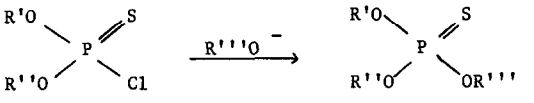
If hydrolysis occurs with inversion, then Ph_3PBr_2 must also react with inversion[7] in order to produce the enantiomer with the sign of rotation unchanged.

Esters of 0–1-naphthylphosphorothioic acid have been used in this study; in interconverting these, five different procedures, two of them I and II being reactions at the P atom (and therefore capable of causing configurational change) and three III–V involving peripheral groups (and therefore presumably not affecting the configuration at phosphorus), were used. These methods were:

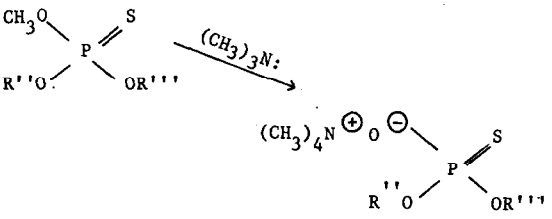
(I) Reaction of a phosphorothioic diester with PCl_5.[4,5]



(II) Reaction of the product of (I), a chloridophosphorothionate with a sodium alkoxide or phenolate[3,8–12] to produce phosphorothionate triesters.

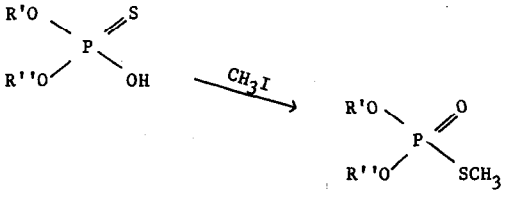


(III) Reaction of an O-methylphosphorothioate with trimethylamine[2] (SN2 displacement on methyl).

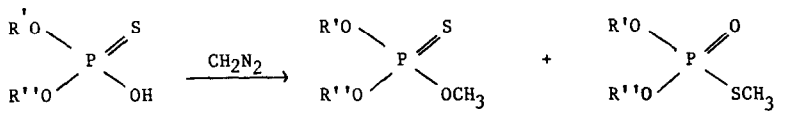


Et(EtO)P(S)OH $[\alpha]_D = +13.9°$ $\xrightarrow{Ph_3PBr_2}$ Et(EtO)P(S)Br $[\alpha]_D = +140.4°$ $\xrightarrow{OH^-}$ Et(EtO)P(S)OH $[\alpha]_D = +13.0°$

(IV) Reaction of a phosphorothioic ester with a methyl iodide[2] to produce S-methylphosphorothiolate triester (reaction at sulphur).



(V) Reaction of a phosphorothioic diester with diazomethane to produce a mixture of phosphorothionate and phosphorothiolate triesters which are easy to isolate by tlc on silicic acid.



The present work was undertaken to make available a series of optically active phosphorus compounds of known or ascertainable absolute configurations. The nucleophilic displacement reactions leading to the enantiomeric phosphorothiono-triesters from the optically active chloridophosphorothionates as precursors are summarised in Table 1 (**10**–**20**). (−) Methyl-n-butyl-1-naphthylphosphorothionate (**16**) was subjected to a detailed stereochemical investigation and a full Walden inversion was attempted. The stereochemical course of such reactions is shown in Fig. 1.

Stereochemical consequences of reactions on (−) *methyl-n-butyl-1-naphthylphosphorothionate.* From the sequence of reactions in Fig. 1, it was found that the PCl_5 reaction (I) on (+) **22** produced (−) **23**, the chloridate, and the methoxide reaction (II) on (−) **23**, which should have produced (−) **16**, appeared to produce (+) **16′**. To resolve this stereochemical result, the reactions (III) and (IV) leading to **21** and **21′** with very large specific rotation compared with the very small specific rotation of **16′**, were attempted. The products **21** and **21′** have the same sign of rotation and they have been obtained by identical sequence of reactions where the configuration at phosphorus is presumably unaffected.

The sequence of reactions (1)–(5) confirming the stereochemical consequences of reactions at phosphorus of (−)-methyl-n-butyl-naphthyl-phosphorothionate (**16**) is summarised in Table 2.

(1) Reactions from −(**16**), methyl-n-butyl 1-naphthyl-phosphorothionate, leading to +(**21**), S-methyl-0-n-butyl-0-1-naphthylphosphorothionate, proceeded via types (III) and (IV) reactions and therefore with retention of configuration at phosphorus.

(2) Reactions from −(**16**) to +(**16′**) proceeded via types I and II reactions and therefore were capable of two inversions of configuration at phosphorus.

(3) Reactions from (**16′**) to (**21′**) proceeded via types III and IV reactions and therefore with retention of configuration.

Sequence (2) must have proceeded with one inversion to generate + (**16″**) or two inversions of configuration, to regenerate (−) **16**, the starting enantiomer. One of the reactions, viz. $CH_3O^{\ominus}$ (methoxyl anion) reaction on (−) **23**, n-butyl 1-naphthylchloridophosphorothionate, is known to proceed with inversion of configuration. Sequence (3) indicates that another reaction in (2) must have proceeded with inversion of configuration because two inversions of configuration are required for the generation of (+)**21′** or two reactions involving retention as in sequence (1) starting with (−)**16** to produce (+) **21**. Since the intermediate reactions of (+)**16′** to (+)**20′** and from (+)**20′** to (+)**21′** are reactions that proceed with retention of configuration, the only reaction that remains is from (+)**22**, n-butyl 1-naphthylphosphorothioic acid to (−)**23** by PCl_5. Therefore the PCl_5 reaction in sequence (2) must have also proceeded with inversion of configuration.

