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SYNTHESIS OF CHIRAL MALATHION AND ISOMALATHION

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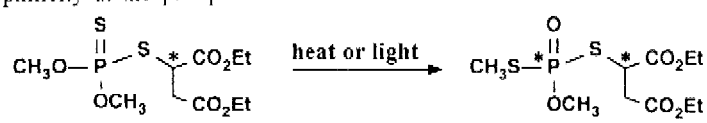
Abstract: *The first synthesis of the chiral isomers of isomalathion and malathion are reported herein.*

Malathion (**1**) is one of the most widely used organophosphate insecticides considered relatively safe to mammals due to rapid degradation by liver carboxylesterases. It has been used effectively for the control of insects on grains, fruits, nuts, cotton, and tobacco including recent use for the control of the medfly outbreak in California. However, as a phosphorothionate, it is prone to thermal and possibly photochemical induced isomerization (Eq.1), leading to the more toxic phosphorodithiolate impurity, isomalathion (**2**).[1-3] Isomalathion was implicated in 1976 for the poisoning of 2800 Pakistani spraymen resulting in 5 deaths.[4]

The toxicity of isomalathion (and other organophosphates) is primarily due to its ability to inhibit acetylcholinesterase (AChE), the enzyme responsible for hydrolysis of the neurotransmitter, acetylcholine.[5] Isomalathion is approximately 1000 times more potent than malathion as an anticholinesterase,[6] owing to enhanced electrophilicity at the phosphorus atom.



Eq. 1

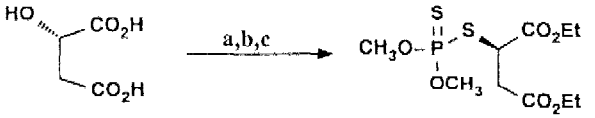
1: malathion **2: isomalathion**

A structurally significant feature of **1** is an asymmetric center at the succinate ligand. The chiral center at carbon would be maintained during the formation of isomalathion, whereas a new chiral center is generated at phosphorus to provide four possible stereoisomers. The stereoselective inhibition of AChE by chiral organophosphates is well documented,[7-11] although few studies have addressed specific P,C-diastereomer sets.[12] In light of these facts and the global importance of malathion use, a synthesis of the chiral isomers of isomalathion is needed to assess their individual contributions to the mode of action. A necessary first objective is a reliable synthesis of chiral malathion, which then will serve as a precursor to the isomalathion stereoisomers.

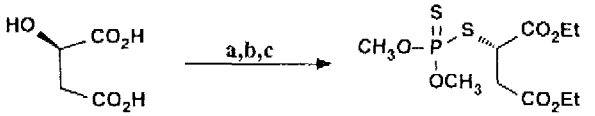
Hassan and Dauterman first reported a synthesis of the O,O-diethyl analog of **1** by reaction of *l*-diethyl bromosuccinate (from *l*-aspartic acid) with O,O-diethyl potassium phosphorodithioate,[13] a sequence requiring three stereochemical processes at carbon. Unfortunately, our attempts to prepare the malathion enantiomers (**1a**, **1b**) by this method proceeded in low yield and reduced optical activity, and an alternative strategy was required.

l-Malic acid (**3a**) was converted to diethyl malate (EtOH, $HCl_{(g)}$, 0 °C, 3h) in 90% yield.[14] The hydroxyl group was converted into a variety of leaving groups (Ts-, Ms, CF_3CO-) and reactions with purified O,O-dimethyl sodium phosphorodithioate[15] were attempted. However, only the triflate (generated *in situ*; Tf_2O, lutidine, -78 °C) was found to undergo the desired substitution resulting in the first synthesis

of R_C-malathion (**1a**) in 72% overall yield from malic acid (Eq. 2). The same synthetic pathway was conducted with *d*-malic acid (**3b**) to form S_C-malathion (**1b**) (Eq. 3). In contrast to the prior preparation of O,O-diethyl-**1**, this method uses only one inversion at the carbon center reducing the opportunity for racemization.[13] We were unable to effect stereoisomer separation with chiral shift reagents.



