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THE STEREOCHEMISTRY OF ENZYMATIC REACTIONS AT PHOSPHORUS

(I) RESOLUTION OF METHYL 1-NAPHTHYL PHOSPHOROTHIONIC ACID

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The stereochemical course of enzymatic reactions involving molecules in which a phosphorus atom constitutes the centre of asymmetry is under study in this laboratory. Examples of such molecules are phosphate triesters of molecular types Pabde and Paabd. These are required either optically active (Pabde type) or stereospecifically labelled with stable or radioactive isotope in the a substituent (Paabd type).

The resolution of phosphonothionic acids via the quinine, brucine and strychnine salts has been described (1, 2, 3); a number of optically active phosphonothiolates have been prepared from the resolved acids by alkylation. The preparation of optically active thiophosphate triesters has only once been described. Hilgetag and Lehmann have reported the resolution of p-nitrophenyl methyl phosphorothionic acid with strychnine methiodide. Alkylation of the enantiomorphs of the acid afforded optically active phosphorothiolates (4, 5).

Methyl 1-naphthyl phosphorothionic acid, prepared as its tetramethylammonium salt, was chosen as the acid for resolution. This choice was made because we have found that dialkyl 1-naphthyl phosphates are suitable substrates for some of the enzyme reactions under study. Experiments with brucine, quinine, D-amphetamine and ephedrine [(-)-2-methylamino-1-phenyl propanol] showed that the latter was the most suitable optically active base for effecting resolution.

Tetramethylammonium methyl 1-naphthyl phosphorothionate and ephedrine hydrochloride when mixed as aqueous solutions in equimolar amounts, gave a 65% yield of crystalline ephedrine methyl 1-naphthyl phosphorothionate with poor melting point (m.p. 138-150°), $[\alpha]_D^{24}$ + 10.5°

(c = 2.15, $CHCl_3$), but with correct n.m.r. spectrum and elemental analysis. Three recrystallizations from aqueous ethanol gave a pure sample of (-)- ephedrine (+)- methyl 1-naphthyl phosphorothionate (I) in 72% yield, m.p. 169-171°, $[\alpha]_D^{24}$ + 33° (c = 1.44, $CHCl_3$). (Found, C, 60.0; H, 6.4; N, 3.4; P, 7.5. Calculated for $C_{21}H_{26}O_4NPS$: C, 60.1; H, 6.3; N, 3.3; P, 7.4). These properties were not altered by further crystallization.

The other isomer, (-)- ephedrine (-)- methyl 1-naphthyl phosphorothionate (II) was more soluble in water and this allowed its isolation from the mother liquor of the preparation stage. A chloroform extract of this mother liquor gave a syrup (yield 25%) with correct n.m.r. spectrum and $[\alpha]_D^{24}$ of - 45.9° (c = 9.20, $CHCl_3$). I and II were treated with methyl iodide in methanol to give (+) and (-) - O-methyl S-methyl 1-naphthyl phosphorothiolates respectively. These compounds crystallized from the syrupy state after storage at -20°. Their properties are summarised in Table I.

TABLE I

Properties of the Enantiomorphs of O-Methyl S-Methyl 1-Naphthyl Phosphorothiolate

Form	m.p.	$[\alpha]_D^{24}$	Analysis
(+)	57-59°	+53.4° (c=6.34, $CHCl_3$)	Found: C, 53.4; H, 5.0; P, 11.7 Calculated for: $C_{12}H_{13}O_3PS$ C, 53.7; H, 4.9; P, 11.5
(-)	55-58°	-51° (c=1.75, $CHCl_3$)	Found: C, 54.0; H, 5.1 Calculated for: $C_{12}H_{13}O_3PS$ C, 53.7, H, 4.9

The n.m.r. spectra of the enantiomorphs were identical and agreed with the expected structure [seven aromatic protons at δ 7.1 - 7.8, three O-methyl protons (doublet) at δ 3.8, 4.02 and three S-methyl protons (doublet) at δ 2.13 and 2.4]. The optical rotatory dispersion curves of both forms were measured in methanolic solution. The two mirror image curves are shown in Figure 1.

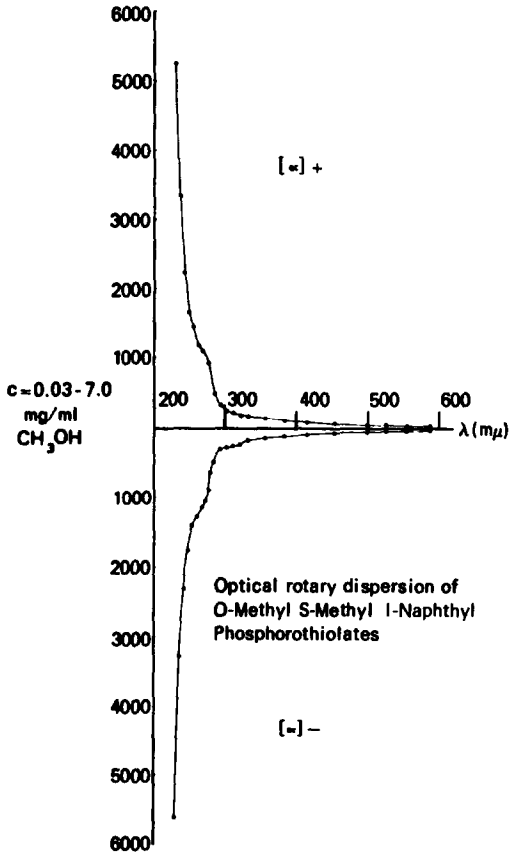

Fig 1

The preparations and resolution of the (+) enantiomorphs were repeated without difficulty with the 4-bromonaphthyl analogues, affording crystalline (-)- ephedrine (+)-methyl 4-bromo-1-naphthyl phosphorothionate, m.p. 149-157°, $[\alpha]_D^{24}$ + 27° (c = 1.028, $CHCl_3$) and (+)- O-methyl S-methyl 4-bromo-1-naphthyl phosphorothiolate (syrup), $[\alpha]_D^{24}$ + 43.4 (c = 2.44, $CHCl_3$).

All of the compounds described above were optically stable when stored for two months as crystals, syrups or solutions in chloroform, ethanol or methanol. They appear to be suitable starting materials for further synthesis of asymmetric phosphoric acid tri-O-esters.

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