The results now obtained indicate that both the PCl_5 and the RO^- reactions occurred with inversion and that the opposite sign of rotation in **16′** was due to a more highly optically active impurity in one of the specimens. Further confirmatory evidence was sought and this was obtained from sequences (4) and (5).

(4) Reactions from (−)**16** to (−)**16″** proceeded via types III and V reactions and since type III proceeds with retention and type V yielded the enantiomer (−)**16″** identical to the starting enantiomer (−)**16**, type V reaction also proceeds with retention of configuration.

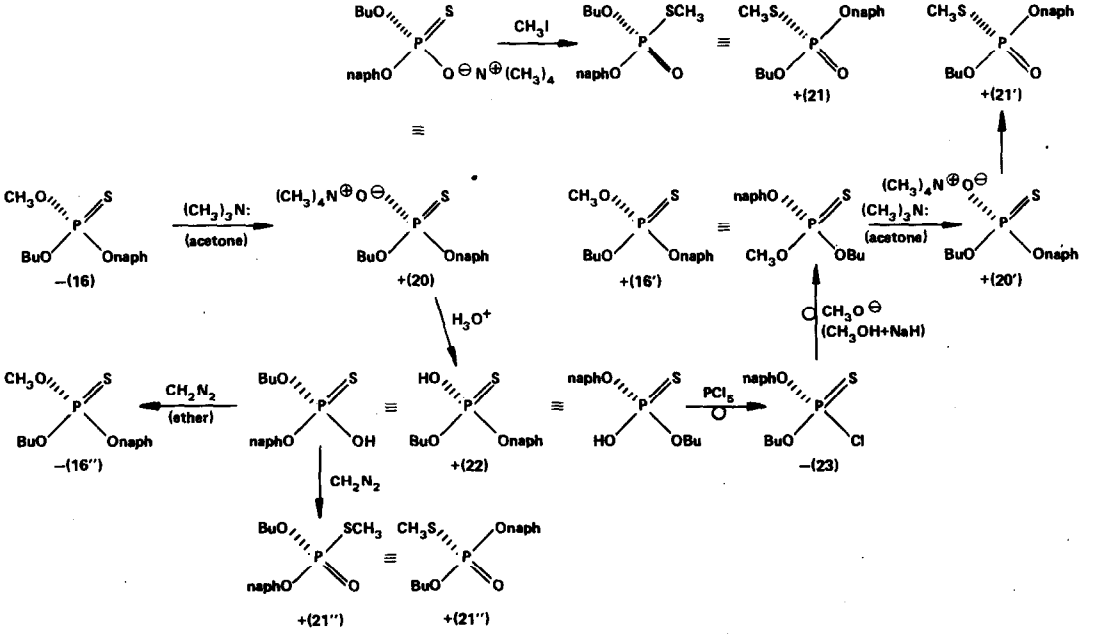


Fig. 1. Stereochemical investigation of (−)-methyl-n-butyl-1-naphthylphosphorothionate.

Table 1. Displacement reactions

Electrophile	Nucleophile		Product	λ	$[\alpha]_\lambda$	
(+)-(MeO)P(S)(O-naphthyl)Cl	EtONa	(10)	(-)-(EtO)(MeO)P(S)(O-naphthyl)	589 365	- 1.036 - 3.607	(c 2.8, $CHCl_3$)
(-)-(MeO)P(S)(O-naphthyl)Cl	EtONa	(11)	(+)-(EtO)(MeO)P(S)(O-naphthyl)	589 365	+ 0.433 + 0.667	(c 6, $CHCl_3$)
(+)-(MeO)P(S)(O-naphthyl)Cl	n-PrONa	(12)	(-)-(MeO)(O-n-propyl)P(S)(O-naphthyl)	589 365	- 0.583 - 2.33	(c 1.2, $CHCl_3$)
(-)-(MeO)P(S)(O-naphthyl)Cl	n-PrONa	(13)	(+)-(MeO)(O-n-Pr)P(S)(O-naphthyl)	589 365	+ 0.786 + 3.862	(c 14.5, $CHCl_3$)
(+)-(MeO)P(S)(O-naphthyl)Cl	Pr^iONa	(14)	(-)-(MeO)(OPr^i)P(S)(O-naphthyl)	589 365	- 0.960 - 4.80	(c 5, $CHCl_3$)
(-)-(MeO)P(S)(O-naphthyl)Cl	Pr^iONa	(15)	(+)-(MeO)(OPr^i)P(S)(O-naphthyl)	589 365	+ 1.20 + 6.086	(c 4, $CHCl_3$)
(+)-(MeO)P(S)(O-naphthyl)Cl	n-butylONa	(16)	(-)-(MeO)(O-n-butyl)P(S)(O-naphthyl)	589 365	- 1.900 - 6.800	(c 1.0, $CHCl_3$)
(-)-(MeO)P(S)(O-naphthyl)Cl	n-butylONa	(17)	(+)-(MeO)(O-n-butyl)P(S)(O-naphthyl)	589 365	+ 1.800 + 6.400	(c 1.6, $CHCl_3$)
(+)-(MeO)P(S)(O-naphthyl)Cl	p-$O_2NC_6H_4ONa$	(18)	(+)-(MeO)($OC_6H_4NO_2$-p)P(S)(O-naphthyl)	589 436	+12.25 +32.917	(c 1.2, $CHCl_3$)
(-)-(MeO)P(S)(O-naphthyl)Cl	p-$O_2NC_6H_4ONa$	(19)	(-)-(MeO)($OC_6H_4NO_2$-p)P(S)(O-naphthyl)	589 436	-12.00 -31.583	(c 1.0, $CHCl_3$)
(-)-(MeO)P(S)(O-naphthyl)Cl	$MeOCH_2CH_2OH$	(20)	(+)-(MeO)(OCH_2CH_2OMe)P(S)(O-naphthyl)	589 365	+ 3.985 +18.621	(c 1.305, $CHCl_3$)