3a: *l*-Malic acid **1a: R_C-malathion** **Eq. 2**

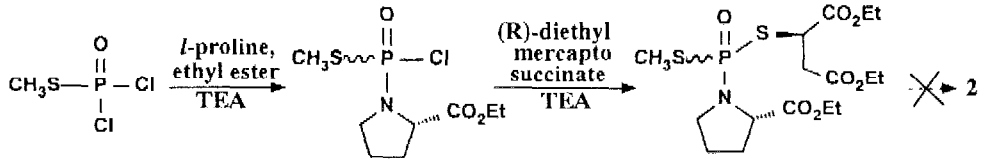


3b: *d*-Malic acid **1b: S_C-malathion** **Eq. 3**

a. EtOH, H^+ b. $(CF_3SO_2)_2O$, lutidine c. $(CH_3O)_2P(S)S^-Na^+$

Diastereomeric mixtures of isomalathion with known stereochemistry at carbon and racemic at phosphorus (R_PR_C/S_PR_C and R_PS_C/S_PS_C) were prepared by a one-flask, phosphorus methyl ester dealkylation (potassium ethyl xanthate, acetone, reflux, 2h) and realkylation with dimethylsulfate (DMS) at the phosphorothioate sulfur (acetone, reflux, 3h, 65%).[6] All attempts at a preparative separation of these diastereomer sets failed. Partial analytical separation (approx. 90%) was accomplished with chiral HPLC (*d*-phenylglycine; hex:i-PA, 75:25, 1.0 mL/min) however, no separation was seen by chiral, capillary GC.

Since there was a lack of discrimination of the physical properties at phosphorus, we redirected our attention to a second resolution process. Our preliminary attempt intended to convert diastereomeric proline amides[16] **6** derived from S-methyl phosphorodichloridate (**4**),[17] into the isomalathion stereoisomers by acidic methanolysis (Eq. 4).[18] However, we were unable to find suitable conditions to convert **6** into **2**.[19]



4 **5** **6** **Eq. 4**

Several chiral phosphorothioic acids have been resolved using alkaloids such as cinchonidine, α-phenethylamine, quinine, and strychnine through fractional recrystallization of the dealkylated esters.[20] However, far fewer phosphorodithioates have been resolved by this approach. Our initial studies attempted to form the desmethyl R_C-malathion and desmethyl S_C-malathion phosphorothioic acid salts of strychnine or brucine. After reflux in methanol with R_C-malathion, both alkaloids deposited crystalline salts. The strychnine salts fractionally crystallized from chloroform/ethyl acetate/ether to furnish the first crop, 70% enriched in one isomer,[21] and therefore, this resolving agent was used for further separation (Scheme 1; Table 1). The second crop was 77% enriched in the other isomer. Repeated fractional recrystallization furnished greater than 98% purity, diastereomeric desmethyl R_C-malathion strychnine salts $\mathbf{7a_1/7a_2}$. These salts were converted to the R_C-isomalathion diastereomers with dimethyl sulfate in 79% yield. Desmethyl S_C-malathion strychnine salts $\mathbf{7b_1/7b_2}$ were fractionally crystallized from methanol/ethyl acetate/ether and similarly converted to $\mathbf{2b_1/2b_2}$. Approximately 10% malathion was formed during the alkylation reaction, which was easily separated by flash chromatography (pet ether/ether, 1:2).[22] Isomalathion diastereomers

derived from a single malathion enantiomer were >96% enriched by ^{31}P NMR. The melting points and spectral characteristics of the alkaloid salts support the eventual enantiomeric relationships between $\mathbf{2a_1}$-$\mathbf{2b_2}$, and $\mathbf{2a_2}$-$\mathbf{2b_1}$. An X-ray investigation of the absolute configuration at phosphorus is currently underway to validate the tentative structural assignments.