Table 2. Syntheses involved in the stereochemical consequences of reactions on (−)-methyl-n-butyl-1-naphthyl-phosphorothionate

Sequence	Reactants	λ	$[\alpha]_\lambda$		Products	λ	$[\alpha]_\lambda$	
(1) (16) − (21)	(−)-MeO(O-n-butyl)P(S)(O-naphthyl), 16 + $(CH_3)_3N$, (acetone)	589 365	− 1.90 − 6.80	(c 1.0, $CHCl_3$)	(+)-$(CH_3)_4N^+ O^- P(S)$(O-n-butyl), (O-napnthyl), 20	589 365	+ 17.60 + 72.70	(c 1.0, $CHCl_3$)
	(+)20 + CH_3I	589 365	+17.60 -72.70		(+)-$(CH_3S)P(O)$(O-n-butyl) (O-naphthyl), 21	589 365	+ 50.90 +201.70	(c 0.287, $CHCl_3$)
(2) (16) − (16')	(+)20 + H_3O^+	589 365	+17.60 -72.70		(+)-(O-n-butyl)(O-naphthyl)P (S)(OH), 22	589 365	+ 22.20 + 94.20	(c 0.36, $CHCl_3$)
	(+)22 + PCl_5	589 365	+22.20 +94.20		(−)-(O-n-butyl)(O-naphthyl)P (S)(Cl), 23	589 365	- 25.50 -107.50	(c 0.106, $CHCl_3$)
	(−)23 + CH_3OH + NaH	589 365	+ 2.20 + 6.30		(+)-(MeO)(O-n-butyl)P(S) (O-naphthyl), 16'	589 365	+ 2.20 + 6.30	(c 0.319, $CHCl_3$)
(3) (16') − (21')	(+)16' + $(CH_3)_3N$, (acetone)	589 365	+ 2.20 + 6.30		(+)20'	589 365	+ 14.30 + 68.0	(c 0.2, $CHCl_3$)
	(+)20' + CH_3I (MeOH)	589 365	+14.30 +68.0		(+)21'	589 365	+ 47.4 +200.0	(c 0.038, $CHCl_3$)
(4) (16') − (16'')	(+)22 + CH_2N_2 (ether)	589 365	+22.2 +94.2		(−)16''	589 365	- 2.0 - 10.0	(c 0.2, $CHCl_3$)
(5) (16) − (21'')	(+)22 + CH_2N_2 (ether)	589 365	+22.2 +94.2		(+)21''	589 365	+ 40.4 +156.1	(I) (c 0.228, $CHCl_3$)
						589 365	+ 44.0 +181.1	(II) (c 0.159, $CHCl_3$)
						589 365	+ 45.0 +192.3	(III) (c 0.130, $CHCl_3$)

(5) Reactions from (−)**16** to (+)**21″** indicate that the final diazomethane reaction also proceeded with retention of configuration since (+)**21″** is identical to (+)**21** which was obtained by independent reactions known to involve retention of configuration as in sequence (3).

The diazomethane reaction V on phosphorothioic acid yielded two products. This step could be useful in (i) checking the optical purity of the phosphorothioate triester prepared via a chloridate, which is a contaminant by this synthetic route and is not easy to separate by chromatography and (ii) it could also afford a synthetic route to the phosphorothioate triester R_f 0.6 ($CHCl_3$), which is easily purifiable by tlc from the phosphorothioic acid R_f 0 ($CHCl_3$). Thus a more highly optically active impurity in one of the specimens in the synthetic pathway leading to (+)**16′** was masking the low negative rotation that should have been produced by **16′**. The optically active impurity was possibly removed in one of the sequence of reactions leading to (+)**21′**.

In conclusion, if the absolute configuration of the (+) phosphorothioic acid, (**22**), in the form of the (−) ephedrine (+) phosphorothionate salt can be determined by X-ray crystallography the absolute configurations of the phosphorothionate and other intermediates in the sequence of reactions will therefore be known.

EXPERIMENTAL

Solvent extracts were dried over Na_2SO_4 unless otherwise stated. Filtered extracts were taken to dryness on a rotary evaporator to remove the solvent. Column chromatography on silicic acid was used for purification and, in the case of optically active compounds, was carried out to constant optical rotation. Synthesis was monitored by tlc. 1,2-Dimethoxyethane was dried over $CaCl_2$, followed by Na. CCl_4 was dried over $CaCl_2$.

A Perkin–Elmer polarimeter 141 was used for measuring the optical rotations.

A 100 MHZ spectrometer was used for the PMR spectroscopy, mass spectrometry was done on an MS-9 (AEI Ltd.) and IR spectroscopy was routinely carried out on a Perkin–Elmer 137 sodium chloride spectrophotometer. NMR, mass spectrometry, IR spectroscopy and elemental analyses were used in identifying and confirming structures of the molecules synthesised in this study.

Dimethyl-1-naphthylphosphorothionate (**1**). 0,0-Dimethyl chlorothiophosphate (161 g) was added dropwise to a stirred soln of 1-naphthol (158 g) and NaOH (44 g) in water (500 ml). The mixture was stirred at 50–60° overnight and was extracted with chloroform.

The chloroform extract was washed with 2% NaOH, followed by aqueous washings and was dried. After column chromatographic purification of the viscous residue using CH_2Cl_2 as mobile phase, yielded 227 g; R_f 0.47 (CH_2Cl_2). (Found: C, 54.3; H, 5.1; P, 11.6. $C_{12}H_{13}O_3PS$ Requires: C, 53.7; H, 4.9; P 11.6%).

The NMR spectrum was found to be consistent with the structure.

Tetramethylammonium methyl-1-naphthylphosphorothionate **2**. Trimethylamine (36.4 ml) in acetone (200 ml) was added to an ice/salt bath cooled soln of **1** (109 g) in acetone (300 ml) with stirring. The reaction was allowed to proceed overnight and the crystals were collected on a Buchner funnel and washed with acetone, yield 120 g; R_f 0.21 (MeOH/benzene 1:4). (Found: C, 53.9; H, 6.6; N, 4.3; P, 9.5. $C_{15}H_{22}O_3NPS$ Requires: C, 55.0; H, 6.8; N, 4.3; P, 9.5%).

Ephedrine methyl - 1 - naphthylphosphorothionate **3**. Compound **2**, (238.4 g) in water (700 ml) was added to a soln of (−) ephedrine hydrochloride (147.2 g) in water (700 ml). The mixture was stirred and was left in the cold room for *ca* 1 hr. The crystals were recrystallised from water/MeOH (1:1) to constant optical rotation thus yielding **3a**, yield 45 g, mp 168°. (Found: C, 59.7; H, 6.3; N, 3.5; P, 7.6. $C_{21}H_{26}O_4$ NPS Requires: C, 60.1; H, 6.3; N, 3.3; P, 7.4%).

The mother liquor was extracted with chloroform and the extract was dried yielding **3b** (31 g) as an oil. **3a** $[\alpha]_{589}+31.240$, $[\alpha]_{365}+136.364$ *c*, 1.210, $CHCl_3$) **3b** $[\alpha]_{589}-35.341$, $[\alpha]_{365}-134.911$ (*c*, 12.32, $CHCl_3$).

(−) - *Methyl - 1 - naphthylphosphorothioic acid* (**4**). Compound **3b** (40.7 g) was dissolved in warm MeOH (125 ml). A soln of NaOH (4 g) in water (25 ml) was added, followed by additional water (600 ml). The turbid soln was extracted with chloroform (200 ml) twice, followed by ether (200 ml). The aqueous phase was separated and kept. The bulked organic extract was extracted with 1% NaOHaq twice. The aqueous layers were combined and further washed with chloroform and then ether, and were added to the original aqueous phase.

The bulked aqueous phase was acidified with conc. HCl and was extracted with chloroform twice. The chloroform extracts were dried, yield 14.3 g. $[\alpha]_{589}-16.958$, $[\alpha]_{365}-53.636$ (*c*, 14.3, $CHCl_3$)

(+) - *Methyl - 1 - naphthylphosphorothioic acid* (**5**). **3a**, (40 g) was used and the procedure as for **4** was followed, yield of (+) enantiomer 16 g. $[\alpha]_{589}+14.156$, $[\alpha]_{365}+57.078$ (*c*, 1.102, $CHCl_3$). Mass spectrum was consistent with the structure.

(−) - S - *Methyl - 0 - methyl - 0 - 1 - naphthylphosphorothiolate* (**6**). **4** (1.27 g) in MeOH (20 ml) was added to $NaHCO_3$ (0.42 g) in MeOH (20 ml). To the clear soln, iodomethane (0.70 g) in MeOH (20 ml) was added. The mixture was stirred and the reaction was allowed to continue overnight. Residue was extracted with ether twice, washed with water and the solvent extract was dried, yield 1.0 g; R_f 0.10 (CH_2Cl_2), R_f 0.36 (diethyl ether). $[\alpha]_{589}-47.786$, $[\alpha]_{365}-182.824$ (*c*, 1.31, $CHCl_3$).

(+) - S - *Methyl - 0 - methyl - 0 - 1 - naphthylphosphorothiolate* (**7**). The (+) **5** was subjected to the same procedure as in synthesis **6**, yield 0.65 g. $[\alpha]_{589}+47.746$, $[\alpha]_{365}+180.127$ (*c*, 1.576, $CHCl_3$). R_f 0.36 (diethyl ether), R_f 0.75 (MeOH)/CH_2Cl_2, 1:9), NMR spectrum was consistent with the structure.

(+) - *Methyl - 1 - naphthylchloridophosphorothionate* (**8**). **4** (25 g) in CCl_4 (400 ml) was added to a stirred suspension of PCl_5 (2.1 g) in CCl_4 (80 ml) at −10–−5° (i-PrOH/CO_2 bath). The reaction time was *ca* 1.5 hr and the reaction was monitored by tlc (CH_2Cl_2). Stirring was continued at +5° for *ca* 0.5 hr. Excess PCl_5 was filtered off. The residue was chromatographed on a silicic acid column (CH_2Cl_2), yield 18 g; R_f 0.63 (CH_2Cl_2). $[\alpha]_{589}+17.4$, $[\alpha]_{365}+77.8$ (*c*, 1.0, $CHCl_3$), mass spectrum was consistent with the structure.

(−) - *Methyl - 1 - naphthylchloridophosphorothionate* (**9**). The (+) acid enantiomer **5** (16.9 g) in CCl_4 (70 ml) was added dropwise to the stirred suspension of PCl_5 (14.1 g) in CCl_4 (140 ml) at −10° in i-PrOH/CO_2 bath. Reaction procedure as for **8** was followed, R_f 0.61 ($CHCl_3$), yield 12 g. $[\alpha]_{589}+17.708$, $[\alpha]_{365}+85.190$ (*c*, 2.208, $CHCl_3$). (Found: C, 48.4; H, 3.5; P, 11.4. $C_{11}H_{10}O_2$ PSCl Requires: C, 48.5; H, 3.7; P, 11.4%).