Scheme 1

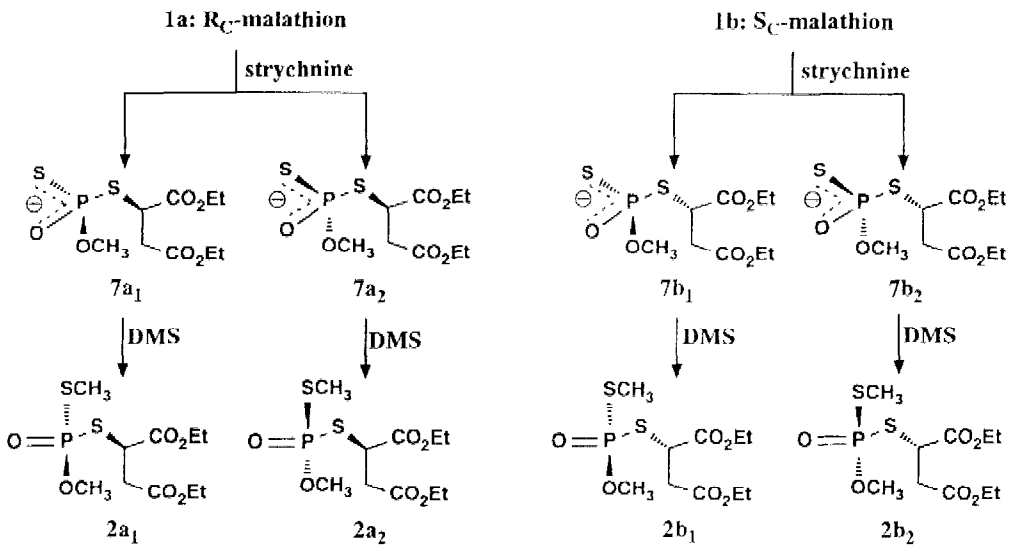


Table 1. Representative Physical and Spectral Data

Compound	mp (0 °C)	$[\alpha]_D^{22}$ (conc, $CHCl_3$)	^{31}P NMR (δ)	^{13}C (δ, S-Me)
1a		+ 81.9 (1.25)	95.98	
1b		- 78.5 (1.25)	96.08	
$2a_1$		+ 43.6 (0.55)	58.41	13.40 (J=15 Hz)
$2a_2$		+ 57.5 (0.57)	56.88	13.15 (J=15 Hz)
$2b_1$		- 64.3 (0.56)	56.96	13.16 (J=15 Hz)
$2b_2$		- 34.2 (0.59)	58.35	13.41 (J=15 Hz)
$7a_1$	159-160	+ 31.2 (0.25)	67.10	
$7a_2$	181-182	+ 16.1 (0.31)	68.10	
$7b_1$	189	- 45.1 (0.26)	68.12	
$7b_2$	158-159	- 61.7 (0.31)	67.18	

During realkylation with dimethylsulfate, a 3-5% loss in the stereochemical integrity at carbon had occurred (based upon the prior ^{31}P NMR assessment of enrichment at the salt stage). Reducing the reaction temperature to 0 °C (2 h) and RT (overnight) solved the problem. Some racemization at carbon is

promoted by the alkaloid base, freed upon reaction of the thioic acid with DMS.

In summary, the first synthesis of the four chiral isomers of isomalathion and the enantiomers of malathion has been accomplished. With the individual stereoisomers of isomalathion available, it will now be possible to probe the interaction with AChE with particular attention upon the effect of chirality at both carbon and phosphorus centers.

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17. Diastereomeric amides **5**, formed by reaction of S-methyl phosphorodichloridate with *l*-proline ethyl ester, were directly converted to the dithiolate amides **6** and separated by flash chromatography (pet ether/ether, 1:3) in an overall yield of 27%.
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21. All recrystallization crops were monitored for percent enrichment by ^{31}P NMR. Doping experiments established the limit of diastereomer contamination as 1-2%. An external reference (H_3PO_4) was used.
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