(−) - *Ethylmethyl - 1 - naphthylphosphorothionate* (**10**). A soln of (+) **8** (2 g) in dimethoxyethane was added dropwise to the stirred soln of Na (0.46 g) in EtOH (0.68 g). The reaction was allowed to proceed overnight. The extract was purified by column chromatography on silicic acid (CH_2Cl_2), yield 1.2 g. $[\alpha]_{589}-1.036$, $[\alpha]_{365}-3.067$ (*c*, 2.8, $CHCl_3$). The triester (1 g) was reacted with trimethylamine to form the tetramethylammonium salt of ethyl-1-naphthylphosphorothioic acid. (Found: C, 55.9; H, 7.1; N, 3.8. $C_{16}H_{24}O_3PNS$ Requires: C, 56.3; H, 7.1; N, 4.1%). NMR spectrum in Fig. 2 was consistent with the structure of (**10**).

(+) - *Ethylmethyl - 1 - naphthylphosphorothionate* (**11**). **9** (2 g) in dimethoxyethane was reacted as in (**10**). NMR spectrum was consistent with the structure. $[\alpha]_{589}+0.433$, $[\alpha]_{365}+0.667$ (*c*, 6, $CHCl_3$).

(−) - *Methyl - 1 - naphthyl - n - propylphosphorothionate* (**12**). Na (0.46 g) was reacted with n-PrOH (1.2 g) and (+) **8** (2.7 g) was added using dimethoxyethane as solvent at 50–60° for about 6 hr. Procedure as in (**10**) was continued. (Found: C, 56.2; H, 5.5; P, 10.6. $C_{14}H_{17}O_3PS$ Requires: C, 56.8; H, 5.8; P, 10.5%). NMR spectrum in Fig. 3 was consistent with the structure. $[\alpha]_{589}-0.583$, $[\alpha]_{365}-2.333$ (*c*, 1.2, $CHCl_3$).

(+) - *Methyl - 1 - naphthyl - n - propylphosphorothionate* (**13**). **9** (4.7 g) was reacted with n-PrOH (1.04 g) and NaH (0.42 g)

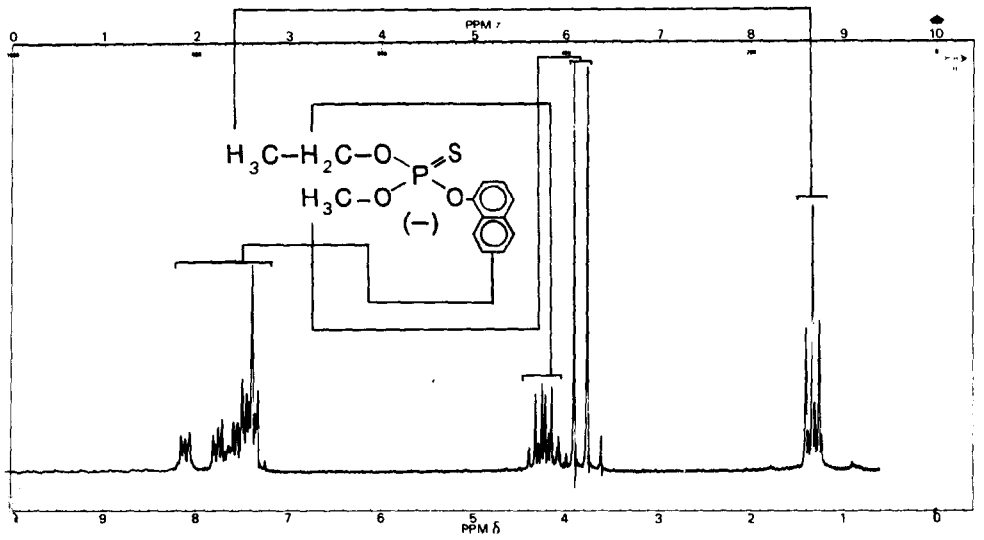


Fig. 2. NMR spectrum of (−)-ethyl methyl-1-naphthylphosphorothionate (**10**).

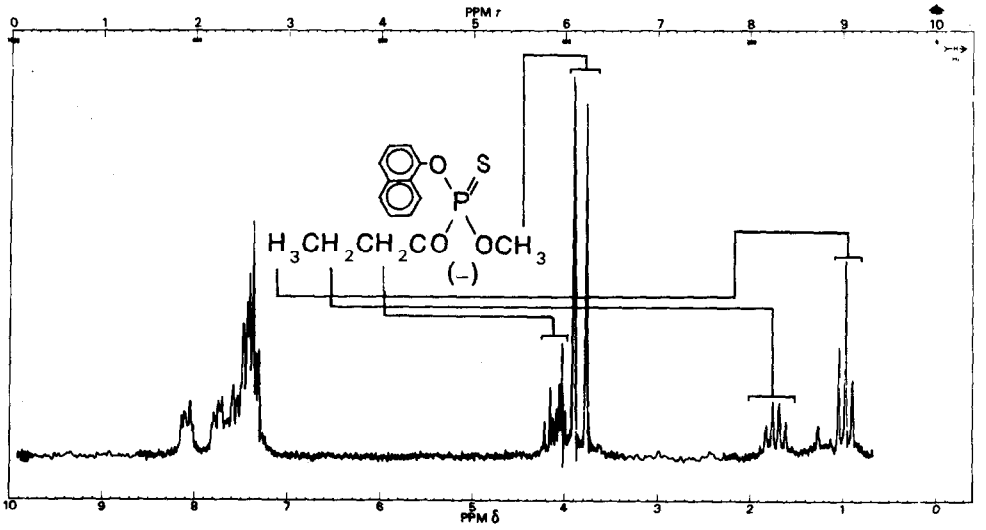


Fig. 3. NMR spectrum of (−)-methyl-1-naphthylpropylphosphorothionate (**12**).

using dimethoxyethane as solvent. Extract was purified by chromatography on silicic acid (CH_2Cl_2), yield 1.5 g. (Found: C, 57.1; H, 5.9; P, 10.8. $C_{14}H_{17}O_3PS$ Requires: C, 56.8; H, 5.8; P, 10.5%). NMR spectrum was consistent with the structure. $[\alpha]_{589}+0.786$, $[\alpha]_{365}+3.862$ (*c*, 14.5, $CHCl_3$).

(−) - *Isopropylmethyl* - 1 - *naphthylphosphorothionate* (**14**). (+) **8** (2 g) in dimethoxyethane was added dropwise to a stirred suspension of Na (0.4 g) in i-PrOH (1 g) at 50–60° overnight. Extract was purified on silicic acid ($CHCl_3$), yield 1.2 g. (Found: C, 57.1; H, 5.6; P, 10.7. $C_{14}H_{17}O_3PS$ Requires: C, 56.8; H, 5.8; P, 10.5%). NMR spectrum was consistent with the structure. $[\alpha]_{589}-0.960$, $[\alpha]_{365}-4.800$ (*c*, 5, $CHCl_3$).

(+) - *Isopropylmethyl* - 1 - *naphthylphosphorothionate* (**15**). (−) **9**, (2 g) was reacted as for **14**, yield 1 g. (Found: C, 57.1; H, 5.7; P, 10.7. $C_{14}H_{17}O_3PS$ Requires: C, 56.8; H, 5.8; P, 10.5%). NMR spectrum in Fig. 4 was consistent with the structure. $[\alpha]_{589}+1.20$, $[\alpha]_{365}+6.086$ (*c*, 4, $CHCl_3$).

(−)*n* - *Butylmethyl* - 1 - *naphthylphosphorothionate* (**16**). (+)**8** (2.0 g) in n-BuOH was added dropwise to a soln of n-BuOH (1.48 g) and NaH (0.5 g). The mixture was stirred at room temp. overnight, yield 1.2 g. The (−)triester (1 g) was reacted with trimethylamine to form the tetramethylammonium salt derivative of n-butyl - 1 - naphthylphosphorothionic acid. (Found: C, 58.8; H, 7.9; N, 3.7. $C_{18}H_{28}O_3PNS$ Requires: C, 58.5; H, 7.6; N, 3.8%). NMR spectrum of the triester as shown in Fig. 5 was found to be consistent with the structure and the optical rotations are as follows: $[\alpha]_{589}-1.900$, $[\alpha]_{365}-6.800$ (*c*, 1.0, $CHCl_3$).

(+)*n* - *Butylmethyl* - 1 - *naphthylphosphorothionate* (**17**). (−)**8** (2.0 g) was reacted as in (**16**). The extract (1.4 g) was purified on silicic acid column ($CHCl_3$) to constant optical rotation, yield 0.8 g. PMR was found to be consistent with the structure. (Found: C, 57.9, H, 6.3; P, 9.9. $C_{15}H_{19}O_3PS$ Requires: C, 58.0; H, 6.2; P, 10.0%). $[\alpha]_{589}+1.800$, $[\alpha]_{365}-6.400$(*c*, 1.6, $CHCl_3$).

(+)*Methyl* - 1 - *naphthyl* - p - *nitrophenylphosphorothionate* (**18**). NaH (0.48 g) was added to a soln of *p*-nitrophenol (2.7 g) in dimethoxyethane (50 ml) with stirring. (+) Methyl-1-naphthyl-chloridophosphorothionate (2.0 g) in dimethoxyethane was added dropwise and the reaction was monitored by tlc ($CHCl_3$) and was allowed to continue overnight (R_f 0.56 $CHCl_3$). Crude extract (4 g) was purified on silicic acid column ($CHCl_3$) for methyl-1-naphthyl-*p*-nitrophenyl-phosphorothionate, yield 2.9 g (solid). (Found: C, 54.7; H, 3.9; N, 3.9. $C_{17}H_{14}O_5NPS$ Requires: C, 54.4; H, 3.8; N, 3.7%). $[\alpha]_{589}+12.250$, $[\alpha]_{436}+32.917$ (*c*, 1.2, $CHCl_3$). The NMR spectrum in Fig. 6 was consistent with the structure.

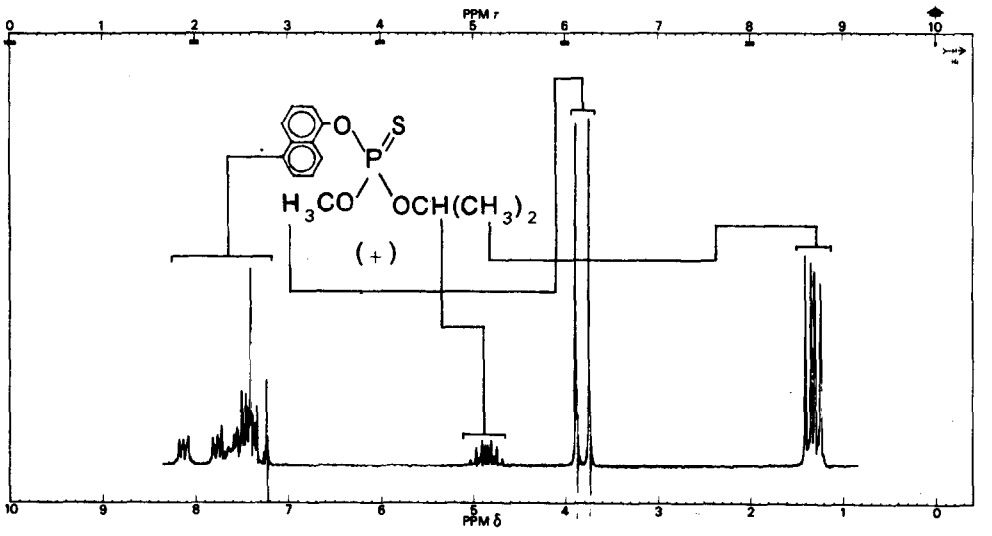


Fig. 4. NMR spectrum of (+)-isopropyl methyl-1-naphthylphosphorothionate (**15**).

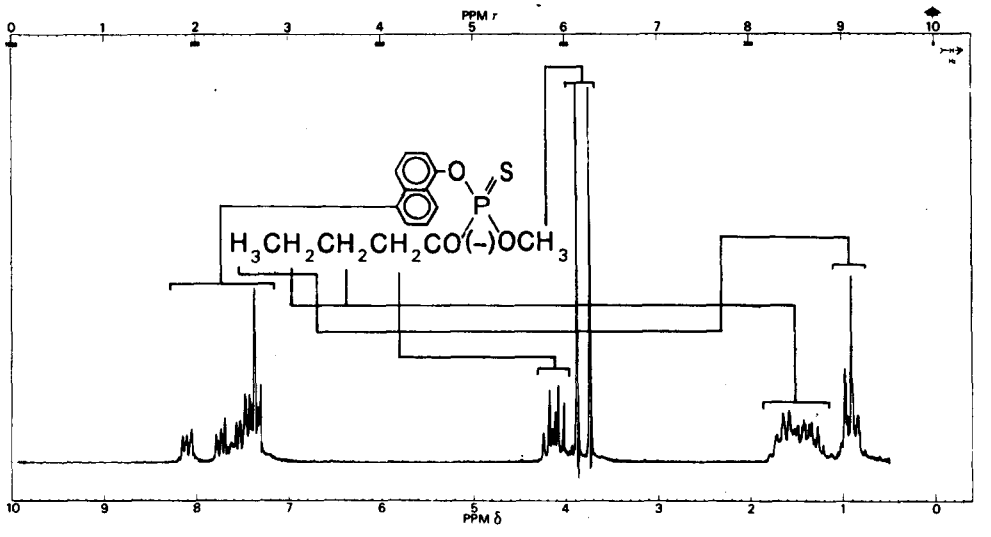


Fig. 5. NMR spectrum of (−)-methyl-n-butyl-1-naphthylphosphorothionate (**16**).

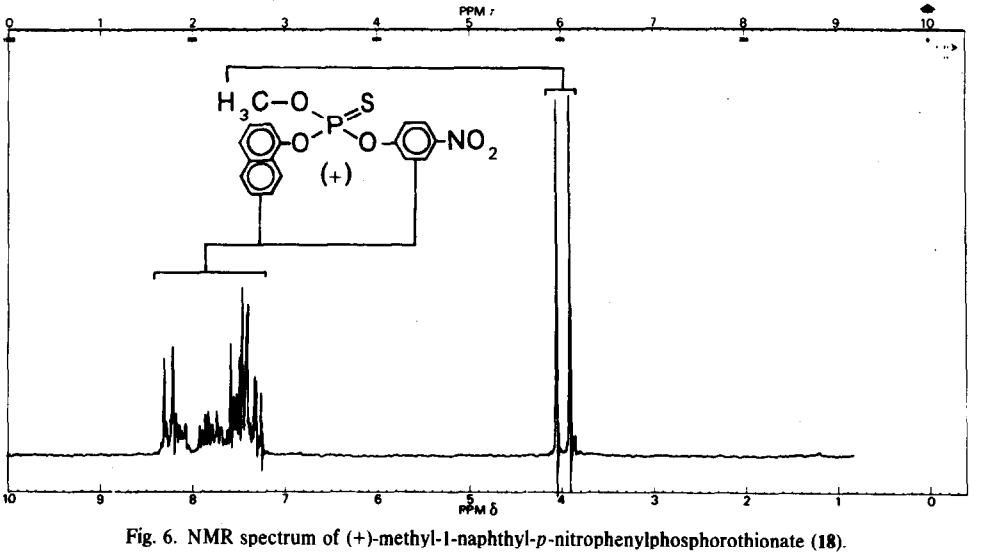


Fig. 6. NMR spectrum of (+)-methyl-1-naphthyl-*p*-nitrophenylphosphorothionate (**18**).

(−)*Methyl - 1 - naphthyl - p - nitrophenylphosphorothionate* (**19**). Synthesis was as in (**10**) using (−)methyl-1-naphthylchloridophosphorothionate, yield 3 g (oil). NMR spectrum was found to be identical with Fig. 6 spectrum. After several months at about −15° the compound solidified. $[\alpha]_{589}$ − 12.00, $[\alpha]_{436}$ − 31.583 (*c*, 1.0, $CHCl_3$).

(+)*Methyl - 2 - methoxyethyl - 1 - naphthylphosphorothionate* (**20**). (−)**9**, (1.4 g), was reacted with n-PrONa (0.4 g) in 2-methoxyethanol (40 ml) at room temp. overnight. The crude extract was purified on silicic acid column (CH_2Cl_2), yield 1 g. (Found: C, 53.4; H, 5.6; P, 10.1. $C_{14}H_{17}O_4PS$ Requires: C, 53.9; H, 5.5; P, 9.9%. $[\alpha]_{589}$ + 3.985, $[\alpha]_{365}$ + 18.621 (*c*, 1.305, $CHCl_3$).

The object of this synthesis was to obtain methyl-1-naphthyl-n-propylphosphorothionate. The structure of the product obtained was confirmed by mass spectrometry as shown in Fig. 7. This synthesis indicates that the 2-methoxyethoxide anion is a better nucleophile than the n-propoxide anion, possibly owing to the inductive effect (−I effect) of the 2-OMe compared with the +I effect of the Me group of the n-propyl.

The syntheses involved in the elucidation of the stereochemistry of (−)-methyl-n-butyl-1-naphthylphosphorothionate. The syntheses of intermediates used are summarised in Table 2, using aliquots of various reactants as in procedures 1–8 and **16** and **21** as appropriate. The diazomethane in ether[13] was added dropwise to the (+)-phosphorothioic acid, (**22**; 70 mg in dry ether) until a faint yellow colour persisted. The ether was evaporated under N_2. The extract in ether was purified by tlc ($CHCl_3$). Two products with R_fs corresponding to 0.1 and 0.6 were obtained. These were isolated and repurified by tlc ($CHCl_3$); the usual procedures of isolation as in the Experimental were followed. R_f 0.1 corresponded to the (+)-S-methyl-0-n-butyl-0-1naphthyl-phosphorothiolate (**21″**) which was consistent with NMR of Fig.

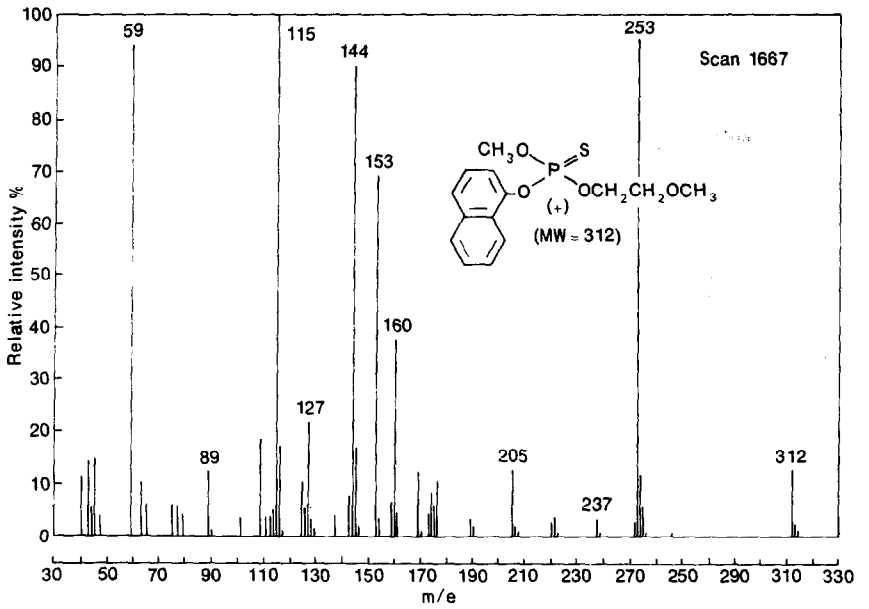


Fig. 7. Mass spectrum of (+)-methyl-2-methoxyethyl-1-naphthylphosphorothionate (**20**).

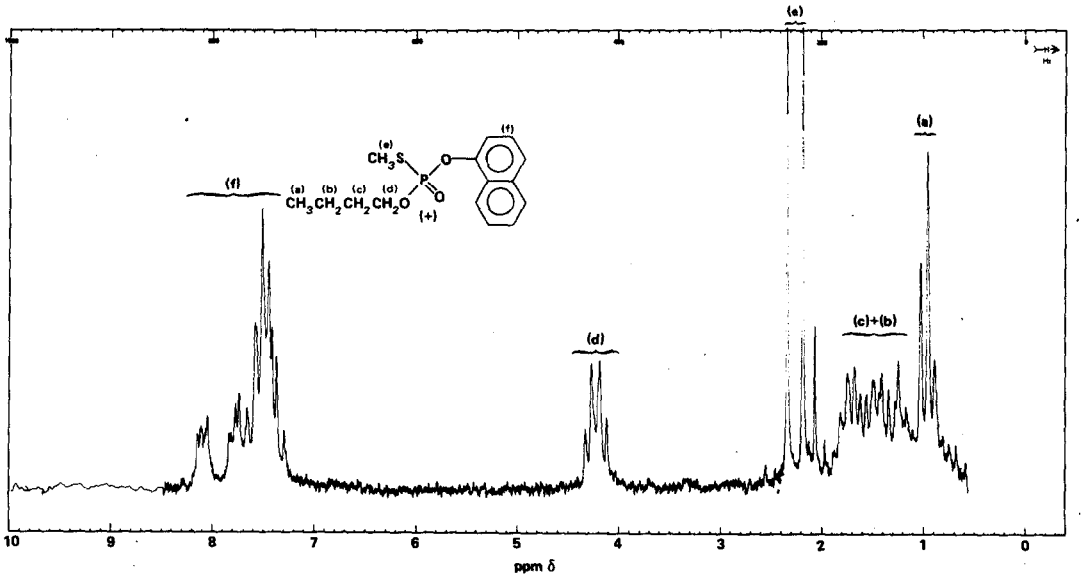


Fig. 8. NMR spectrum of (+)-S-methyl-0-n-butyl-0-1-naphthylphosphorothiolate (**21″**) from diazomethane reaction (CCl_4).

8. R_f 0.6 corresponded to **16''**, (−)-methyl-n-butyl-1-naphthyl-phosphorothionate as confirmed by NMR, and mass spectrometry.

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